TGF-β INHIBITORS

BACKGROUND

Field of Invention

[0001] This invention relates to the field of compounds, pharmaceutical compositions comprising them, and methods of using the compounds and compositions. This invention relates more particularly to the field of imidazole and thiazole compounds and pharmaceutical compositions thereof, methods of inhibiting TGF-β with the compounds, and methods of treating and/or preventing disease with the compounds.

Technical Background

[0002] Growth and Differentiation Factor-8 (GDF-8), also known as myostatin, and TGF-β1 are members of the Transforming Growth Factor-beta (TGF-β) superfamily of structurally related growth factors, all of which possess physiologically important growth-regulatory and morphogenetic properties (Kingsley *et al.* (1994) Genes Dev., 8: 133-46; Hoodless *et al.* (1998) Curr. Topics Microbiol. Immunol., 228: 235-72). For example, activation of TGF-β1 signaling and expansion of extracellular matrix are early and persistent contributors to the development and progression of fibrotic disorders, such as involved in chronic renal disease and vascular disease. Border W. A., et al, N. Engl. J. Med., 1994; 331(19), 1286-92. GDF-8 is a negative regulator of skeletal muscle mass. For example, GDF-8 is highly expressed in the developing and adult skeletal muscle. The GDF-8 null mutation in transgenic mice is characterized by a marked hypertrophy and hyperplasia of the skeletal muscle (McPherron *et al.* (1997) Nature, 387: 83-90). Similar increases in skeletal muscle mass are evident in naturally occurring mutations of GDF-8 in cattle (Ashmore *et al.* (1974) Growth, 38: 501 507; Swatland and Kieffer (1994) J. Anim. Sci., 38: 752-757; McPherron and Lee (1997) Proc. Natl. Acad. Sci. USA, 94: 12457-12461; and Kambadur *et al.* (1997) Genome Res., 7: 910-915). Because GDF-8 is expressed in both developing and adult muscles, it is not clear whether it regulates muscle mass during development or in adults. Recent studies have also shown that muscle wasting associated with HIV-infection in humans is accompanied by increases in GDF-8 protein expression (Gonzalez-Cadavid *et al.* (1998) PNAS, 95: 14938-43). In addition, GDF-8 can modulate the production of muscle-specific enzymes (*e.g.*, creatine kinase) and modulate myoblast cell proliferation (WO 00/43781).

[0003] A number of human and animal disorders are associated with loss or functional impairment of muscle tissue, including muscular dystrophy, muscle atrophy, congestive obstructive pulmonary disease, muscle wasting syndrome, sarcopenia, and cachexia. To date,

very few reliable or effective therapies exist for these disorders. However, the terrible symptoms associated with these disorders may be substantially reduced by employing therapies that increase the amount of muscle tissue in patients suffering from the disorders. While not curing the conditions, such therapies would significantly improve the quality of life for these patients and could ameliorate some of the effects of these diseases.

[0004] In addition to its growth-regulatory and morphogenetic properties in skeletal muscle, GDF-8 may also be involved in a number of other physiological processes, including glucose homeostasis in the development of type 2 diabetes and adipose tissue disorders, such as obesity. For example, GDF-8 modulates pre-adipocyte differentiation to adipocytes (Kim *et al.* (2001) BBRC, 281: 902-906).

[0005] Alteration in TGF-β signaling are associated with a wide variety of human disorders including fibrosis, inflammatory, skeletal, muscular and cardiovascular disorders as well as cancer (Harradine, et al,2006, Annals of Medicine 38:403-14). In human cancer, TGF-β signaling alterations can occur in the germline or arise spontaneously in various cancer types. TGF-β is also a potent inducer of angiogenesis, which provides a critical support system for solid tumors as well as a mechanism for tumor cell dissemination (Buijs et al., 2011, Curr Pharmaceutical Biotech, 12:2121-37). Therefore multiple strategies to inhibit TGF-β signaling have been exploited in various disease states.

[0006] There are also a number of conditions associated with a loss of bone, including osteoporosis, especially in the elderly and/or postmenopausal women. Currently available therapies for these conditions work by inhibiting bone resorption.

[0007] Like TGF-β-1, -2, and -3, the GDF-8 protein is synthesized as a precursor protein consisting of an amino-terminal propeptide and a carboxy-terminal mature domain (McPherron and Lee, (1997) Proc. Natl. Acad. Sci. USA, 94: 12457-12461). Before cleavage, the precursor GDF-8 protein forms a homodimer. The amino-terminal propeptide is then cleaved from the mature domain. The cleaved propeptide may remain noncovalently bound to the mature domain dimer, inactivating its biological activity (Miyazono *et al.* (1988) J. Biol. Chem., 263: 6407-6415; Wakefield *et al.* (1988) J. Biol. Chem., 263; 7646-7654; and Brown *et al.* (1990) Growth Factors, 3: 35-43). It is believed that two GDF-8 propeptides bind to the GDF-8 mature dimer (Thies *et al.* (2001) Growth Factors, 18: 251-259). Due to this inactivating property, the propeptide is known as the "latency-associated peptide" (LAP), and the complex of mature domain and propeptide is commonly referred to as the "small latent complex" (Gentry and Nash (1990) Biochemistry, 29: 6851-6857; Derynck *et al.* (1995) Nature, 316: 701-705; and Massague (1990) Ann. Rev. Cell Biol., 12: 597-641). Other

proteins are also known to bind to GDF-8 or structurally related proteins and inhibit their biological activity. Such inhibitory proteins include follistatin, and potentially, follistatin-related proteins (Gamer *et al.* (1999) Dev. Biol., 208: 222-232). The mature domain is believed to be active as a homodimer when the propeptide is removed.

[0008] GDF-8 is highly conserved in sequence and in function across species. The amino acid sequence of murine and human GDF-8 is identical, as is the pattern of mRNA expression (McPherron *et al.* (1997) Nature 387: 83-90; Gonzalez-Cadavid *et al.* (1998) Proc. Natl. Acad. Sci. USA 95: 14938-14943). This conservation of sequence and function suggests that inhibition of GDF-8 in humans is likely to have a similar effect to inhibition of GDF-8 in mice.

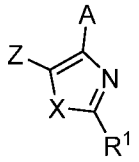
[0009] US Patent No. 7,320,789 shows that GDF-8 antibodies in mouse models can increase muscle strength (*e.g.*, for treating sarcopenia), increase muscle mass and strength in dystrophic muscle (*e.g.*, for treating Duchenne's muscular dystrophy), increase bone mass and bone density (*e.g.*, for prevention and treatment of osteoporosis), augment bone healing (*e.g.*, for treating an established muscle or bone degenerative disease (*e.g.*, fracture repair and spine fusion, preventing the decline in bone mass, microarchitecture and strength associated with estrogen deficiency, increasing trabecular bone density), and are useful for treatment of metabolic disorders such as type 2 diabetes, impaired glucose tolerance, metabolic syndrome (*e.g.*, syndrome X), insulin resistance induced by trauma (*e.g.*, burns), and adipose tissue disorders (*e.g.*, obesity).

SUMMARY

[0010] In view of the foregoing, we recognized that new therapeutic agents that inhibit the activity of one or more members of the TGF-β superfamily may useful and therefore desirable for treating human or animal disorders in which an increase in muscle tissue would be therapeutically beneficial, particularly muscle and adipose tissue disorders, bone degenerative diseases, neuromuscular disorders, and diabetes.

[0011] Accordingly, the present invention comprises compounds, pharmaceutical compositions comprising them, and methods of using them to inhibit TGF-β superfamily activity both *in vitro* and *in vivo* and to treat and/or prevent disease by inhibiting TGF-β superfamily activity.

[0012] Disclosed herein are compounds having structural formula (I):



(I)

[0013] and pharmaceutically acceptable salts, prodrugs, and *N*-oxides thereof (and solvates and hydrates thereof), wherein X, A, Z, R^1 and R′ are as described herein.

[0014] Also disclosed herein are pharmaceutical compositions. Examples of such compositions include those having at least one pharmaceutically acceptable carrier, diluent, and/or excipient together with a compound, pharmaceutically acceptable salt, prodrug, or *N*-oxide (or solvate or hydrate) as described herein.

[0015] Another aspect of the present invention comprises methods for treating and/or preventing disease by blocking GDF 8, TGF-β, activin or combinations thereof. Accordingly, the invention also comprises methods for treating disease using the presently disclosed compounds and pharmaceutical compositions.

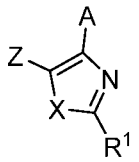
[0016] Another aspect of the invention is the use of the compounds described herein to block TGF-β superfamily activity *in vitro* and *in vivo* for the purpose of studying their role in biological processes.

[0017] All publications referenced herein are incorporated by reference in their entirety to the extent they are not inconsistent with the teachings presented herein.

DETAILED DESCRIPTION

[0018] In one aspect, the invention comprises compounds that inhibit TGF-β.

[0019] In embodiment $I°_1$ of this first aspect, the compounds have structural formula (I°):



(I°)

[0020] or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, or a solvate or hydrate thereof,

[0021] wherein

X is -S- or -N(R′)-;

R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -(C_0-C_{12}alkyl)-Cak or -(C_0-C_6alkyl)-Hca, each optionally substituted with 1 to 3 moieties that are each

independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -OR^{S0}, C_1-C_6alkyl-$OR^{S0'}$, -$C(O)OR^{S0}$, -$C(O)R^{S0}$, -$C(O)NR^{S0}{}_2$, -R^{S0} or cyano;

wherein each R^{S0} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -OR^{S1}, -$NR^{S1}{}_2$, -SR^{S1} or -$N(R^{S1})C(O)R^{S1}$, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

wherein each R^{S1} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

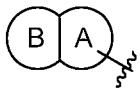
or R′ and R^1 combined with the atoms to which they are attached form a five- to eight-membered ring;

A is phenyl optionally substituted with one to five R^2 groups, wherein

each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl, -C_1-C_6alkoxy, -C_1-C_6haloalkoxy, -NO_2, -$N(R^{S2})C(O)R^{S2}$, -OR^{S2}, -$C(O)NR^{S2}{}_2$, -$N(R^{S2})S(O)_2R^{S2}$, -$S(O)_2R^{S2}$, -(C_0-C_6alkyl)-Ar or -CN, wherein each alkyl, haloalkyl and alkoxy are optionally substituted with 1, 2, 3, or 4 groups that are each independently halogen, cyano, nitro, -OR^{S2}, -SR^{S2}, -$NR^{S2}{}_2$, -$C(O)OR^{S2}$, -$C(O)NR^{S2}{}_2$, -$C(O)R^{S2}$, -$S(O)R^{S2}$, -$S(O)_2R^{S2}$, -$S(O)OR^{S2}$, -$S(O)_2OR^{S2}$, -$S(O)NR^{S2}{}_2$, -$S(O)_2NR^{S2}{}_2$, -$OC(O)R^{S2}$, -$OC(O)OR^{S2}$, -$OC(O)NR^{S2}{}_2$, -$N(R^{S2})C(O)R^{S2}$, -$N(R^{S2})C(O)OR^{S2}$, -$N(R^{S2})C(O)NR^{S2}{}_2$, -$N(R^{S2})S(O)R^{S2}$, -$N(R^{S2})S(O)_2R^{S2}$, C_1-C_6alkyl, or C_1-C_6haloalkyl;

wherein each R^{S2} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

Z is

a fused bicyclic ring of the formula, 

, wherein

ring A is Ar or 5- or 6-membered Het,

ring B is 5- or 6-membered Het,

wherein

Z is optionally substituted by one or two -R^Z groups that are each independently halogen, cyano, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}haloalkyl, -C_1-C_6alkoxy, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Hca, -OR^{S3}, -SR^{S3}, -$NR^{S3}{}_2$, -$C(O)R^{S3}$, -$C(O)OR^{S3}$, -$C(O)NR^{S3}{}_2$, -$C(NR^{S3})NR^{S3}OR^{S3}$, -$S(O)_2NR^{S3}{}_2$, -$S(O)_2R^{S3}$, -$OC(O)R^{S3}$, -$N(R^{S3})C(O)R^{S3}$, -$OC(O)OR^{S3}$, -$OC(O)NR^{S3}{}_2$, -$N(R^{S3})C(O)OR^{S3}$, -$N(R^{S3})C(O)NR^{S3}{}_2$, -$N(R^{S3f})S(O)_2R^{S3}$, -$OP(O)(OR^{S3})_2$ or -CH_2-$OP(O)(OR^{S3})$, wherein each alkyl, haloalkyl and alkoxy is optionally substituted by one or two -R^{Z2} groups;

wherein each R^{S3} is independently hydrogen, -$NR^{S3}{}_2$, -OR^{S3}, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -$C(O)NR^{S4}{}_2$ or cyano; and

each -R^{Z2} is independently halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, -C_1-C_6alkoxy, -OR^{S4}, -SR^{S4}, -$NR^{S4}{}_2$, -$C(O)R^{S4}$, -$C(O)OR^{S4}$, -$C(O)NR^{S4}{}_2$, -$S(O)_2NR^{S4}{}_2$, -$S(O)_2R^{S4}$, -$OC(O)R^{S4}$, -$N(R^{S4})C(O)R^{S4}$, -$OC(O)OR^{S4}$, -$OC(O)NR^{S4}{}_2$, -$N(R^{S4})C(O)OR^{S4}$, -$N(R^{S4})C(O)NR^{S4}{}_2$, -$N(R^{S4})S(O)_2R^{S4}$, -$OP(O)(OR^{S4})_2$ or -CH_2-$OP(O)(OR^{S4})$; and

wherein each R^{S4} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with one or two C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

[0022] In embodiment I°′, the compounds are of embodiment $I°_1$, provided that the compound is not any compound expressly recited in "Benzothiazole Based Inhibitors of p38a MAP Kinase" Liu, C. *et al.* Bioorganic & Medicinal Chemistry Letters (2008), 18(6), 1874-1879; International Publication No. WO 2004014900 A1; International Publication No. WO 2002072576 A1; or "Potent, Orally Active Heterocycle-Based Combretastatin A-4 Analogues: Synthesis, Structure-Activity Relationship" Wang, L. *et al.* Journal of Medicinal Chemistry (2002), 45(8), 1697-1711.

[0023] In embodiment $I°_2$, the compounds are of embodiment $I°_1$, provided that the compound is not:

6-(4-phenyl-1H-imidazol-5-yl)-1H-benzo[d]imidazol-2-amine;

5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-methyl-6-(4-phenyl-1H-imidazol-5-yl)-1H-benzo[d][1,2,3]triazole;

6-(4-phenyl-1H-imidazol-5-yl)benzo[d]thiazol-2-amine;

1-isopropyl-6-(4-phenyl-1H-imidazol-5-yl)-1H-benzo[d][1,2,3]triazole;

N-benzyl-6-(4-phenyl-1H-imidazol-5-yl)-1H-benzo[d]imidazol-2-amine;

1-ethyl-6-(4-(m-tolyl)-1H-imidazol-5-yl)-1H-benzo[d][1,2,3]triazole;

6-(4-(4-fluorophenyl)-1H-imidazol-5-yl)-1-methyl-1H-benzo[d][1,2,3]triazole;

1-ethyl-6-(4-(4-fluorophenyl)-1H-imidazol-5-yl)-1H-benzo[d][1,2,3]triazole;

1-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1,3-dimethyl-5-(4-phenyl-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

N-isopropyl-6-(4-phenyl-1H-imidazol-5-yl)benzo[d]thiazol-2-amine;

1-methyl-6-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

6-(4-(4-fluorophenyl)-1H-imidazol-5-yl)-1-isopropyl-1H-benzo[d][1,2,3]triazole;

6-(4-(4-fluoro-3-methylphenyl)-1H-imidazol-5-yl)-1-methyl-1H-benzo[d][1,2,3]triazole;

1-ethyl-6-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1,3-dimethyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1,3-diethyl-5-(4-phenyl-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-isopropyl-6-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

6-(4-(4-fluoro-3-methylphenyl)-1H-imidazol-5-yl)-1-isopropyl-1H-benzo[d][1,2,3]triazole;

5-(4-(4-fluorophenyl)-1H-imidazol-5-yl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

6-(4-(4-fluoro-3-methylphenyl)-1H-imidazol-5-yl)-1-isopropyl-1H-benzo[d][1,2,3]triazole;

3-ethyl-1-methyl-5-(4-(m*-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-ethyl-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-phenyl-6-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1,3-diethyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-isopropyl-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-isopropyl-1-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-methyl-1-phenyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-ethyl-1-isopropyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

6-(5-(2-fluorophenyl)-1H-imidazol-4-yl)-N-isopropylbenzo[d]thiazol-2-amine;

1,3-dipropyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1,3-diisopropyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1,3-diethyl-5-(4-(4-fluorophenyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-methyl-1-(m-tolyl)-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-cyclopropyl-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(isopropylsulfonyl)-5-(4-phenyl-1H-imidazol-5-yl)-1H-benzo[d]imidazol-2-amine;

1-(isopropylsulfonyl)-6-(4-phenyl-1H-imidazol-5-yl)-1H-benzo[d]imidazol-2-amine;

1-cyclobutyl-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-cyclohexyl-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-methyl-1-(o-tolyl)-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-(4-(4-fluorophenyl)-1H-imidazol-5-yl)-3-methyl-1-phenyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-cyclopentyl-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

(R)-N-(sec-butyl)-6-(5-(2-fluorophenyl)-1H-imidazol-4-yl)benzo[d]thiazol-2-amine;

1-(3,4-dimethylphenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1,3-diethyl-5-(5-(3-methoxyphenyl)-1H-imidazol-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-cyclobutyl-3-ethyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-cyclopentyl-3-ethyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(3-chlorophenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(3-fluorophenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(4-fluorophenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(4-chlorophenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

6-(4-(4-fluorophenyl)-1H-imidazol-5-yl)-1-(isopropylsulfonyl)-1H-benzo[d]imidazol-2-amine;

1-(4-methoxyphenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(2-fluorophenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(2-chlorophenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

6-(5-(3-fluorophenyl)-1H-imidazol-4-yl)-1-(isopropylsulfonyl)-1H-benzo[d]imidazol-2-amine;

1,3-bis(cyclopropylmethyl)-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

6-(5-(2-fluorophenyl)-1H-imidazol-4-yl)-1-(isopropylsulfonyl)-1H-benzo[d]imidazol-2-amine;

3-(4-methoxybenzyl)-1-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(3,4-difluorophenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1-(4-(trifluoromethyl)phenyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1-(3-(trifluoromethyl)phenyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-methyl-1-(thiophen-3-yl)-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1-(2-(trifluoromethyl)phenyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

N-benzyl-1-(isopropylsulfonyl)-6-(4-phenyl-1H-imidazol-5-yl)-1H-benzo[d]imidazol-2-amine;

6-(5-(2,4-difluorophenyl)-1H-imidazol-4-yl)-1-(isopropylsulfonyl)-1H-benzo[d]imidazol-2-amine;

6-(5-(2,3-difluorophenyl)-1H-imidazol-4-yl)-1-(isopropylsulfonyl)-1H-benzo[d]imidazol-2-amine;

1-(3,4-dimethoxyphenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(benzo[d][1,3]dioxol-5-yl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(isopropylsulfonyl)-6-(4-(3-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)-1H-benzo[d]imidazol-2-amine;

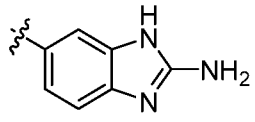
3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1-(3,4,5-trimethoxyphenyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

or a pharmaceutically acceptable salt thereof.

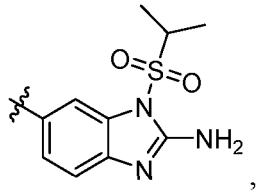
[0024] In embodiment I°_3, the compounds are of embodiment I°_1, provided that

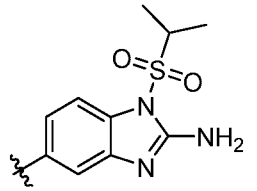
(a) when ring A is Ar, ring B is not triazolyl or imidazolidin-2-onyl; and

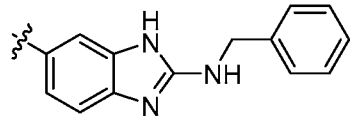
(b) Z is not

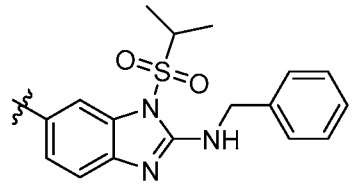
(1) 

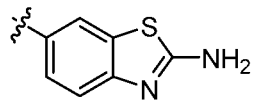
,

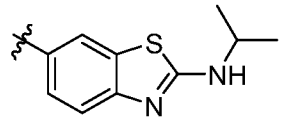
(2)  ,

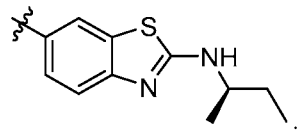
(3)  ,

(4)  ,

(5)  ,

(6)  ,

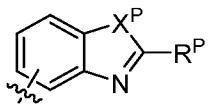
(7)  or

(8)  .

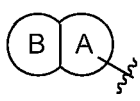
[0025] In embodiment I°_4, the compounds are of embodiment I°_1, provided that

(a) when ring A is Ar, ring B is not triazolyl or imidazolidin-2-onyl; and

(b) Z is not

 .

[0026] In embodiment I°_5, the compounds are of embodiment I°_1, wherein Z is

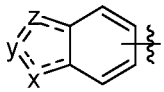
(a) a fused bicyclic ring of the formula,  , wherein

(1) ring A is -Ar, and

ring B is a 6-membered Het; or

(2) ring A is 6-membered Het, and

ring B is a 5-membered Het; or

(b) 

wherein

z is CH, O, S or N;

y is CH, CH_2, or N; and

x is CH, O, S, N(R^a);

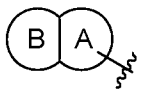
provided that when z is N and x is N(R^a), y is not N;

wherein R^a is hydrogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl, -C(O)OR, -C(O)NR_2, -C(O)R, -S(O)R, -$S(O)_2$R, -S(O)OR, -$S(O)_2$OR, -S(O)NR_2, -$S(O)_2NR_2$, -OC(O)R, -OC(O)OR, -OC(O)NR_2;

wherein each R is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

wherein Z is optionally substituted by one or two -R^Z groups.

[0027] In embodiment I°$_6$, the compounds are of embodiment I°$_1$, wherein Z is

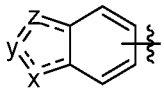
(a) a fused bicyclic ring of the formula,  , wherein

(1) ring A is -Ar, and

ring B is a 6-membered Het; or

(2) ring A is 6-membered Het, and

ring B is a 5-membered Het; or

(b) 

wherein

z is CH, O, S or N;

y is CH, CH_2, or N; and

x is CH, O, S, N(R^a);

provided that when z is N and x is N(R^a), y is not N;

wherein

Z is optionally substituted by one or two -R^Z groups that are each independently halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, -C_1-C_6alkoxy, -OR^{S3}, -SR^{S3}, -$C(O)R^{S3}$, -$C(O)OR^{S3}$, -$C(O)NR^{S3}_2$, -$S(O)_2NR^{S3}_2$, -$OC(O)R^{S3}$, -$N(R^{S3})C(O)R^{S3}$, -$OC(O)OR^{S3}$, -$OC(O)NR^{S3}_2$, -$N(R^{S3})C(O)OR^{S3}$, -$N(R^{S3})C(O)NR^{S3}_2$, -$N(R^{S3})S(O)_2R^{S3}$, -$OP(O)(OR^{S3})_2$ or -CH_2-$OP(O)(OR^{S3})$, wherein each alkyl, haloalkyl and alkoxy is optionally substituted by one or two -R^{Z2} groups.

[0028] In embodiment $I°_7$, the compounds are of any one of embodiments I_1 - I_6 or I′, wherein

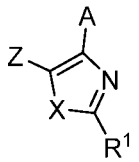
R′ is hydrogen or C_1-C_6alkyl; and

R^1 is hydrogen or C_1-C_6alkyl.

[0029] In embodiment I_8, the compounds are of any one of embodiments $I°_1$ - $I°_6$ or I°′, wherein X is -S-.

[0030] In embodiment $I°_8$, the compounds are of any one of embodiments $I°_1$ - $I°_6$ or I°′, wherein X is -N(R′)-.

[0031] In embodiment I_1 of this first aspect, the compounds have structural formula (I):



(I)

or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, or a solvate or hydrate thereof,

wherein

X is -S- or -N(R′)-;

R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -OR^{S1}, -NR^{S1}_2, -SR^{S1}, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

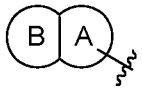
wherein each R^{S1} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

A is phenyl optionally substituted with one to five R^2 groups, wherein

each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl, -C_1-C_6alkoxy, -NO_2 or -CN, wherein each alkyl, haloalkyl and alkoxy are optionally substituted with 1, 2, 3, or 4 groups that are each independently halogen, cyano, nitro, -OR^{S2}, -SR^{S2}, -NR^{S2}_2, -$C(O)OR^{S2}$, -$C(O)NR^{S2}_2$, -$C(O)R^{S2}$, -$S(O)R^{S2}$, -$S(O)_2R^{S2}$, -$S(O)OR^{S2}$, -$S(O)_2OR^{S2}$, -$S(O)NR^{S2}_2$, -$S(O)_2NR^{S2}_2$, -$OC(O)R^{S2}$, -$OC(O)OR^{S2}$, -$OC(O)NR^{S2}_2$, -$N(R^{S2})C(O)R^{S2}$, -$N(R^{S2})C(O)OR^{S2}$, -$N(R^{S2})C(O)NR^{S2}_2$, -$N(R^{S2})S(O)R^{S2}$, -$N(R^{S2})S(O)_2R^{S2}$, C_1-C_6alkyl, or C_1-C_6haloalkyl;

wherein each R^{S2} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

Z is

a fused bicyclic ring of the formula, 

, wherein

ring A is Ar or 5- or 6-membered Het,

ring B is 5- or 6-membered Het,

wherein

Z is optionally substituted by one or two -R^Z groups that are each independently halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, -C_1-C_6alkoxy, -OR^{S3}, -SR^{S3}, -NR^{S3}_2, -$C(O)R^{S3}$, -$C(O)OR^{S3}$, -$C(O)NR^{S3}_2$, -$S(O)_2NR^{S3}_2$, -$S(O)_2R^{S3}$, -$OC(O)R^{S3}$, -$N(R^{S3})C(O)R^{S3}$, -$OC(O)OR^{S3}$, -$OC(O)NR^{S3}_2$, -$N(R^{S3})C(O)OR^{S3}$, -$N(R^{S3})C(O)NR^{S3}_2$, -$N(R^{S3f})S(O)_2R^{S3}$, -$OP(O)(OR^{S3})_2$ or -CH_2-$OP(O)(OR^{S3})$, wherein each alkyl, haloalkyl and alkoxy is optionally substituted by one or two -R^{Z2} groups;

wherein each R^{S3} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano; and

each -R^{Z2} is independently halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, -C_1-C_6alkoxy, -OR^{S4}, -SR^{S4}, -NR^{S4}_2, -$C(O)R^{S4}$, -$C(O)OR^{S4}$, -$C(O)NR^{S4}_2$, -$S(O)_2NR^{S4}_2$, -$S(O)_2R^{S4}$, -$OC(O)R^{S4}$, -$N(R^{S4})C(O)R^{S4}$, -$OC(O)OR^{S4}$,

$-OC(O)NR^{S4}{}_2$, $-N(R^{S4})C(O)OR^{S4}$, $-N(R^{S4})C(O)NR^{S4}{}_2$, $-N(R^{S4})S(O)_2R^{S4}$, $-OP(O)(OR^{S4})_2$ or $-CH_2-OP(O)(OR^{S4})$; and

wherein each R^{S4} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

[0032] In some embodiments of formulae (I°) and (I), R^{S0}, R^{S1}, R^{S2}, R^{S3} and R^{S4} are optionally substituted with one C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

[0033] In embodiment I′, the compounds are of embodiment I_1, provided that the compound is not any compound expressly recited in "Benzothiazole Based Inhibitors of p38a MAP Kinase" Liu, C. *et al.* Bioorganic & Medicinal Chemistry Letters (2008), 18(6), 1874-1879; International Publication No. WO 2004014900 A1; International Publication No. WO 2002072576 A1; or "Potent, Orally Active Heterocycle-Based Combretastatin A-4 Analogues: Synthesis, Structure-Activity Relationship" Wang, L. *et al.* Journal of Medicinal Chemistry (2002), 45(8), 1697-1711.

[0034] In embodiment I_2, the compounds are of embodiment I_1, provided that the compound is not:

6-(4-phenyl-1H-imidazol-5-yl)-1H-benzo[d]imidazol-2-amine;
5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;
1-methyl-6-(4-phenyl-1H-imidazol-5-yl)-1H-benzo[d][1,2,3]triazole;
6-(4-phenyl-1H-imidazol-5-yl)benzo[d]thiazol-2-amine;
1-isopropyl-6-(4-phenyl-1H-imidazol-5-yl)-1H-benzo[d][1,2,3]triazole;
N-benzyl-6-(4-phenyl-1H-imidazol-5-yl)-1H-benzo[d]imidazol-2-amine;
1-ethyl-6-(4-(m-tolyl)-1H-imidazol-5-yl)-1H-benzo[d][1,2,3]triazole;
6-(4-(4-fluorophenyl)-1H-imidazol-5-yl)-1-methyl-1H-benzo[d][1,2,3]triazole;
1-ethyl-6-(4-(4-fluorophenyl)-1H-imidazol-5-yl)-1H-benzo[d][1,2,3]triazole;
1-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;
1,3-dimethyl-5-(4-phenyl-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;
N-isopropyl-6-(4-phenyl-1H-imidazol-5-yl)benzo[d]thiazol-2-amine;
1-methyl-6-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;
6-(4-(4-fluorophenyl)-1H-imidazol-5-yl)-1-isopropyl-1H-benzo[d][1,2,3]triazole;
6-(4-(4-fluoro-3-methylphenyl)-1H-imidazol-5-yl)-1-methyl-1H-benzo[d][1,2,3]triazole;
1-ethyl-6-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;
1,3-dimethyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1,3-diethyl-5-(4-phenyl-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-isopropyl-6-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

6-(4-(4-fluoro-3-methylphenyl)-1H-imidazol-5-yl)-1-isopropyl-1H-benzo[d][1,2,3]triazole;

5-(4-(4-fluorophenyl)-1H-imidazol-5-yl)-1,3-dimethyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

6-(4-(4-fluoro-3-methylphenyl)-1H-imidazol-5-yl)-1-isopropyl-1H-benzo[d][1,2,3]triazole;

3-ethyl-1-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-ethyl-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-phenyl-6-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1,3-diethyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-isopropyl-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-isopropyl-1-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-methyl-1-phenyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-ethyl-1-isopropyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

6-(5-(2-fluorophenyl)-1H-imidazol-4-yl)-N-isopropylbenzo[d]thiazol-2-amine;

1,3-dipropyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1,3-diisopropyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1,3-diethyl-5-(4-(4-fluorophenyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-methyl-1-(m-tolyl)-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-cyclopropyl-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(isopropylsulfonyl)-5-(4-phenyl-1H-imidazol-5-yl)-1H-benzo[d]imidazol-2-amine;

1-(isopropylsulfonyl)-6-(4-phenyl-1H-imidazol-5-yl)-1H-benzo[d]imidazol-2-amine;

1-cyclobutyl-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-cyclohexyl-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-methyl-1-(o-tolyl)-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

5-(4-(4-fluorophenyl)-1H-imidazol-5-yl)-3-methyl-1-phenyl-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-cyclopentyl-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

(R)-N-(sec-butyl)-6-(5-(2-fluorophenyl)-1H-imidazol-4-yl)benzo[d]thiazol-2-amine;

1-(3,4-dimethylphenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1,3-diethyl-5-(5-(3-methoxyphenyl)-1H-imidazol-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-cyclobutyl-3-ethyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-cyclopentyl-3-ethyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(3-chlorophenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(3-fluorophenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(4-fluorophenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(4-chlorophenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

6-(4-(4-fluorophenyl)-1H-imidazol-5-yl)-1-(isopropylsulfonyl)-1H-benzo[d]imidazol-2-amine;

1-(4-methoxyphenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(2-fluorophenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(2-chlorophenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

6-(5-(3-fluorophenyl)-1H-imidazol-4-yl)-1-(isopropylsulfonyl)-1H-benzo[d]imidazol-2-amine;

1,3-bis(cyclopropylmethyl)-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

6-(5-(2-fluorophenyl)-1H-imidazol-4-yl)-1-(isopropylsulfonyl)-1H-benzo[d]imidazol-2-amine;

3-(4-methoxybenzyl)-1-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(3,4-difluorophenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1-(4-(trifluoromethyl)phenyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1-(3-(trifluoromethyl)phenyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-methyl-1-(thiophen-3-yl)-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1-(2-(trifluoromethyl)phenyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

N-benzyl-1-(isopropylsulfonyl)-6-(4-phenyl-1H-imidazol-5-yl)-1H-benzo[d]imidazol-2-amine;

6-(5-(2,4-difluorophenyl)-1H-imidazol-4-yl)-1-(isopropylsulfonyl)-1H-benzo[d]imidazol-2-amine;

6-(5-(2,3-difluorophenyl)-1H-imidazol-4-yl)-1-(isopropylsulfonyl)-1H-benzo[d]imidazol-2-amine;

1-(3,4-dimethoxyphenyl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(benzo[d][1,3]dioxol-5-yl)-3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

1-(isopropylsulfonyl)-6-(4-(3-(trifluoromethyl)phenyl)-1H-imidazol-5-yl)-1H-benzo[d]imidazol-2-amine;

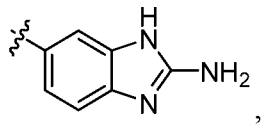
3-methyl-5-(4-(m-tolyl)-1H-imidazol-5-yl)-1-(3,4,5-trimethoxyphenyl)-1,3-dihydro-2H-benzo[d]imidazol-2-one;

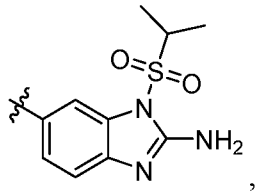
or a pharmaceutically acceptable salt thereof.

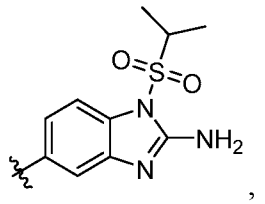
[0035] In embodiment I_3, the compounds are of embodiment I_1, provided that

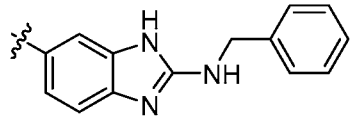
(a) when ring A is Ar, ring B is not triazolyl or imidazolidin-2-onyl; and

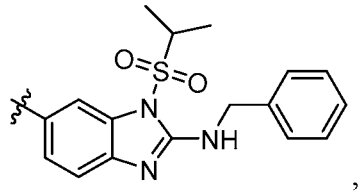
(b) Z is not

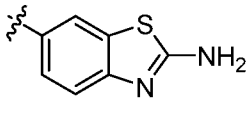
(1)  ,

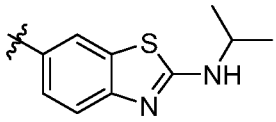
(2)  ,

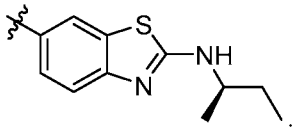
(3)  ,

(4)  ,

(5)  ,

(6)  ,

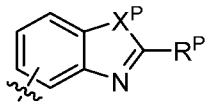
(7)  or

(8)  .

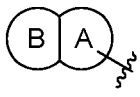
[0036] In embodiment I_4, the compounds are of embodiment I_1, provided that

(a) when ring A is Ar, ring B is not triazolyl or imidazolidin-2-onyl; and

(b) Z is not

 .

[0037] In embodiment I_5, the compounds are of embodiment I_1, wherein Z is

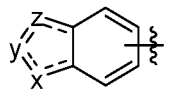
(a) a fused bicyclic ring of the formula,  , wherein

(1) ring A is -Ar, and

ring B is a 6-membered Het; or

(2) ring A is 6-membered Het, and

ring B is a 5-membered Het; or

(b) 

wherein

z is CH, O, S or N;

y is CH, CH_2, or N; and

x is CH, O, S, $N(R^a)$;

provided that when z is N and x is $N(R^a)$, y is not N;

wherein R^a is hydrogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl, -C(O)OR, -$C(O)NR_2$, -C(O)R, -S(O)R, -$S(O)_2$R, -S(O)OR, -$S(O)_2$OR, -$S(O)NR_2$, -$S(O)_2NR_2$, -OC(O)R, -OC(O)OR, -$OC(O)NR_2$;

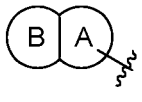
wherein each R is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-

C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

wherein Z is optionally substituted by one or two $-R^Z$ groups.

[0038] In embodiment I_6, the compounds are of embodiment I_1, wherein

Z is

(a) a fused bicyclic ring of the formula, 

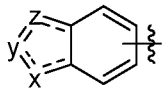
, wherein

(1) ring A is -Ar, and

ring B is a 6-membered Het; or

(2) ring A is 6-membered Het, and

ring B is a 5-membered Het; or

(b) 

wherein

z is CH, O, S or N;

y is CH, CH_2, or N; and

x is CH, O, S, $N(R^a)$;

provided that when z is N and x is $N(R^a)$, y is not N;

wherein

Z is optionally substituted by one or two $-R^Z$ groups that are each independently halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, -C_1-C_6alkoxy, $-OR^{S3}$, $-SR^{S3}$, $-C(O)R^{S3}$, $-C(O)OR^{S3}$, $-C(O)NR^{S3}{}_2$, $-S(O)_2NR^{S3}{}_2$, $-OC(O)R^{S3}$, $-N(R^{S3})C(O)R^{S3}$, $-OC(O)OR^{S3}$, $-OC(O)NR^{S3}{}_2$, $-N(R^{S3})C(O)OR^{S3}$, $-N(R^{S3})C(O)NR^{S3}{}_2$, $-N(R^{S3})S(O)_2R^{S3}$, $-OP(O)(OR^{S3})_2$ or $-CH_2$-$OP(O)(OR^{S3})$, wherein each alkyl, haloalkyl and alkoxy is optionally substituted by one or two $-R^{Z2}$ groups.

[0039] In embodiment I_7, the compounds are of any one of embodiments I_1 - I_6 or I′, wherein

R′ is hydrogen or C_1-C_6alkyl; and

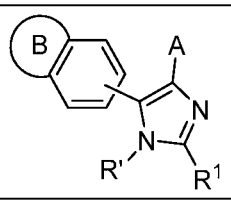
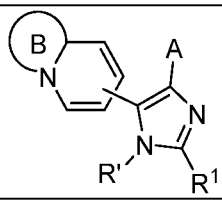
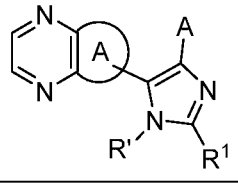
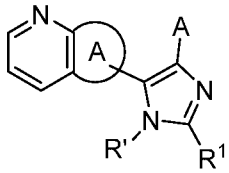
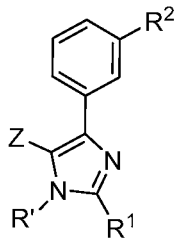
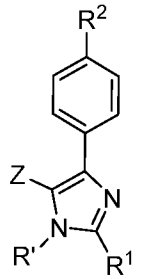
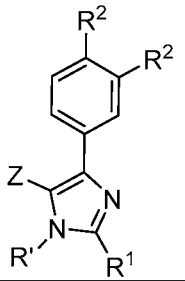
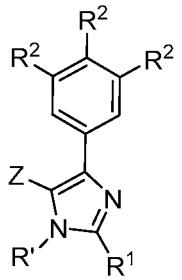
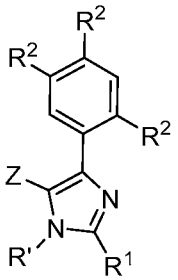
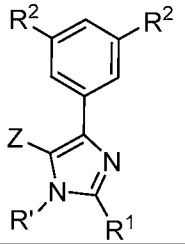
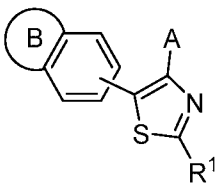
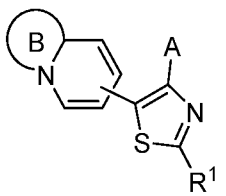
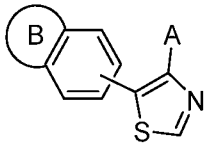
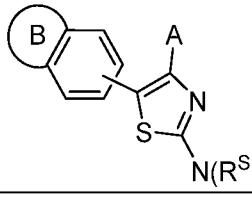
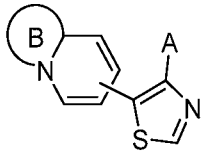
R^1 is hydrogen or C_1-C_6alkyl.

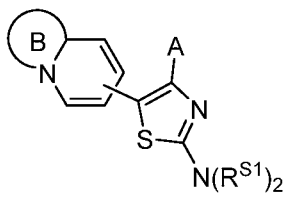
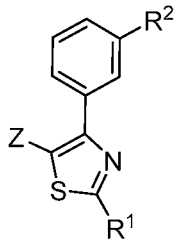
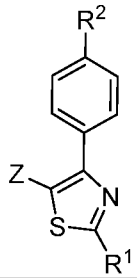
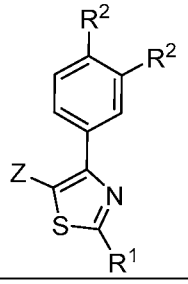
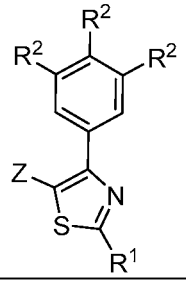
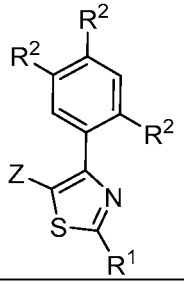
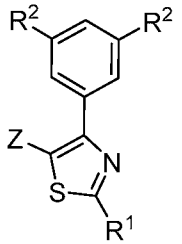
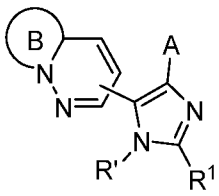
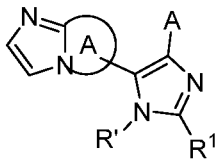
[0040] In embodiment I_8, the compounds are of any one of embodiments I_1 - I_6 or I′, wherein X is -S-.

[0041] In embodiment I_8, the compounds are of any one of embodiments I_1 - I_6 or I′, wherein X is -N(R′)-.

[0042] The invention further comprises subgenera of formula (I) in which structural formula (I), A, Z, R′ and R^1 are any group or combinations of groups as defined hereinbelow (*e.g.*, wherein the compound is of structural formula (I) as defined in any of the above embodiments and A is phenyl optionally substituted with one R^2 group, wherein R^2 is halogen; or the compound is formula (Ib), A is group (1c), Z is group (2b), R′ is group (3i) and R^1 is group (4a)):

[0043] **Structural Formulae (Ia) – (Ix) under Formula (I):**

		
(Ia)	(Ib)	(Ic)
		
(Id)	(Ie)	(If)
		
(Ig)	(Ih)	(Ii)
		
(Ij)	(Ik)	(Il)
		
(Im)	(In)	(Io)

		
(Ip)	(Iq)	(Ir)
		
(Is)	(It)	(Iu)
		
(Iv)	(Iw)	(Ix)

[0044] **A is selected from one of the following groups (1a) – (1ddd):**

(1a) A is phenyl optionally substituted with one to five R^2 groups, wherein

each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl, -C_1-C_6alkoxy, -NO_2 or -CN, wherein each alkyl, haloalkyl and alkoxy are optionally substituted with 1, 2, 3, or 4 groups that are each independently halogen, cyano, nitro, -OR^{S2}, -SR^{S2}, -NR^{S2}_2, -$C(O)OR^{S2}$, -$C(O)NR^{S2}_2$, -$C(O)R^{S2}$, -$S(O)R^{S2}$, -$S(O)_2R^{S2}$, -$S(O)OR^{S2}$, -$S(O)_2OR^{S2}$, -$S(O)NR^{S2}_2$, -$S(O)_2NR^{S2}_2$, -$OC(O)R^{S2}$, -$OC(O)OR^{S2}$, -$OC(O)NR^{S2}_2$, -$N(R^{S2})C(O)R^{S2}$, -$N(R^{S2})C(O)OR^{S2}$, -$N(R^{S2})C(O)NR^{S2}_2$, -$N(R^{S2})S(O)R^{S2}$, -$N(R^{S2})S(O)_2R^{S2}$, C_1-C_6alkyl, or C_1-C_6haloalkyl;

wherein each R^{S2} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

(1b) The group of **(1a)**, wherein A is phenyl substituted with one to five R^2 groups.

(1c) The group of **(1a)**, wherein A is phenyl substituted with one to three R^2 groups.

(1d) The group of **(1a)**, wherein A is phenyl substituted with one or two R^2 groups.

(1e) The group of **(1a)**, wherein A is phenyl substituted with one R^2 groups.

(1f) The group of **(1a)**, wherein A is unsubstituted phenyl.

(1g) Any of groups of **(1a) - (1e)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl, -C_1-C_6alkoxy, -NO_2 or -CN.

(1h) Any of groups of **(1a) - (1e)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl or -C_1-C_6alkoxy.

(1i) Any of groups of **(1a) - (1e)**, wherein each R^2 is independently -NO_2 or -CN.

(1j) Any of groups of **(1a) - (1e)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl or -C_1-C_6alkoxy.

(1k) Any of groups of **(1a) - (1e)**, wherein each R^2 is independently halogen or -C_1-C_6alkyl.

(1l) Any of groups of **(1a) - (1e)**, wherein each R^2 is independently halogen.

(1m) Any of groups of **(1a) - (1e)**, wherein each R^2 is independently fluoro or chloro.

(1n) Any of groups of **(1a) - (1e)**, wherein each R^2 is fluoro.

(1o) Any of groups of **(1a) - (1e)**, wherein each R^2 is chloro.

(1p) Any of groups of **(1a) - (1e)**, wherein each R^2 is independently -C_1-C_6alkyl.

(1q) Any of groups of **(1a) - (1e)**, wherein each R^2 is independently methyl, ethyl n-propyl or i-propyl.

(1r) Any of groups of **(1a) - (1e)**, wherein each R^2 is independently methyl or ethyl.

(1s) Any of groups of **(1a) - (1e)**, wherein each R^2 is methyl.

(1t) Any of groups of **(1a) - (1e)**, wherein each R^2 is ethyl.

(1u) Any of groups of **(1a) - (1e)**, wherein each R^2 is independently -C_1-C_6alkoxy.

(1v) Any of groups of **(1a) - (1e)**, wherein each R^2 is independently methoxy or ethoxy.

(1w) Any of groups of **(1a) - (1e)**, wherein each R^2 is methoxy.

(1x) Any of groups of **(1a) - (1e)**, wherein each R^2 is ethoxy.

(1y) Any of groups of **(1b)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl, -C_1-C_6alkoxy, -NO_2 or -CN.

(1z) Any of groups of **(1b)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl or -C_1-C_6alkoxy.

(1aa) Any of groups of **(1b)**, wherein each R^2 is independently -NO_2 or -CN.

(1bb) Any of groups of **(1b)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl or -C_1-C_6alkoxy.

(1cc) Any of groups of **(1b)**, wherein each R^2 is independently halogen or -C_1-C_6alkyl.

(1dd) Any of groups of **(1b)**, wherein each R^2 is independently halogen.

(1ee) Any of groups of **(1b)**, wherein each R^2 is independently -C_1-C_6alkyl.

(1ff) Any of groups of **(1b)**, wherein each R^2 is independently -C_1-C_6alkoxy.

(1gg) Any of groups of **(1c)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl, -C_1-C_6alkoxy, -NO_2 or -CN.

(1hh) Any of groups of **(1c)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl or -C_1-C_6alkoxy.

(1ii) Any of groups of **(1c)**, wherein each R^2 is independently -NO_2 or -CN.

(1jj) Any of groups of **(1c)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl or -C_1-C_6alkoxy.

(1kk) Any of groups of **(1c)**, wherein each R^2 is independently halogen or -C_1-C_6alkyl.

(1ll) Any of groups of **(1c)**, wherein each R^2 is independently halogen.

(1mm) Any of groups of **(1c)**, wherein each R^2 is independently -C_1-C_6alkyl.

(1nn) Any of groups of **(1c)**, wherein each R^2 is independently -C_1-C_6alkoxy.

(1oo) Any of groups of **(1d)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl, -C_1-C_6alkoxy, -NO_2 or -CN.

(1pp) Any of groups of **(1d)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl or -C_1-C_6alkoxy.

(1qq) Any of groups of **(1d)**, wherein each R^2 is independently -NO_2 or -CN.

(1rr) Any of groups of **(1d)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl or -C_1-C_6alkoxy.

(1ss) Any of groups of **(1d)**, wherein each R^2 is independently halogen or -C_1-C_6alkyl.

(1tt) Any of groups of **(1d)**, wherein each R^2 is independently halogen.

(1uu) Any of groups of **(1d)**, wherein each R^2 is independently -C_1-C_6alkyl.

(1vv) Any of groups of **(1d)**, wherein each R^2 is independently -C_1-C_6alkoxy.

(1ww) Any of groups of **(1e)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl, -C_1-C_6alkoxy, -NO_2 or -CN.

(1xx) Any of groups of **(1e)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl or -C_1-C_6alkoxy.

(1yy) Any of groups of **(1e)**, wherein each R^2 is independently -NO_2 or -CN.

(1zz) Any of groups of **(1e)**, wherein each R^2 is independently halogen, -C_1-C_6alkyl or -C_1-C_6alkoxy.

(1aaa) Any of groups of **(1e)**, wherein each R^2 is independently halogen or -C_1-C_6alkyl.

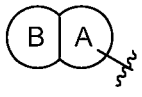
(1bbb) Any of groups of **(1e)**, wherein each R^2 is independently halogen.

(1ccc) Any of groups of **(1e)**, wherein each R^2 is independently -C_1-C_6alkyl.

(1ddd) Any of groups of **(1e)**, wherein each R^2 is independently -C_1-C_6alkoxy.

[0045] Z is selected from one of the following groups (2a) – (2ccc):

(2a) Z is

a fused bicyclic ring of the formula, 

, wherein

ring A is Ar or 5- or 6-membered Het,

ring B is 5- or 6-membered Het,

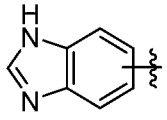
wherein

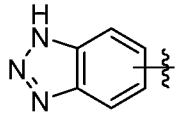
Z is optionally substituted by one or two -R^Z groups that are each independently halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, -C_1-C_6alkoxy, -OR^{S3}, -SR^{S3}, -NR^{S3}_2, -$C(O)R^{S3}$, -$C(O)OR^{S3}$, -$C(O)NR^{S3}_2$, -$S(O)_2NR^{S3}_2$, -$S(O)_2R^{S3}$, -$OC(O)R^{S3}$, -$N(R^{S3})C(O)R^{S3}$, -$OC(O)OR^{S3}$, -$OC(O)NR^{S3}_2$, -$N(R^{S3})C(O)OR^{S3}$, -$N(R^{S3})C(O)NR^{S3}_2$, -$N(R^{S3})S(O)_2R^{S3}$, -$OP(O)(OR^{S3})_2$ or -CH_2-$OP(O)(OR^{S3})$, wherein each alkyl, haloalkyl and alkoxy is optionally substituted by one or two -R^{Z2} groups;

wherein each R^{S3} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano; and

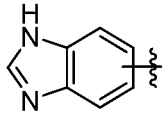
each -R^{Z2} is independently halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, -C_1-C_6alkoxy, -OR^{S4}, -SR^{S4}, -NR^{S4}_2, -$C(O)R^{S4}$, -$C(O)OR^{S4}$, -$C(O)NR^{S4}_2$, -$S(O)_2NR^{S4}_2$, -$S(O)_2R^{S4}$, -$OC(O)R^{S4}$, -$N(R^{S4})C(O)R^{S4}$, -$OC(O)OR^{S4}$, -$OC(O)NR^{S4}_2$, -$N(R^{S4})C(O)OR^{S4}$, -$N(R^{S4})C(O)NR^{S4}_2$, -$N(R^{S4})S(O)_2R^{S4}$, -$OP(O)(OR^{S4})_2$ or -CH_2-$OP(O)(OR^{S4})$;

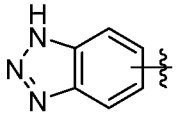
wherein each R^{S4} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

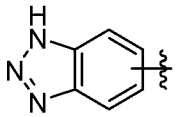
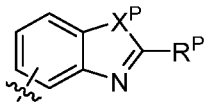
(2b) Z is as described in **(2a)**, provided that Z is not 

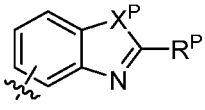
, 

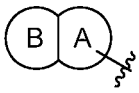
or a substituted analog thereof.

(2c) Z is as described in **(2a)**, provided that Z is not  or a substituted analog thereof.

(2d) Z is as described in **(2a)**, provided that Z is not  or a substituted analog thereof.

(2e) Z is as described in **(2a)**, provided that Z is not  or a substituted analog thereof, or  , wherein X^P is -N(H)-, -S-, or -N[$S(O)_2{}^iPr$]-, and R^P is $-NH_2$, $-N(H)CH_2Ph$, $-N(H)^iPr$ or -N(H)C(Me)Et.

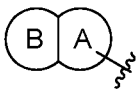
(2f) Z is as described in **(2a)**, provided that Z is not  , wherein X^P is -N(H)-, -S-, or -N[$S(O)_2{}^iPr$]-, and R^P is $-NH_2$, $-N(H)CH_2Ph$, $-N(H)^iPr$ or -N(H)C(Me)Et.

(2g) Z is a fused bicyclic ring of the formula,  , wherein

ring A is Ar or 5- or 6-membered Het; and

ring B is 5- or 6-membered Het; wherein

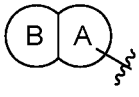
optionally substituted as described in **(2a)** above.

(2h) Z is a fused bicyclic ring of the formula,  , wherein

ring A is Ar; and

ring B is 5- or 6-membered Het; wherein

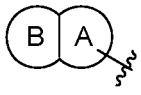
optionally substituted as described in **(2a)** above.

(2i) Z is a fused bicyclic ring of the formula,  , wherein

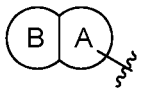
ring A is Ar; and

ring B is 5- membered Het; wherein

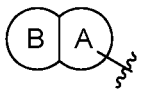
optionally substituted as described in **(2a)** above.

(2j) Z is a fused bicyclic ring of the formula, 

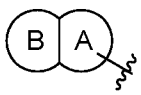
, wherein
ring A is Ar; and
ring B is 6-membered Het; wherein
optionally substituted as described in **(2a)** above.

(2k) Z is a fused bicyclic ring of the formula, 

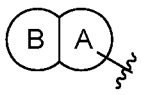
, wherein
ring A is 5-membered Het; and
ring B is 5- or 6-membered Het; wherein
optionally substituted as described in **(2a)** above.

(2l) Z is a fused bicyclic ring of the formula, 

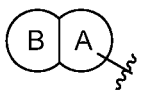
, wherein
ring A is 5-membered Het; and
ring B is 5-membered Het; wherein
optionally substituted as described in **(2a)** above.

(2m) Z is a fused bicyclic ring of the formula, 

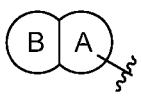
, wherein
ring A is 5-membered Het; and
ring B is 6-membered Het; wherein
optionally substituted as described in **(2a)** above.

(2n) Z is a fused bicyclic ring of the formula, 

, wherein
ring A is 6-membered Het; and
ring B is 5- or 6-membered Het; wherein
optionally substituted as described in **(2a)** above.

(2o) Z is a fused bicyclic ring of the formula, 

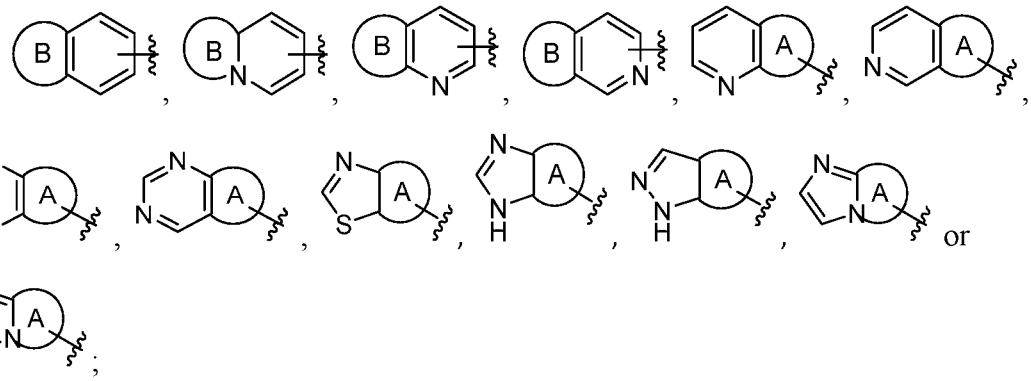
, wherein
ring A is 6-membered Het; and
ring B is 5-membered Het; wherein
optionally substituted as described in **(2a)** above.

(2p) Z is a fused bicyclic ring of the formula, 

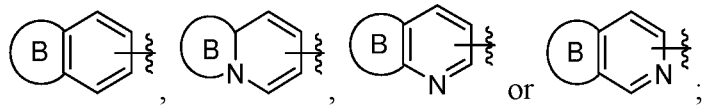
, wherein
ring A is 6-membered Het; and

ring B is 6-membered Het; wherein

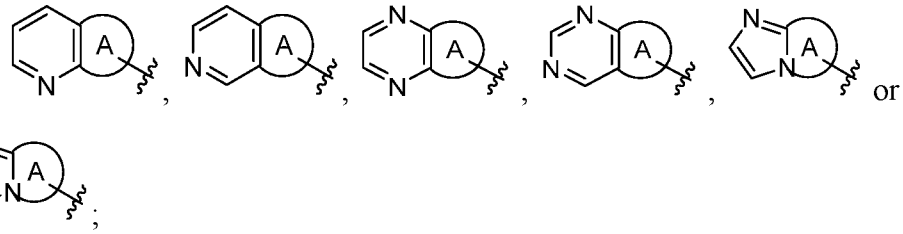
optionally substituted as described in **(2a)** above.

(2q) Z is  ;

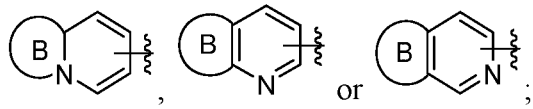
wherein ring A and B are as described in **(2a)**, and Z is optionally substituted as described in **(2a)** above.

(2r) Z is  ;

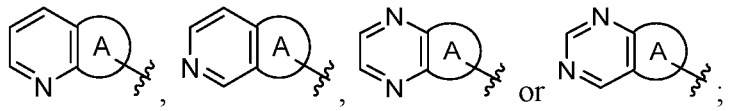
wherein ring B is as described in **(2a)**, and Z is optionally substituted as described in **(2a)** above.

(2s) Z is  ;

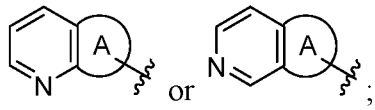
wherein ring A is as described in **(2a)**, and Z is optionally substituted as described in **(2a)** above.

(2t) Z is  ;

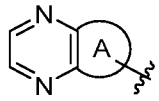
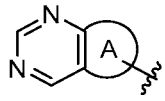
wherein ring B is as described in **(2a)**, and Z is optionally substituted as described in **(2a)** above.

(2u) Z is  ;

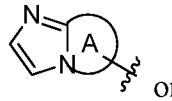
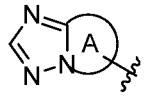
wherein ring A is as described in **(2a)**, and Z is optionally substituted as described in **(2a)** above.

(2v) Z is  ;

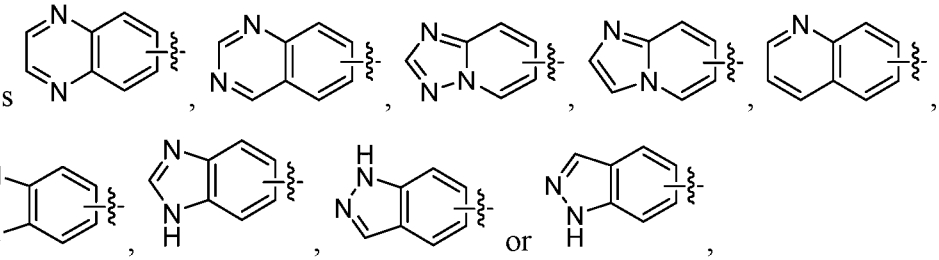
wherein ring A is as described in **(2a)**, and Z is optionally substituted as described in **(2a)** above.

(2w) Z is  or  ;

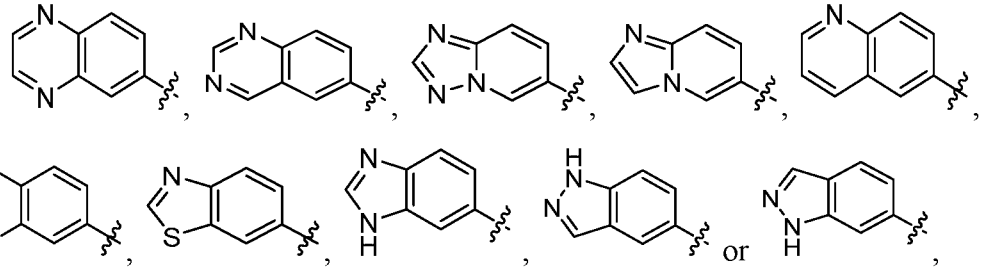
wherein ring A is as described in **(2a)**, and Z is optionally substituted as described in **(2a)** above.

(2x) Z is  or  ;

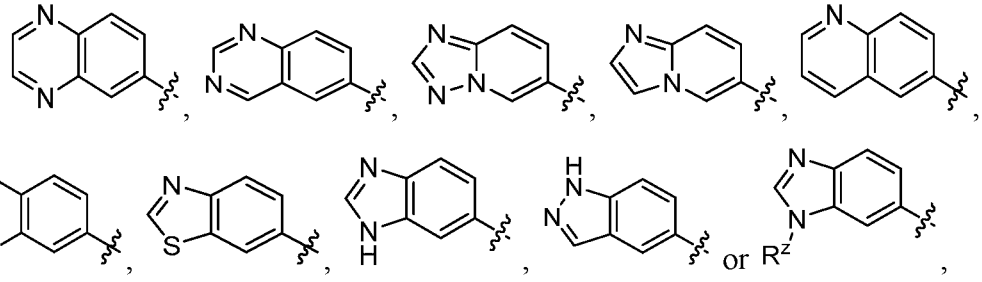
wherein ring A is as described in **(2a)**, and Z is optionally substituted as described in **(2a)** above.

(2y) Z is 

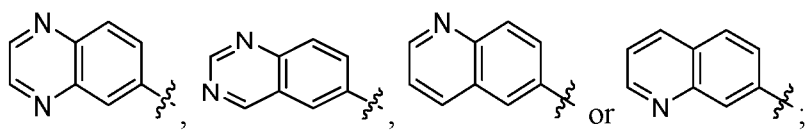
each optionally substituted as described in **(2a)** above.

(2z) Z is 

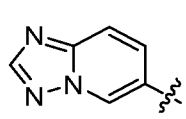
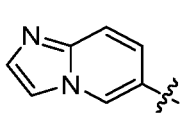
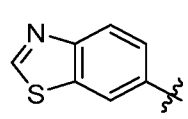
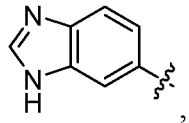
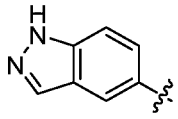
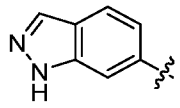
each optionally substituted as described in **(2a)** above.

(2aa) Z is 

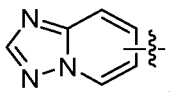
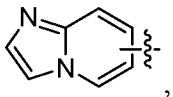
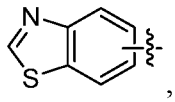
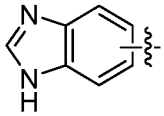
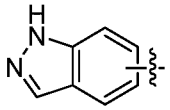
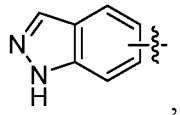
wherein each R^Z is independently hydrogen or -C_1-C_6alkyl.

(2bb) Z is  ;

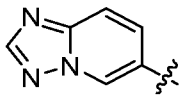
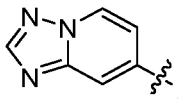
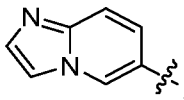
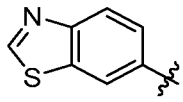
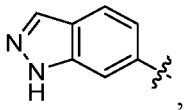
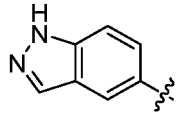
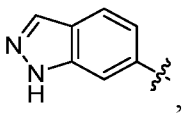
each optionally substituted as described in **(2a)** above.

(2cc) Z is  ,  ,  ,  ,  or  ,

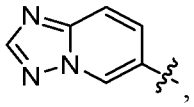
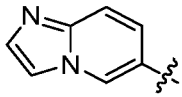
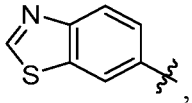
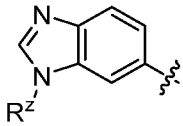
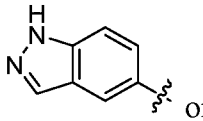
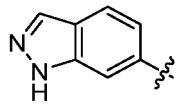
each optionally substituted as described in **(2a)** above.

(2dd) Z is  ,  ,  ,  ,  or  ,

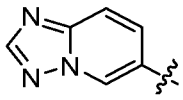
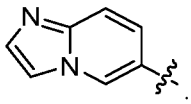
each optionally substituted as described in **(2a)** above.

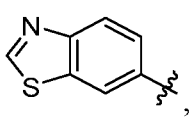
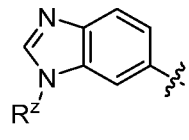
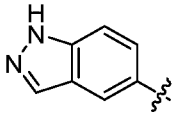
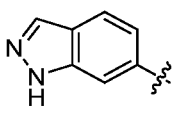
(2ee) Z is  ,  ,  ,  ,  ,  or  ,

each optionally substituted as described in **(2a)** above.

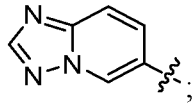
(2ff) Z is  ,  ,  ,  ,  or  ,

wherein each R^Z is independently hydrogen or -C_1-C_6alkyl.

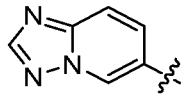
(2gg) Z is  or  .

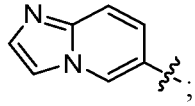
(2hh) Z is  ,  ,  or  ,

wherein each R^Z is independently hydrogen or -C_1-C_6alkyl.

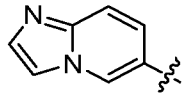
(2ii) Z is  ;

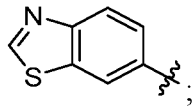
optionally substituted as described in **(2a)**.

(2jj) Z is  .

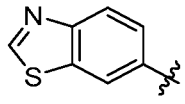
(2kk) Z is  ;

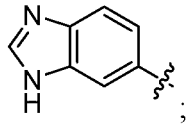
optionally substituted as described in **(2a)** above.

(2ll) Z is  .

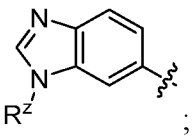
(2mm) Z is  ;

optionally substituted as described in **(2a)** above.

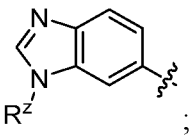
(2nn) Z is  .

(2oo) Z is  ;

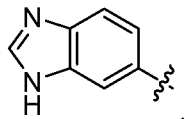
optionally substituted as described in **(2a)** above.

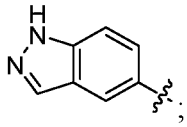
(2pp) Z is  ;

wherein each R^Z is independently hydrogen or -C_1-C_6alkyl.

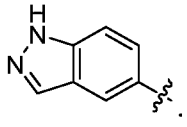
(2qq) Z is  ;

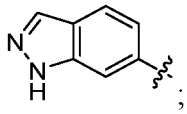
wherein each R^Z is methyl.

(2rr) Z is  .

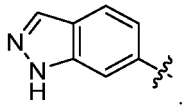
(2ss) Z is  ;

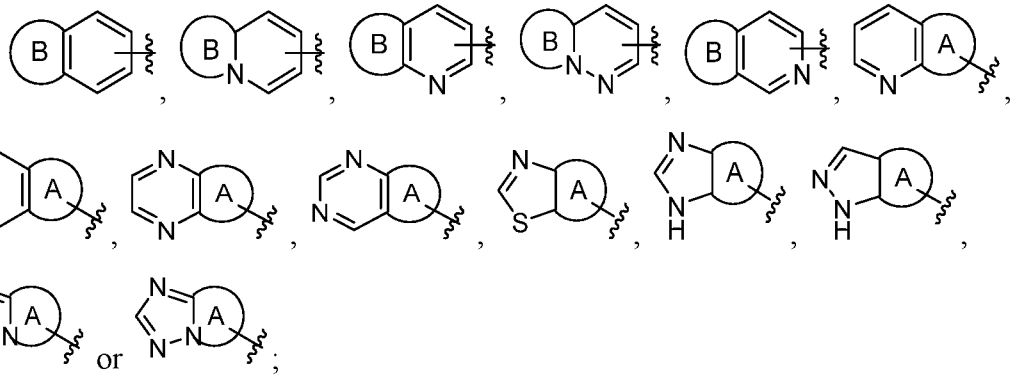
optionally substituted as described in **(2a)** above.

(2tt) Z is  .

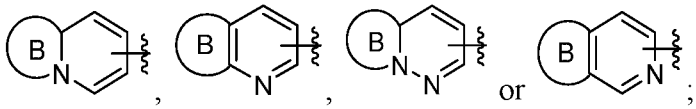
(2uu) Z is  ;

wherein R^Z is as described in **(2a)**.

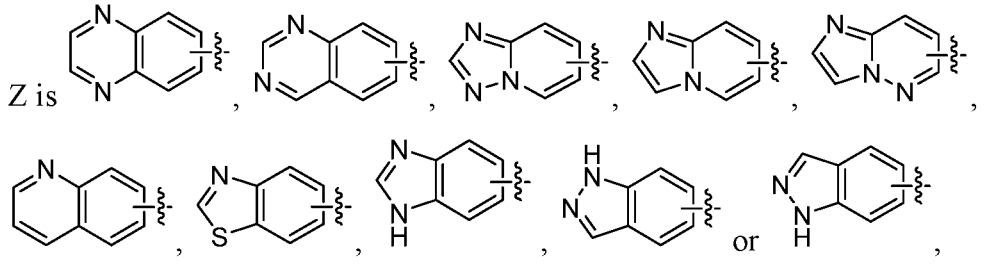
(2vv) Z is  .

(2ww) Z is  ;

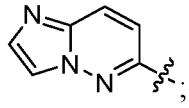
wherein ring A and B are as described in **(2a)**, and Z is optionally substituted as described in **(2a)** above.

(2xx) Z is  ;

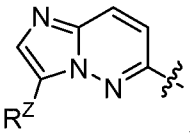
wherein ring B is as described in **(2a)**, and Z is optionally substituted as described in **(2a)** above.

(2yy) Z is  ,

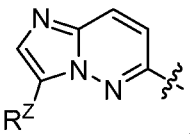
each optionally substituted as described in **(2a)** above.

(2zz) Z is  ;

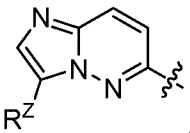
optionally substituted as described in **(2a)** above.

(2aaa) Z is  ;

wherein R^Z is hydrogen, -C_1-C_6alkyl, cyano, -C(O)NR^{S3}_2 or C_{1-6}alkyl-OR^{S3}.

(2bbb) Z is  ;

wherein R^Z is cyano, -C(O)NR^{S3}_2 or C_{1-6}alkyl-OR^{S3}.

(2ccc) Z is  ;

wherein R^Z is cyano, -C(O)NH_2 or C_{1-6}alkyl-OH.

[0046] **R′ is selected from one of the following groups (3a) – (3kk):**

(3a) R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

(3b) R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, each optionally substituted with 1 or 2 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

(3c) R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, each optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

(3d) R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, each optionally substituted with 1 to 3 moieties that are each independently halogen or cyano.

(3e) R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, each optionally substituted with 1 to 3 moieties that are each halogen.

(3f) R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl or C_1-C_6alkyloxy.

(3g) R′ is hydrogen, C_1-C_6alkyl or C_1-C_6haloalkyl.

(3h) R′ is hydrogen, C_1-C_6alkyl or C_1-C_6alkyloxy.

(3i) R′ is hydrogen or C_1-C_6alkyl.

(3j) R′ is hydrogen.

(3k) R′ is C_1-C_6alkyl.

(3l) R′ is hydrogen, methyl, ethyl, n-propyl, i-propyl.

(3m) R′ is hydrogen or methyl.

(3n) R′ is hydrogen or ethyl.

(3o) R′ is methyl.

(3p) R′ is ethyl.

(3q) R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -(C_0-C_{12}alkyl)-Cak or -(C_0-C_6alkyl)-Hca, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -OR^{S0}, C_1-C_6alkyl-$OR^{S0'}$, -$C(O)OR^{S0}$, -$C(O)R^{S0}$, -$C(O)NR^{S0}{}_2$, -R^{S0} or cyano;

wherein each R^{S0} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

(3r) R′ is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -(C_0-C_{12}alkyl)-Cak or -(C_0-C_6alkyl)-Hca, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -OR^{S0}, C_1-C_6alkyl-$OR^{S0'}$, -$C(O)OR^{S0}$, -$C(O)R^{S0}$, -$C(O)NR^{S0}{}_2$, -R^{S0} or cyano;

wherein each R^{S0} is as described in **(3q)** above.

(3s) R′ is hydrogen, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -(C_0-C_{12}alkyl)-Cak or -(C_0-C_6alkyl)-Hca, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -OR^{S0}, C_1-C_6alkyl-$OR^{S0'}$, -$C(O)OR^{S0}$, -$C(O)R^{S0}$, -$C(O)NR^{S0}{}_2$, -R^{S0} or cyano;

wherein each R^{S0} is as described in **(3q)** above.

(3t) R′ is hydrogen, C_1-C_6alkyl, C_1-C_6alkyloxy, -(C_0-C_{12}alkyl)-Cak or -(C_0-C_6alkyl)-Hca, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -OR^{S0}, C_1-C_6alkyl-$OR^{S0'}$, -$C(O)OR^{S0}$, -$C(O)R^{S0}$, -$C(O)NR^{S0}{}_2$ or cyano;

wherein each R^{S0} is as described in **(3q)** above.

(3u) R′ is hydrogen, -(C_0-C_{12}alkyl)-Cak or -(C_0-C_6alkyl)-Hca, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -OR^{S0}, C_1-C_6alkyl-$OR^{S0'}$, -$C(O)OR^{S0}$, -$C(O)R^{S0}$, -$C(O)NR^{S0}{}_2$, -R^{S0} or cyano;

wherein each R^{S0} is as described in **(3q)** above.

(3v) R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -(C_0-C_{12}alkyl)-Cak or -(C_0-C_6alkyl)-Hca, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -OR^{S0}, C_1-C_6alkyl-$OR^{S0'}$, -$C(O)OR^{S0}$, -$C(O)R^{S0}$, -$C(O)NR^{S0}{}_2$, -R^{S0} or cyano;

wherein each R^{S0} is as described in **(3q)** above.

(3w) R′ is hydrogen, C_1-C_6alkyl or C_1-C_6haloalkyl, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -OR^{S0}, C_1-C_6alkyl-$OR^{S0'}$, -$C(O)OR^{S0}$, -$C(O)R^{S0}$, -$C(O)NR^{S0}{}_2$, -R^{S0} or cyano;

wherein each R^{S0} is as described in **(3q)** above.

(3x) Any of groups **(3q)** - **(3w)**, wherein each R^{S0} is independently C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are unsubstituted.

(3y) Any of groups **(3q)** - **(3w)**, wherein each R^{S0} is independently C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

(3z) Any of groups **(3q)** - **(3w)**, wherein each R^{S0} is independently hydrogen, C_1-C_6alkyl, C_1- -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Cak, Hca and alkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

(3aa) Any of groups **(3q)** - **(3w)**, wherein each R^{S0} is independently hydrogen, C_1-C_6alkyl, C_1- -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Cak, Hca and alkyl are unsubstituted.

(3bb) Any of groups **(3q)** - **(3w)**, wherein each R^{S0} is independently hydrogen, C_1-C_6alkyl or C_1-C_6haloalkyl.

(3cc) R′ and R^1 combined with the atoms to which they are attached form a five- to eight-membered ring.

(3dd) R′ and R^1 combined with the atoms to which they are attached form a five- to eight-membered Hca, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -OR^{S0}, C_1-C_6alkyl-$OR^{S0'}$, -$C(O)OR^{S0}$, -$C(O)R^{S0}$, -$C(O)NR^{S0}{}_2$ or cyano.

(3ee) R′ and R^1 combined with the atoms to which they are attached form a five- to eight-membered Hca, each optionally substituted with 1 or 2 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -OR^{S0}, C_1-C_6alkyl-$OR^{S0'}$, -$C(O)OR^{S0}$, -$C(O)R^{S0}$, -$C(O)NR^{S0}{}_2$ or cyano.

(3ff) R′ and R^1 combined with the atoms to which they are attached form a five- to eight-membered Hca, each optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -OR^{S0}, C_1-C_6alkyl-$OR^{S0'}$, -$C(O)OR^{S0}$, -$C(O)R^{S0}$, -$C(O)NR^{S0}{}_2$ or cyano.

(3gg) R′ and R^1 combined with the atoms to which they are attached form a five- to eight-membered Hca, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, C_1-C_6haloalkyl, -$C(O)OR^{S0}$, -$C(O)R^{S0}$, -$C(O)NR^{S0}{}_2$ or cyano.

(3hh) R′ and R^1 combined with the atoms to which they are attached form a five- to eight-membered Hca, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, C_1-C_6haloalkyl, -$C(O)OR^{S0}$, -$C(O)R^{S0}$ or -$C(O)NR^{S0}{}_2$.

(3ii) R′ and R^1 combined with the atoms to which they are attached form a five- to eight-membered Hca, each optionally substituted with C_1-C_6alkyl, C_1-C_6haloalkyl, -$C(O)OR^{S0}$, -$C(O)R^{S0}$, -$C(O)NR^{S0}{}_2$ or cyano.

(3jj) R′ and R^1 combined with the atoms to which they are attached form a five- to eight-membered Hca, each optionally substituted with C_1-C_6alkyl, C_1-C_6haloalkyl, -$C(O)OR^{S0}$, -$C(O)R^{S0}$ or -$C(O)NR^{S0}{}_2$.

(3kk) R′ and R^1 combined with the atoms to which they are attached form an unsubstituted five- to eight-membered Hca.

[0047] **R^1 is selected from one of the following groups (4a) – (4gg):**

(4a) R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -OR^{S1}, -$NR^{S1}{}_2$, -SR^{S1}, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

(4b) R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -OR^{S1}, -$NR^{S1}{}_2$, -SR^{S1}, each optionally substituted with 1 or 2 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

(4c) R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -OR^{S1}, -$NR^{S1}{}_2$, -SR^{S1}, each optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

(4d) R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -OR^{S1}, -$NR^{S1}{}_2$, -SR^{S1}, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl or halogen.

(4e) R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -OR^{S1}, -$NR^{S1}{}_2$, -SR^{S1}, each optionally substituted with cyano.

(4f) R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -OR^{S1}, -$NR^{S1}{}_2$ or -SR^{S1}.

(4g) R^1 is C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, $-OR^{S1}$, $-NR^{S1}_2$ or $-SR^{S1}$.

(4h) R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl or C_1-C_6alkyloxy.

(4i) R^1 is C_1-C_6alkyl, C_1-C_6haloalkyl or C_1-C_6alkyloxy.

(4j) R^1 is hydrogen, $-OR^{S1}$, $-NR^{S1}_2$ or $-SR^{S1}$.

(4k) R^1 is $-OR^{S1}$, $-NR^{S1}_2$ or $-SR^{S1}$.

(4l) R^1 is hydrogen, C_1-C_6alkyl or $-NR^{S1}_2$.

(4m) R^1 is C_1-C_6alkyl or $-NR^{S1}_2$.

(4n) R^1 is hydrogen, C_1-C_6alkyl or $-OR^{S1}$.

(4o) R^1 is C_1-C_6alkyl or $-OR^{S1}$.

(4p) R^1 is hydrogen, C_1-C_6alkyl or $-SR^{S1}$.

(4q) R^1 is C_1-C_6alkyl or $-SR^{S1}$.

(4r) R^1 is hydrogen or C_1-C_6alkyl.

(4s) R^1 is hydrogen or $-NR^{S1}_2$.

(4t) R^1 is $-NR^{S1}_2$.

(4u) R^1 is hydrogen.

(4v) R^1 is C_1-C_6alkyl.

(4w) R^1 is hydrogen, methyl, ethyl, n-propyl, i-propyl.

(4x) R^1 is hydrogen or methyl.

(4y) R^1 is hydrogen or ethyl.

(4z) R^1 is methyl.

(4aa) R^1 is ethyl.

(4bb) R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, $-OR^{S1}$, $-NR^{S1}_2$, $-SR^{S1}$ or $-N(R^{S1'})C(O)R^{S1'}$, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

(4cc) Any of groups **(4a)** - **(4q)**, wherein each R^{S1} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

(4dd) Any of groups **(4a)** - **(4q)**, wherein each R^{S1} is independently hydrogen or C_1-C_6alkyl.

(4ee) Any of groups **(4a)** - **(4q)**, wherein each R^{S1} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are unsubstituted.

(4ff) Any of groups **(4a) - (4q)**, wherein each R^{S1} is independently hydrogen, C_1-C_6alkyl, or C_1-C_6haloalkyl, wherein alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

(4gg) Any of groups **(4a) - (4q)**, wherein each R^{S1} is independently hydrogen, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca and alkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

Particular embodiments of this aspect of the invention comprise compounds of any one of the formulae (I), (I′) and (Ia) – (Ix), each as defined in each of the following rows (or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, or a solvate or hydrate thereof), wherein each entry is a group number as defined above (*e.g.*, **(4z)** refers to R^1 is methyl), and a dash "-" indicates that the variable is as defined in embodiment I_1 or defined according to any one of the applicable variable definitions **(1a)-(1ddd), (2a)-(2ccc), (3a)-(3kk)** and **(4a)-(4gg)** [*e.g.*, when R^1 is a dash, it can be either as defined in any of embodiments I_1 - I_7 or any one of definitions (**4a**)-(**4gg**)]:

	(I)	A	Z	R′	R^1
(1)-1	(Ia)	(1a)	(2a)	(3a)	(4a)
(1)-2	(Io)	(1c)	(2b)	(3i)	(4f)
(1)-3	(Ic)	(1d)	(2g)	(3j)	(4j)
(1)-4	(Id)	(1e)	(2i)	(3k)	(4l)
(1)-5	(Ie)	(1h)	(2a)	(3l)	(4r)
(1)-6	(If)	(1k)	(2q)	(3m)	(4u)
(1)-7	(Ig)	(1l)	(2r)	(3n)	(4v)
(1)-8	(Ih)	(1n)	(2t)	(3o)	(4x)
(1)-9	(Ii)	(1s)	(2x)	(3p)	(4y)
(1)-10	(Ij)	(1gg)	(2y)	(3i)	(4z)
(1)-11	(Ib)	(1jj)	(2aa)	(3j)	(4r)
(1)-12	(Ic)	(1kk)	(2ff)	(3k)	(4u)
(1)-13	(Id)	(1ll)	(2qq)	(3l)	(4v)
(1)-14	(Il)	(1mm)	(2tt)	(3j)	(4v)
(1)-15	(Ic)	(1ss)	(2vv)	(3k)	(4a)
(1)-16	(Ia)	(1tt)	(2g)	(3l)	(4f)

	(I)	A	Z	R′	R^1
(1)-17	(Ib)	(1uu)	(2i)	(3m)	(4j)
(1)-18	(Im)	(1xx)	(2a)	(3n)	(4l)
(1)-19	(Id)	(1aaa)	(2q)	(3o)	(4r)
(1)-20	(Ie)	(1bbb)	(2ff)	(3p)	(4u)
(1)-21	(If)	(1ccc)	(2qq)	(3n)	(4v)
(1)-22	(Is)	(1aaa)	(2qq)	(3o)	(4x)
(1)-23	(Ih)	(1bbb)	(2ff)	(3p)	(4y)
(1)-24	(Ii)	(1ccc)	(2qq)	(3n)	(4z)
(1)-25	(Ij)	(1uu)	(2i)	(3o)	(4r)
(1)-26	(Ih)	(1xx)	(2a)	(3p)	(4u)
(1)-27	(Ii)	(1s)	(2q)	(3j)	(4v)
(1)-28	(Iv)	(1gg)	(2ff)	(3k)	(4j)
(1)-29	(Ic)	(1d)	(2qq)	(3l)	(4l)
(1)-30	(Id)	(1a)	(2b)	(3m)	(4j)
(1)-31	(Ie)	(1c)	(2g)	(3n)	(4l)
(1)-32	(Ir)	(1d)	(2i)	(3o)	(4r)

	(I)	A	Z	R′	R^1
(1)-33	(Ig)	(1s)	(2a)	(3p)	(4r)
(1)-34	(Ih)	(1bbb)	(2q)	(3n)	(4j)
(1)-35	(Ii)	(1ccc)	(2r)	(3o)	(4l)
(1)-36	(Ij)	(1d)	(2t)	(3p)	(4r)
(1)-37	(If)	(1e)	(2x)	(3j)	(4f)
(1)-38	(Ik)	(1h)	(2y)	(3k)	(4j)
(1)-39	(Ib)	(1k)	(2aa)	(3l)	(4l)
(1)-40	(Ic)	(1l)	(2ff)	(3a)	(4l)
(1)-41	(Ip)	(1n)	(2vv)	(3i)	(4r)
(1)-42	(Ic)	(1s)	(2g)	(3j)	(4f)
(1)-43	(Id)	(1gg)	(2i)	(3k)	(4j)
(1)-44	(Ie)	(1jj)	(2a)	(3l)	(4l)
(1)-45	(If)	(1kk)	(2q)	(3m)	(4r)
(1)-46	(Ig)	(1ll)	(2a)	(3n)	(4a)
(1)-47	(Ih)	(1mm)	(2b)	(3o)	(4f)
(1)-48	(Ii)	(1ss)	(2g)	(3p)	(4j)
(1)-49	(Ij)	(1tt)	(2i)	(3n)	(4l)
(1)-50	(It)	(1uu)	(2a)	(3j)	(4r)
(1)-51	(Ii)	(1xx)	(2q)	(3k)	(4u)
(1)-52	(Ij)	(1aaa)	(2r)	(3l)	(4v)
(1)-53	(Ic)	(1bbb)	(2t)	(3m)	(4x)
(1)-54	(Id)	(1ccc)	(2x)	(3i)	(4y)
(1)-55	(Iq)	(1l)	(2y)	(3j)	(4z)
(1)-56	(If)	(1n)	(2aa)	(3k)	(4r)
(1)-57	(Ig)	(1s)	(2ff)	(3l)	(4u)
(1)-58	(Ih)	(1a)	(2qq)	(3m)	(4v)
(1)-59	(Ii)	(1c)	(2tt)	(3n)	(4r)
(1)-60	(Ij)	(1d)	(2vv)	(3o)	(4u)
(1)-61	(It)	(1e)	(2r)	(3p)	(4v)
(1)-62	(Ii)	(1h)	(2t)	(3j)	(4j)

	(I)	A	Z	R′	R^1
(1)-63	(Ij)	(1k)	(2x)	(3k)	(4l)
(1)-64	(Ia)	(1l)	(2y)	(3l)	(4r)
(1)-65	(Ib)	(1n)	(2aa)	(3m)	(4f)
(1)-66	(Ic)	(1s)	(2ff)	(3l)	(4j)
(1)-67	(Ik)	(1gg)	(2qq)	(3a)	(4l)
(1)-68	(Ib)	(1jj)	(2tt)	(3i)	(4v)
(1)-69	(Ic)	(1kk)	(2vv)	(3j)	(4a)
(1)-70	(Id)	(1ll)	(2ff)	(3i)	(4f)
(1)-71	(Iq)	(1mm)	(2qq)	(3j)	(4j)
(1)-72	(If)	(1ss)	(2i)	(3k)	(4l)
(1)-73	(Is)	(1tt)	(2a)	(3l)	(4r)
(1)-74	(Ih)	(1uu)	(2q)	(3m)	(4a)
(1)-75	(Ii)	(1xx)	(2b)	(3n)	(4f)
(1)-76	(Iv)	(1aaa)	(2g)	(3o)	(4j)
(1)-77	(If)	(1bbb)	(2i)	(3p)	(4l)
(1)-78	(Ia)	(1ccc)	(2a)	(3i)	(4a)
(1)-79	(Ib)	(1n)	(2q)	(3j)	(4f)
(1)-80	(In)	(1s)	(2r)	(3k)	(4j)
(1)-81	(Ic)	(1gg)	(2t)	(3j)	(4l)
(1)-82	(Id)	(1aaa)	(2x)	(3k)	(4r)
(1)-83	(Ie)	(1bbb)	(2y)	(3l)	(4u)
(1)-84	(If)	(1ccc)	(2aa)	(3m)	(4v)
(1)-85	(Ig)	(1l)	(2ff)	(3k)	(4x)
(1)-86	(Ih)	(1n)	(2qq)	(3l)	(4y)
(1)-87	(Iu)	(1s)	(2tt)	(3a)	(4z)
(1)-88	(Ij)	(1d)	(2vv)	(3i)	(4r)
(1)-89	(Il)	(1e)	(2vv)	(3j)	(4u)
(1)-90	(Ic)	(1h)	(2g)	(3k)	(4v)
(1)-91	(Id)	(1k)	(2i)	(3l)	(4j)
(1)-92	(Ib)	(1l)	(2a)	(3m)	(4l)

	(I)	A	Z	R′	R^1
(1)-93	(Im)	(1n)	(2q)	(3n)	(4a)
(1)-94	(Id)	(1s)	(2i)	(3o)	(4f)
(1)-95	(Ie)	(1gg)	(2a)	(3p)	(4l)
(1)-96	(Ir)	(1jj)	(2q)	(3a)	(4r)
(1)-97	(Ig)	(1kk)	(2r)	(3i)	(4u)
(1)-98	(Ih)	(1ll)	(2t)	(3j)	(4v)
(1)-99	(Ii)	(1mm)	(2x)	(3i)	(4x)
(1)-100	(Ij)	(1ss)	(2y)	(3j)	(4y)
(1)-101	(Ih)	(1tt)	(2aa)	(3i)	(4z)
(1)-102	(Iu)	(1uu)	(2ff)	(3j)	(4r)
(1)-103	(Ij)	(1xx)	(2qq)	(3k)	(4a)
(1)-104	(Ic)	(1aaa)	(2tt)	(3l)	(4f)
(1)-105	(Id)	(1bbb)	(2vv)	(3a)	(4j)
(1)-106	(Ie)	(1ccc)	(2r)	(3i)	(4l)
(1)-107	(If)	(1h)	(2vv)	(3j)	(4r)
(1)-108	(Ik)	(1k)	(2g)	(3j)	(4u)
(1)-109	(Ib)	(1l)	(2i)	(3k)	(4v)
(1)-110	(Ic)	(1n)	(2a)	(3l)	(4x)
(1)-111	(Id)	(1s)	(2q)	(3a)	(4y)
(1)-112	(Ie)	(1gg)	(2qq)	(3i)	(4z)
(1)-113	(If)	(1jj)	(2tt)	(3j)	(4j)
(1)-114	(Ig)	(1kk)	(2vv)	(3j)	(4l)
(1)-115	(It)	(1ll)	(2ff)	(3k)	(4a)
(1)-116	(Ii)	(1mm)	(2qq)	(3l)	(4f)
(1)-117	(Ij)	(1ss)	(2i)	(3m)	(4v)
(1)-118	(Io)	(1tt)	(2a)	(3k)	(4j)
(1)-119	(Ic)	(1uu)	(2q)	(3l)	(4l)
(1)-120	(Id)	(1xx)	(2ff)	(3m)	(4a)
(1)-121	(Ig)	(1aaa)	(2qq)	(3n)	(4f)
(1)-122	(Ih)	(1bbb)	(2b)	(3o)	(4l)

	(I)	A	Z	R′	R^1
(1)-123	(Iq)	(1ccc)	(2g)	(3p)	(4r)
(1)-124	(If)	(1l)	(2i)	(3i)	(4u)
(1)-125	(Ig)	(1n)	(2a)	(3j)	(4v)
(1)-126	(Ih)	(1s)	(2q)	(3k)	(4x)
(1)-127	(Ib)	(1d)	(2r)	(3l)	(4y)
(1)-128	(Ic)	(1e)	(2t)	(3a)	(4z)
(1)-129	(Id)	(1h)	(2x)	(3i)	(4j)
(1)-130	(Ie)	(1k)	(2y)	(3j)	(4l)
(1)-131	(Ir)	(1n)	(2aa)	(3k)	(4a)
(1)-132	(Ig)	(1s)	(2ff)	(3l)	(4f)
(1)-133	(Ih)	(1gg)	(2qq)	(3m)	(4v)
(1)-134	(Ii)	(1gg)	(2tt)	(3n)	(4j)
(1)-135	(Ij)	(1jj)	(2vv)	(3o)	(4l)
(1)-136	(Ih)	(1kk)	(2g)	(3p)	(4a)
(1)-137	(Ii)	(1ll)	(2i)	(3a)	(4f)
(1)-138	(Iv)	(1mm)	(2a)	(3i)	(4j)
(1)-139	(Ic)	(1ss)	(2q)	(3j)	(4l)
(1)-140	(Id)	(1tt)	(2b)	(3a)	(4r)
(1)-141	(Iq)	(1uu)	(2g)	(3i)	(4u)
(1)-142	(If)	(1xx)	(2i)	(3j)	(4v)
(1)-143	(Ig)	(1aaa)	(2a)	(3i)	(4x)
(1)-144	(Ih)	(1bbb)	(2q)	(3j)	(4y)
(1)-145	(Ii)	(1ccc)	(2r)	(3k)	(4z)
(1)-146	(Ij)	(1l)	(2t)	(3l)	(4j)
(1)-147	(It)	(1n)	(2x)	(3m)	(4l)
(1)-148	(Ii)	(1s)	(2y)	(3n)	(4a)
(1)-149	(Iv)	(1n)	(2aa)	(3o)	(4f)
(1)-150	(Id)	(1s)	(2ff)	(3p)	(4a)
(1)-151	(Ia)	(1n)	(2qq)	(3i)	(4f)
(1)-152	(Ib)	(1s)	(2tt)	(3j)	(4u)

	(I)	A	Z	R′	R^1
(1)-153	(Im)	(1gg)	(2vv)	(3k)	(4v)
(1)-154	(Id)	(1c)	(2vv)	(3l)	(4j)
(1)-155	(Ie)	(1d)	(2g)	(3i)	(4l)
(1)-156	(If)	(1e)	(2i)	(3j)	(4a)
(1)-157	(Is)	(1h)	(2a)	(3k)	(4f)
(1)-158	(Ih)	(1k)	(2q)	(3l)	(4u)
(1)-159	(Ii)	(1l)	(2g)	(3m)	(4v)
(1)-160	(Ij)	(1n)	(2i)	(3n)	(4j)
(1)-161	(Ih)	(1s)	(2a)	(3o)	(4l)
(1)-162	(Iu)	(1gg)	(2q)	(3p)	(4a)
(1)-163	(Ij)	(1jj)	(2g)	(3a)	(4f)
(1)-164	(Ic)	(1kk)	(2i)	(3i)	(4j)
(1)-165	(Id)	(1ll)	(2a)	(3j)	(4l)
(1)-166	(Ie)	(1mm)	(2q)	(3a)	(4r)
(1)-167	(If)	(1ss)	(2r)	(3i)	(4u)
(1)-168	(Ig)	(1tt)	(2t)	(3j)	(4v)
(1)-169	(Ih)	(1uu)	(2x)	(3k)	(4x)
(1)-170	(Iu)	(1xx)	(2y)	(3l)	(4y)
(1)-171	(Ij)	(1aaa)	(2aa)	(3m)	(4z)
(1)-172	(Ie)	(1bbb)	(2ff)	(3n)	(4j)
(1)-173	(If)	(1ccc)	(2qq)	(3o)	(4l)
(1)-174	(Is)	(1n)	(2tt)	(3p)	(4a)
(1)-175	(Ih)	(1s)	(2vv)	(3a)	(4f)
(1)-176	(Ih)	(1gg)	(2g)	(3i)	(4r)
(1)-177	(Ii)	(1e)	(2i)	(3j)	(4u)
(1)-178	(Iv)	(1h)	(2a)	(3k)	(4j)
(1)-179	(Ic)	(1k)	(2q)	(3l)	(4l)
(1)-180	(Id)	(1l)	(2a)	(3a)	(4r)
(1)-181	(Ie)	(1n)	(2b)	(3i)	(4f)
(1)-182	(Ir)	(1s)	(2g)	(3j)	(4r)

	(I)	A	Z	R′	R^1
(1)-183	(Ig)	(1gg)	(2i)	(3k)	(4u)
(1)-184	(Ih)	(1jj)	(2a)	(3l)	(4v)
(1)-185	(Ii)	(1kk)	(2q)	(3m)	(4u)
(1)-186	(Ij)	(1ll)	(2r)	(3n)	(4v)
(1)-187	(It)	(1mm)	(2t)	(3o)	(4x)
(1)-188	(Ii)	(1ss)	(2x)	(3p)	(4y)
(1)-189	(Ij)	(1tt)	(2y)	(3i)	(4z)
(1)-190	(Ig)	(1uu)	(2aa)	(3j)	(4r)
(1)-191	(Ih)	(1xx)	(2ff)	(3k)	(4u)
(1)-192	(Ih)	(1aaa)	(2qq)	(3l)	(4v)
(1)-193	(Iu)	(1tt)	(2tt)	(3i)	(4j)
(1)-194	(Ij)	(1uu)	(2vv)	(3j)	(4l)
(1)-195	(Ig)	(1xx)	(2vv)	(3k)	(4a)
(1)-196	(It)	(1l)	(2y)	(3l)	(4f)
(1)-197	(Ic)	(1n)	(2aa)	(3m)	(4f)
(1)-198	(Id)	(1s)	(2ff)	(3n)	(4j)
(1)-199	(Ie)	(1n)	(2g)	(3o)	(4l)
(1)-200	(If)	(1s)	(2i)	(3p)	(4r)
(1)-201	(Ig)	(1gg)	(2a)	(3a)	(4u)
(1)-202	(Ih)	(1d)	(2q)	(3i)	(4v)
(1)-203	(Ii)	(1a)	(2a)	(3j)	(4x)
(1)-204	(Ij)	(1c)	(2b)	(3n)	(4y)
(1)-205	(Iq)	(1d)	(2g)	(3o)	(4z)
(1)-206	(If)	(1e)	(2i)	(3p)	(4j)
(1)-207	(Ig)	(1h)	(2a)	(3k)	(4l)
(1)-208	(Ih)	(1k)	(2q)	(3l)	(4r)
(1)-209	(In)	(1l)	(2r)	(3a)	(4u)
(1)-210	(Id)	(1n)	(2t)	(3i)	(4v)
(1)-211	(Ie)	(1n)	(2x)	(3j)	(4x)
(1)-212	(If)	(1s)	(2y)	(3k)	(4y)

	(I)	A	Z	R′	R^1
(1)-213	(Is)	(1gg)	(2aa)	(3l)	(4z)
(1)-214	(Ih)	(1kk)	(2ff)	(3m)	(4j)
(1)-215	(Ii)	(1ll)	(2qq)	(3n)	(4l)
(1)-216	(Ij)	(1mm)	(2tt)	(3o)	(4a)
(1)-217	(Ih)	(1ss)	(2vv)	(3p)	(4f)
(1)-218	(Ii)	(1tt)	(2ff)	(3n)	(4v)
(1)-219	(Ij)	(1uu)	(2qq)	(3o)	(4a)
(1)-220	(Ig)	(1xx)	(2i)	(3p)	(4f)
(1)-221	(Ih)	(1aaa)	(2a)	(3a)	(4j)
(1)-222	(It)	(1bbb)	(2q)	(3i)	(4l)
(1)-223	(Ii)	(1ccc)	(2ff)	(3j)	(4r)
(1)-224	(Iv)	(1tt)	(2qq)	(3k)	(4u)
(1)-225	(Id)	(1uu)	(2vv)	(3l)	(4v)
(1)-226	(Ie)	(1xx)	(2g)	(3m)	(4x)
(1)-227	(If)	(1gg)	(2i)	(3a)	(4y)
(1)-228	(Is)	(1c)	(2a)	(3i)	(4z)
(1)-229	(Ih)	(1d)	(2q)	(3j)	(4j)
(1)-230	(Ib)	(1e)	(2i)	(3k)	(4l)
(1)-231	(Ic)	(1n)	(2a)	(3l)	(4r)
(1)-232	(Id)	(1s)	(2q)	(3m)	(4j)
(1)-233	(Ik)	(1gg)	(2r)	(3n)	(4l)
(1)-234	(Ib)	(1d)	(2vv)	(3o)	(4r)
(1)-235	(Ic)	(1s)	(2g)	(3p)	(4u)
(1)-236	(Id)	(1gg)	(2i)	(3a)	(4v)
(1)-237	(Iq)	(1jj)	(2a)	(3i)	(4x)
(1)-238	(If)	(1kk)	(2q)	(3j)	(4y)
(1)-239	(Ig)	(1n)	(2qq)	(3k)	(4z)
(1)-240	(Ih)	(1s)	(2tt)	(3l)	(4j)
(1)-241	(Ii)	(1gg)	(2vv)	(3m)	(4l)
(1)-242	(Ij)	(1tt)	(2vv)	(3n)	(4r)

	(I)	A	Z	R′	R^1
(1)-243	(Im)	(1uu)	(2y)	(3o)	(4u)
(1)-244	(Id)	(1xx)	(2aa)	(3j)	(4v)
(1)-245	(Ia)	(1aaa)	(2ff)	(3k)	(4x)
(1)-246	(Im)	(1bbb)	(2i)	(3l)	(4y)
(1)-247	(Id)	(1ccc)	(2a)	(3m)	(4z)
(1)-248	(Ic)	(1tt)	(2q)	(3p)	(4a)
(1)-249	(Id)	(1uu)	(2r)	(3n)	(4f)
(1)-250	(Ik)	(1xx)	(2vv)	(3o)	(4j)
(1)-251	(If)	(1n)	(2g)	(3j)	(4l)
(1)-252	(Ig)	(1s)	(2i)	(3k)	(4r)
(1)-253	(Ih)	(1gg)	(2a)	(3l)	(4u)
(1)-254	(Ih)	(1c)	(2q)	(3m)	(4v)
(1)-255	(Iu)	(1d)	(2qq)	(3p)	(4x)
(1)-256	(Ij)	(1e)	(2tt)	(3j)	(4y)
(1)-257	(Ic)	(1h)	(2vv)	(3k)	(4z)
(1)-258	(Id)	(1k)	(2y)	(3l)	(4l)
(1)-259	(Ic)	(1l)	(2aa)	(3m)	(4r)
(1)-260	(Id)	(1n)	(2ff)	(3l)	(4u)
(1)-261	(Ia)	(1s)	(2qq)	(3i)	(4v)
(1)-262	(Ip)	(1n)	(2tt)	(3j)	(4x)
(1)-263	(Ic)	(1s)	(2vv)	(3k)	(4y)
(1)-264	(Id)	(1gg)	(2vv)	(3l)	(4z)
(1)-265	(Ie)	(1ll)	(2y)	(3m)	(4l)
(1)-266	(If)	(1mm)	(2aa)	(3n)	(4r)
(1)-267	(Ig)	(1ss)	(2ff)	(3o)	(4u)
(1)-268	(Ih)	(1tt)	(2a)	(3p)	(4v)
(1)-269	(Ii)	(1n)	(2b)	(3n)	(4x)
(1)-270	(Iv)	(1s)	(2g)	(3o)	(4y)
(1)-271	(Ic)	(1gg)	(2i)	(3p)	(4z)
(1)-272	(Id)	(1bbb)	(2a)	(3j)	(4j)

	(I)	A	Z	R′	R^1
(1)-273	(Ik)	(1ccc)	(2q)	(3k)	(4l)
(1)-274	(Ic)	(1n)	(2r)	(3l)	(4a)
(1)-275	(Id)	(1s)	(2t)	(3m)	(4f)
(1)-276	(Ie)	(1gg)	(2x)	(3k)	(4j)
(1)-277	(If)	(1d)	(2a)	(3l)	(4l)
(1)-278	(Is)	(1xx)	(2b)	(3m)	(4r)
(1)-279	(Ih)	(1n)	(2g)	(3n)	(4j)
(1)-280	(Ii)	(1s)	(2i)	(3o)	(4l)
(1)-281	(Ij)	(1gg)	(2a)	(3p)	(4r)
(1)-282	(Ih)	(1d)	(2q)	(3n)	(4u)
(1)-283	(Iu)	(1e)	(2r)	(3o)	(4v)
(1)-284	(Ij)	(1h)	(2t)	(3p)	(4x)
(1)-285	(Ig)	(1k)	(2x)	(3n)	(4y)
(1)-286	(It)	(1l)	(2y)	(3o)	(4z)
(1)-287	(Ih)	(1n)	(2aa)	(3p)	(4j)
(1)-288	(Ii)	(1s)	(2ff)	(3j)	(4l)
(1)-289	(Ij)	(1gg)	(2qq)	(3k)	(4r)
(1)-290	(In)	(1jj)	(2tt)	(3l)	(4j)
(1)-291	(Id)	(1kk)	(2vv)	(3m)	(4l)
(1)-292	(Iq)	(1ll)	(2g)	(3l)	(4r)
(1)-293	(If)	(1mm)	(2i)	(3m)	(4j)
(1)-294	(Ig)	(1ss)	(2a)	(3j)	(4l)
(1)-295	(Ih)	(1n)	(2q)	(3k)	(4r)
(1)-296	(Ii)	(1s)	(2r)	(3l)	(4u)
(1)-297	(Iv)	(1gg)	(2t)	(3m)	(4v)
(1)-298	(Ie)	(1aaa)	(2x)	(3n)	(4x)
(1)-299	(Ir)	(1bbb)	(2y)	(3o)	(4y)
(1)-300	(Ig)	(1ccc)	(2aa)	(3p)	(4z)
(1)-301	(Iw)	(1e)	(2ww)	(3q)	(4u)
(1)-302	(Ix)	(1h)	(2xx)	(3r)	(4bb)

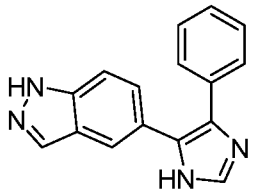
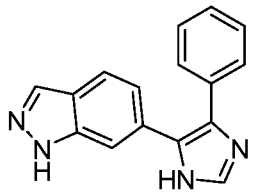
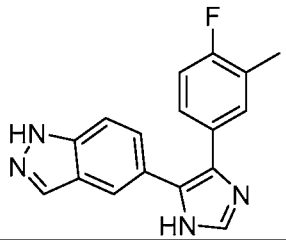
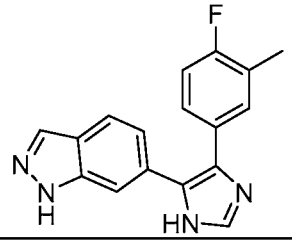
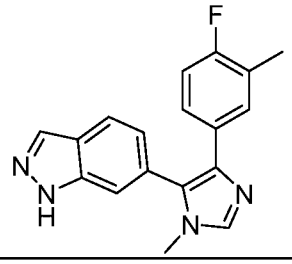
	(I)	A	Z	R′	R^1
(1)-303	(Iw)	(1k)	(2yy)	(3s)	(4cc)
(1)-304	(Ix)	(1l)	(2zz)	(3t)	(4dd)
(1)-305	(Iw)	(1n)	(2aaa)	(3u)	(4ee)
(1)-306	(Ix)	(1s)	(2bbb)	(3v)	(4ff)
(1)-307	(Iw)	(1gg)	(2ccc)	(3w)	(4gg)
(1)-308	(Ix)	(1jj)	(2ww)	(3x)	(4u)
(1)-309	(Iw)	(1kk)	(2xx)	(3y)	(4bb)
(1)-310	(Ix)	(1ll)	(2yy)	(3z)	(4cc)
(1)-311	(Iw)	(1mm)	(2zz)	(3aa)	(4dd)
(1)-312	(Ix)	(1ss)	(2aaa)	(3bb)	(4ee)
(1)-313	(Iw)	(1n)	(2bbb)	(3cc)	(4ff)
(1)-314	(Ix)	(1s)	(2ccc)	(3dd)	(4gg)
(1)-315	(Iw)	(1gg)	(2ww)	(3ee)	(4u)
(1)-316	(Ix)	(1aaa)	(2xx)	(3ff)	(4bb)
(1)-317	(Iw)	(1bbb)	(2yy)	(3gg)	(4cc)
(1)-318	(Ix)	(1s)	(2zz)	(3hh)	(4dd)
(1)-319	(Iw)	(1a)	(2aaa)	(3ii)	(4ee)
(1)-320	(Ix)	(1c)	(2bbb)	(3jj)	(4ff)
(1)-321	(Iw)	(1d)	(2ccc)	(3kk)	(4gg)
(1)-322	(Ix)	(1e)	(2aaa)	(3cc)	(4u)
(1)-323	(Iw)	(1h)	(2bbb)	(3ff)	(4bb)
(1)-324	(Ix)	(1k)	(2ccc)	(3cc)	(4cc)
(1)-325	(Iw)	(1l)	(2yy)	(3aa)	(4u)
(1)-326	(Ix)	(1n)	(2zz)	(3pp)	(4bb)
(1)-327	(Iw)	(1s)	(2aaa)	(3kk)	(4cc)
(1)-328	(Ix)	(1gg)	(2bbb)	(3q)	(4bb)
(1)-329	(Iw)	(1jj)	(2ccc)	(3r)	(4cc)
(1)-330	(Ix)	(1kk)	(2ww)	(3s)	(4dd)
(1)-331	(Iw)	(1ll)	(2xx)	(3t)	(4ee)
(1)-332	(Ix)	(1mm)	(2yy)	(3u)	(4ff)

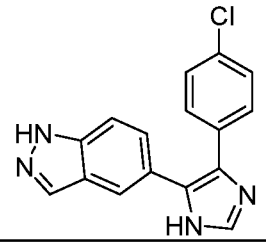
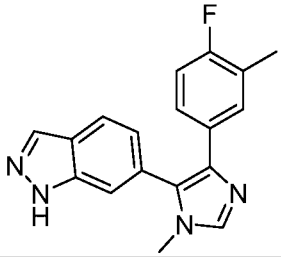
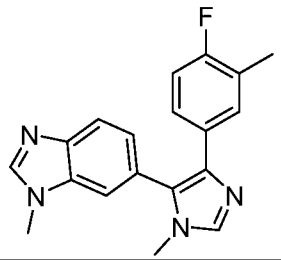
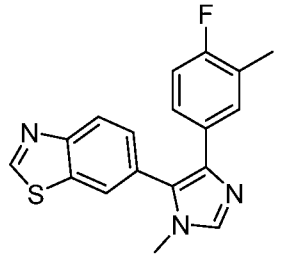
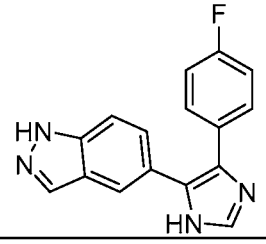
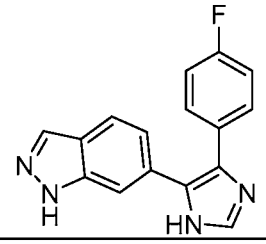
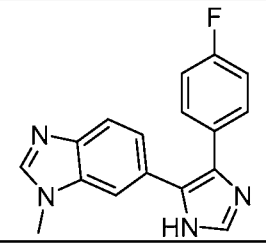
	(I)	A	Z	R′	R^1
(1)-333	(Iw)	(1ss)	(2zz)	(3v)	(4gg)
(1)-334	(Ix)	(1tt)	(2aaa)	(3dd)	(4u)
(1)-335	(Iw)	(1uu)	(2ww)	(3ee)	(4bb)
(1)-336	(Ix)	(1xx)	(2xx)	(3ff)	(4cc)

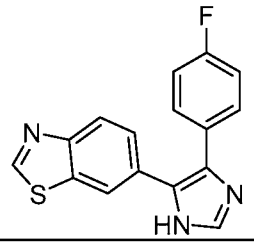
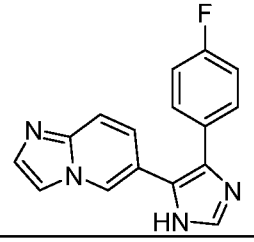
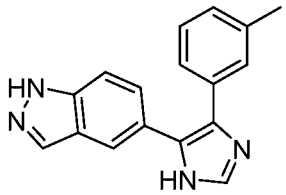
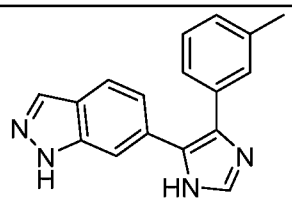
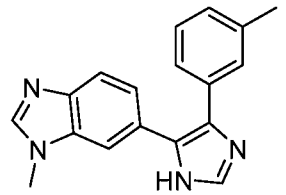
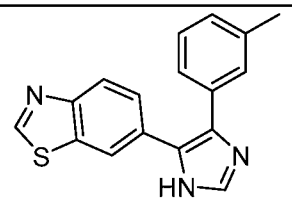
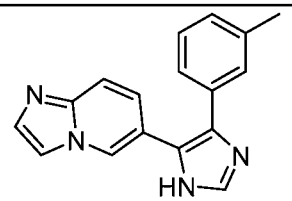
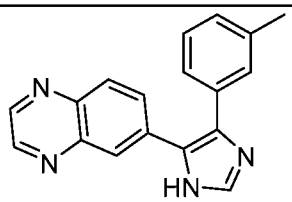
	(I)	A	Z	R′	R^1
(1)-337	(Iw)	(1aaa)	(2yy)	(3gg)	(4bb)
(1)-338	(Ix)	(1bbb)	(2zz)	(3hh)	(4cc)
(1)-339	(Iw)	(1d)	(2aaa)	(3ii)	(4dd)
(1)-340	(Ix)	(1e)	(2bbb)	(3dd)	(4ee)

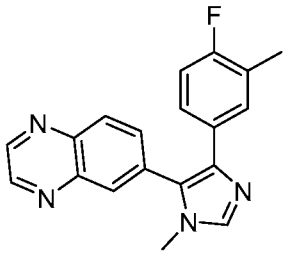
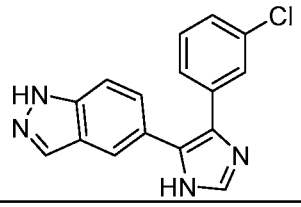
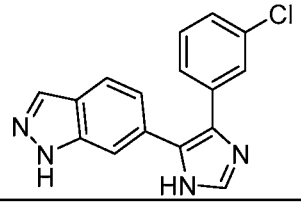
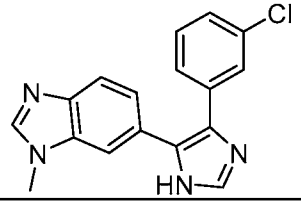
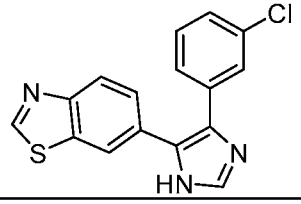
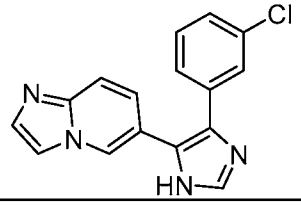
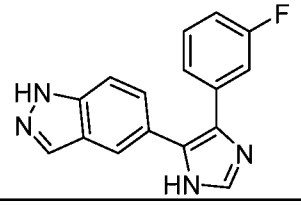
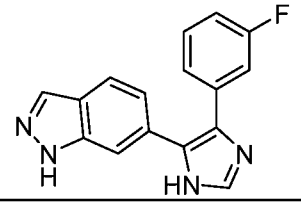
[0048] In some embodiments, the compound of formulae (I), (I′) or (Ia) - (Ix) is one of the following compounds (or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, or a solvate or hydrate thereof):

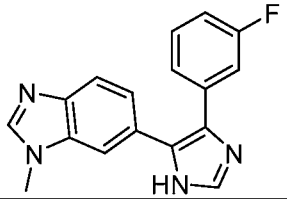
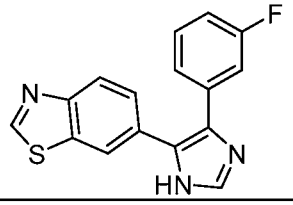
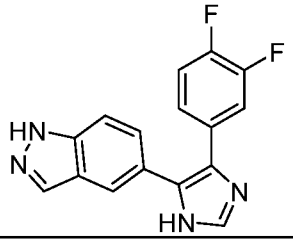
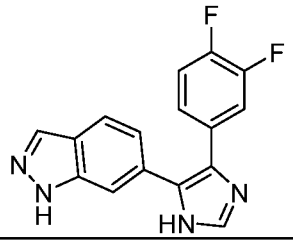
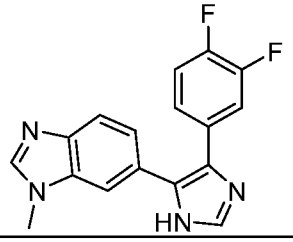
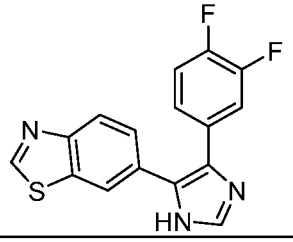
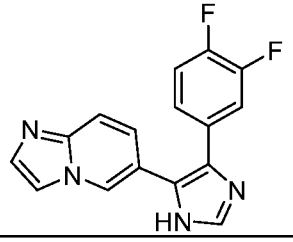
Table A

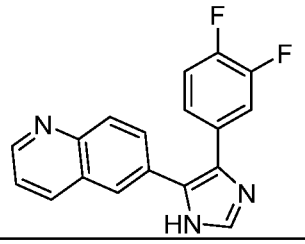
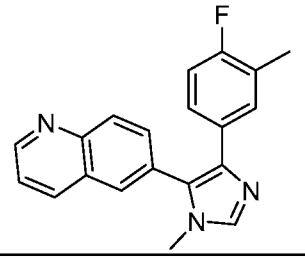
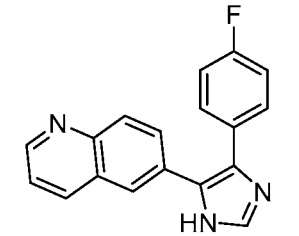
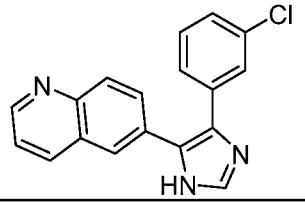
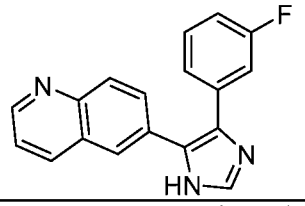
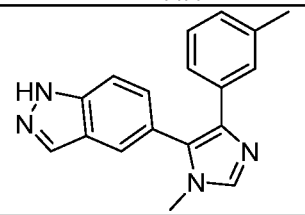
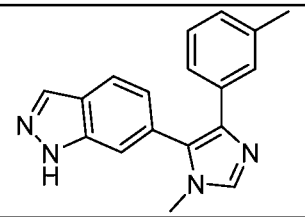
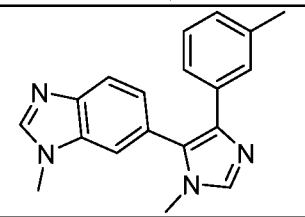
No.	Structure	Name
1		5-(4-Phenyl-1*H*-imidazol-5-yl)-1*H*-indazole
2		6-(4-Phenyl-1*H*-imidazol-5-yl)-1*H*-indazole
3		5-(4-(4-Fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
4		6-(4-(4-Fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
5		6-(4-(4-Fluoro-3-methylphenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole

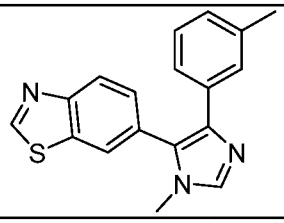
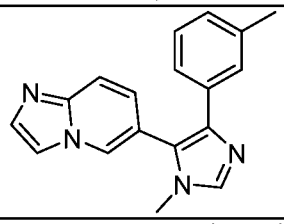
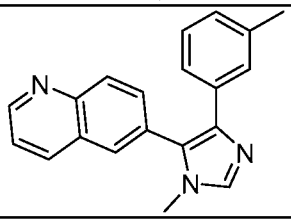
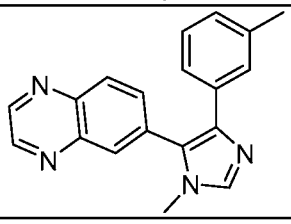
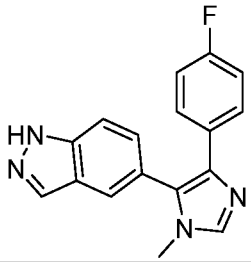
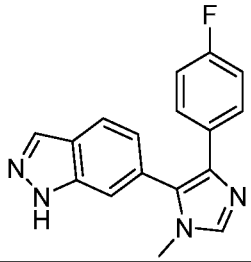
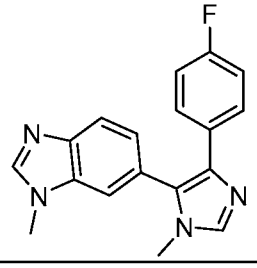
No.	Structure	Name
6		5-(4-(4-Chlorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
7		6-(4-(4-Fluoro-3-methylphenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
8		6-(4-(4-Fluoro-3-methylphenyl)-1-methyl-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole
9		6-(4-(4-Fluoro-3-methylphenyl)-1-methyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole
10		5-(4-(4-Fluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
11		6-(4-(4-Fluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
12		6-(4-(4-Fluorophenyl)-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole

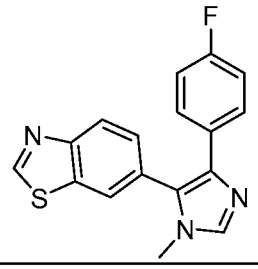
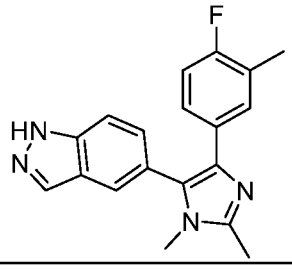
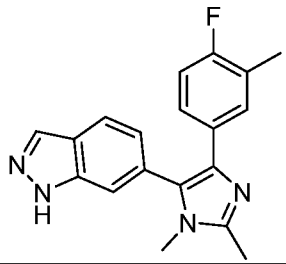
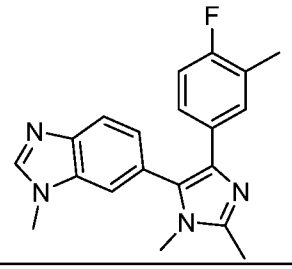
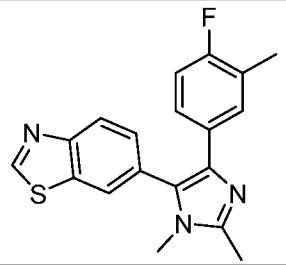
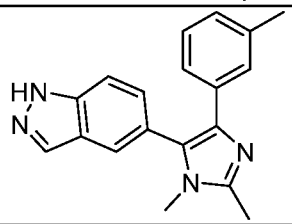
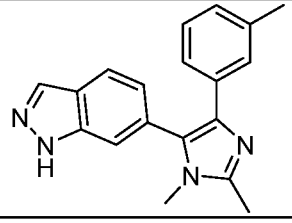
No.	Structure	Name
13		6-(4-(4-Fluorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole
14		6-(4-(4-Fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
15		5-(4-(*m*-Tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole
16		-(4-(*m*-Tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole
17		1-Methyl-6-(4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-benzo[*d*]imidazole
18		6-(4-(*m*-Tolyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole
19		6-(4-(*m*-Tolyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
20		6-(4-(*m*-Tolyl)-1*H*-imidazol-5-yl)quinoxaline

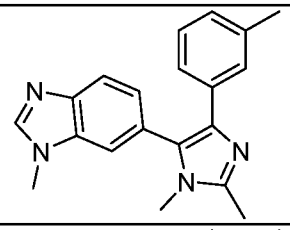
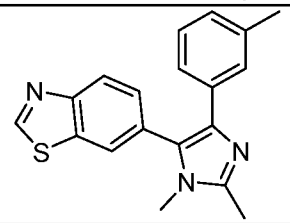
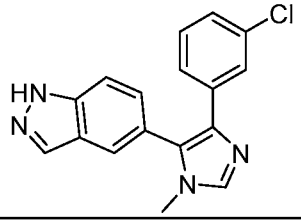
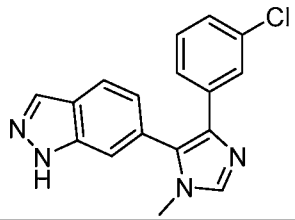
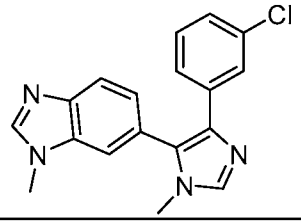
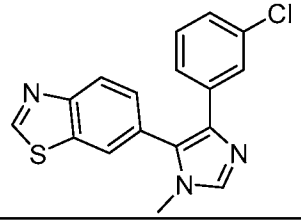
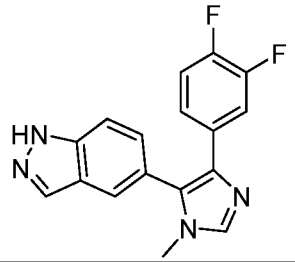
No.	Structure	Name
21		6-(4-(4-Fluoro-3-methylphenyl)-1-methyl-1*H*-imidazol-5-yl)quinoxaline
22		5-(4-(3-Chlorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
23		6-(4-(3-Chlorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
24		6-(4-(3-Chlorophenyl)-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole
25		6-(4-(3-Chlorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole
26		6-(4-(3-Chlorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
27		5-(4-(3-Fluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
28		6-(4-(3-Fluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole

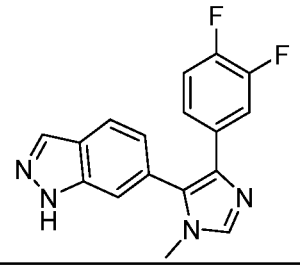
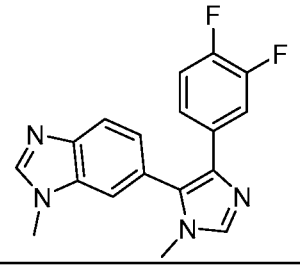
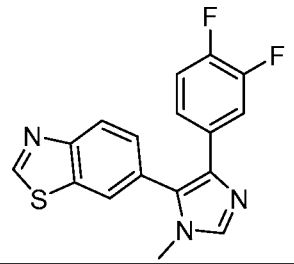
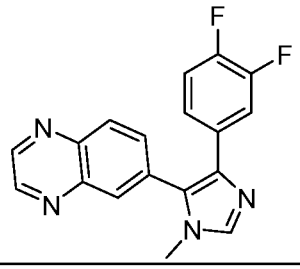
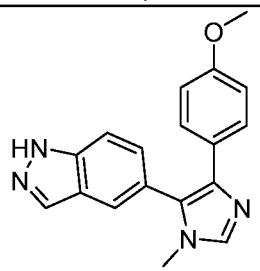
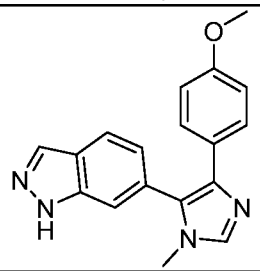
No.	Structure	Name
29		6-(4-(3-Fluorophenyl)-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole
30		6-(4-(3-Fluorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole
31		5-(4-(3,4-Difluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
32		6-(4-(3,4-Difluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
33		6-(4-(3,4-Difluorophenyl)-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole
34		6-(4-(3,4-Difluorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole
35		6-(4-(3,4-Difluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine

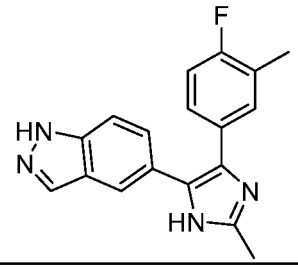
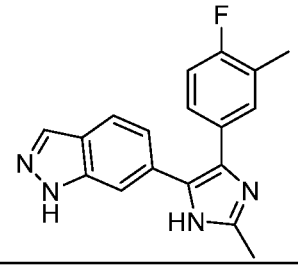
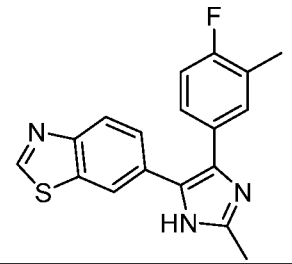
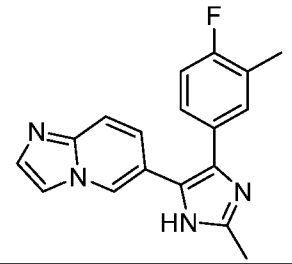
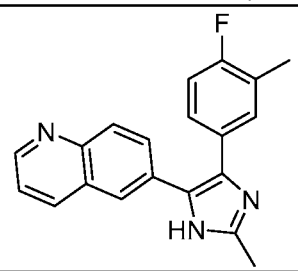
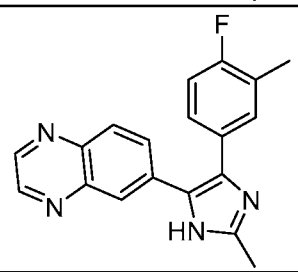
No.	Structure	Name
36		6-(4-(3,4-Difluorophenyl)-1*H*-imidazol-5-yl)quinoline
37		6-(4-(4-Fluoro-3-methylphenyl)-1-methyl-1*H*-imidazol-5-yl)quinoline
38		6-(4-(4-Fluorophenyl)-1*H*-imidazol-5-yl)quinoline
39		6-(4-(3-Chlorophenyl)-1*H*-imidazol-5-yl)quinoline
40		6-(4-(3-Fluorophenyl)-1*H*-imidazol-5-yl)quinoline
41		5-(1-Methyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole
42		6-(1-Methyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole
43		1-Methyl-6-(1-methyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-benzo[*d*]imidazole

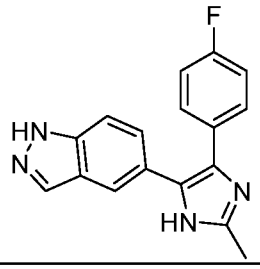
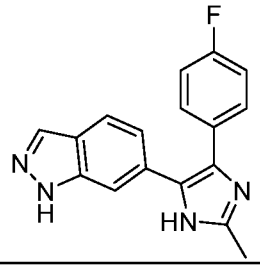
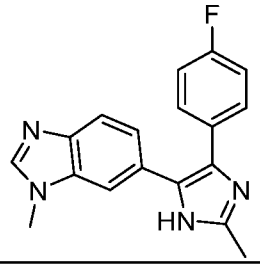
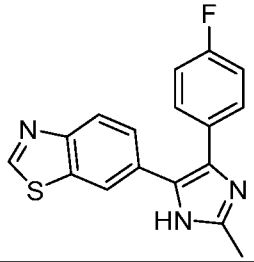
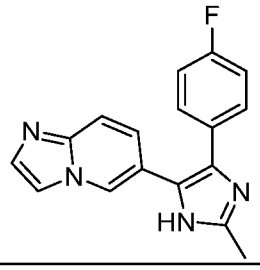
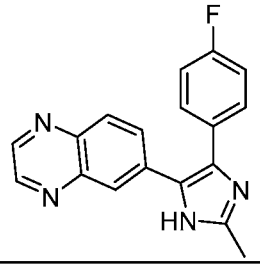
No.	Structure	Name
44		6-(1-Methyl-4-(m-tolyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole
45		6-(1-Methyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
46		6-(1-Methyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)quinoline
47		6-(1-Methyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)quinoxaline
48		-(4-(4-Fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
49		6-(4-(4-Fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
50		6-(4-(4-Fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole

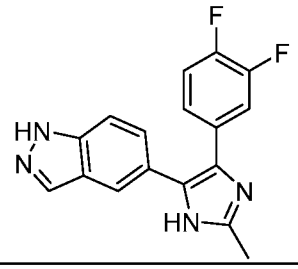
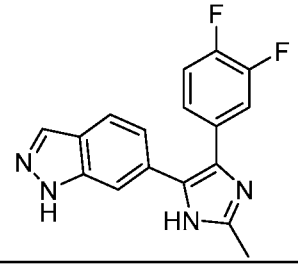
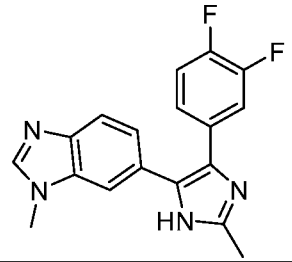
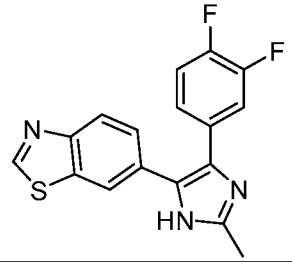
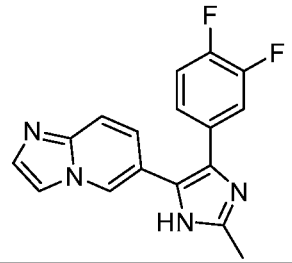
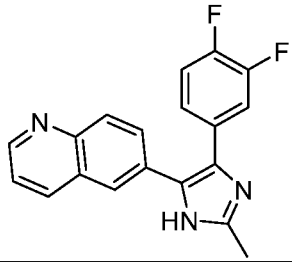
No.	Structure	Name
51		6-(4-(4-Fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole
52		5-(4-(4-Fluoro-3-methylphenyl)-1,2-dimethyl-1*H*-imidazol-5-yl)-1*H*-indazole
53		6-(4-(4-Fluoro-3-methylphenyl)-1,2-dimethyl-1*H*-imidazol-5-yl)-1*H*-indazole
54		6-(4-(4-Fluoro-3-methylphenyl)-1,2-dimethyl-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole
55		6-(4-(4-Fluoro-3-methylphenyl)-1,2-dimethyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole
56		5-(1,2-Dimethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole
57		6-(1,2-Dimethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole

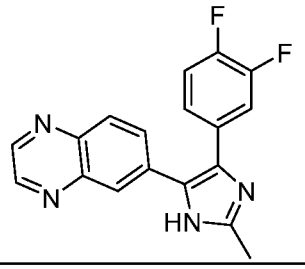
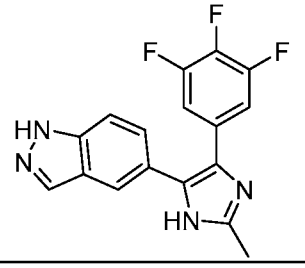
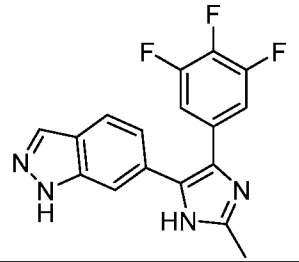
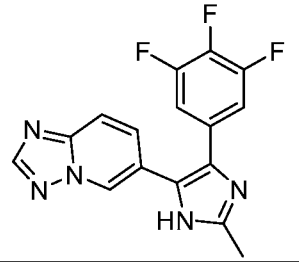
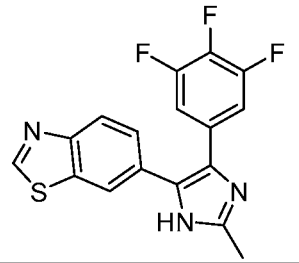
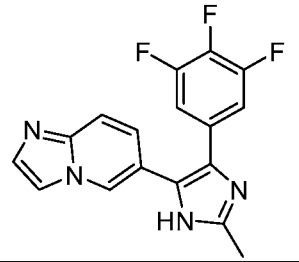
No.	Structure	Name
58		6-(1,2-Dimethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole
59		6-(1,2-Dimethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole
60		5-(4-(3-Chlorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
61		6-(4-(3-Chlorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
62		6-(4-(3-Chlorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole
63		6-(4-(3-Chlorophenyl)-1-methyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole
64		5-(4-(3,4-Difluorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole

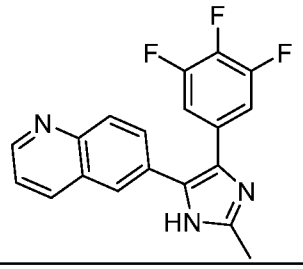
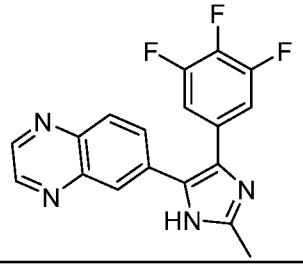
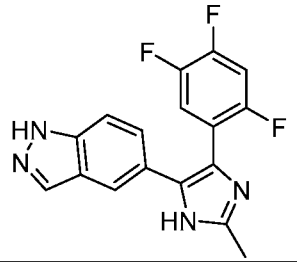
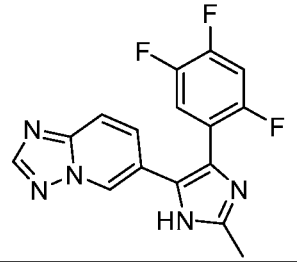
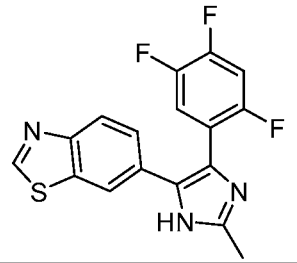
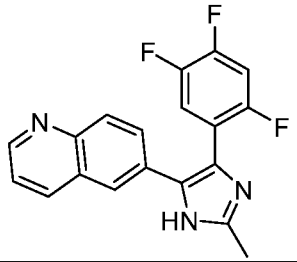
No.	Structure	Name
65		6-(4-(3,4-Difluorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
66		6-(4-(3,4-Difluorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole
67		6-(4-(3,4-Difluorophenyl)-1-methyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole
68		6-(4-(3,4-Difluorophenyl)-1-methyl-1*H*-imidazol-5-yl)quinoxaline
69		5-(4-(4-Methoxyphenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
70		6-(4-(4-Methoxyphenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole

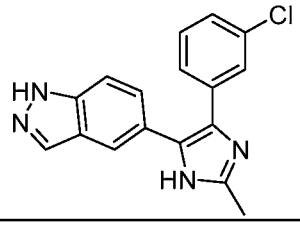
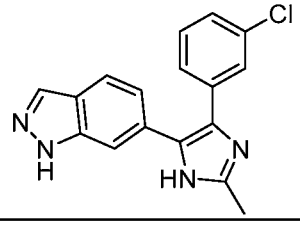
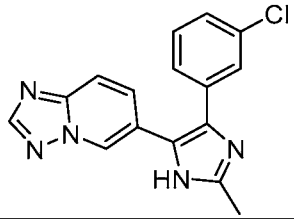
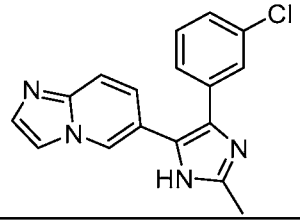
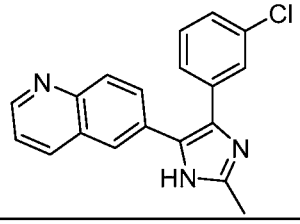
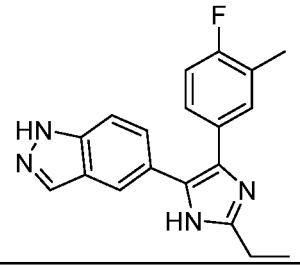
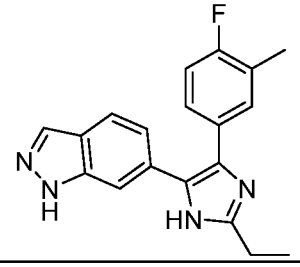
No.	Structure	Name
71		5-(4-(4-Fluoro-3-methylphenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
72		6-(4-(4-Fluoro-3-methylphenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
73		6-(4-(4-Fluoro-3-methylphenyl)-2-methyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole
74		6-(4-(4-Fluoro-3-methylphenyl)-2-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
75		6-(4-(4-Fluoro-3-methylphenyl)-2-methyl-1*H*-imidazol-5-yl)quinoline
76		6-(4-(4-Fluoro-3-methylphenyl)-2-methyl-1*H*-imidazol-5-yl)quinoxaline

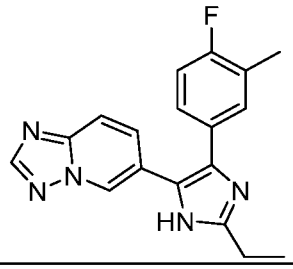
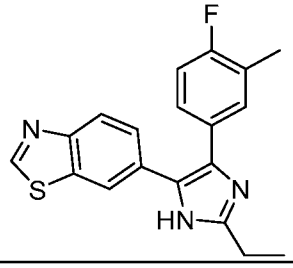
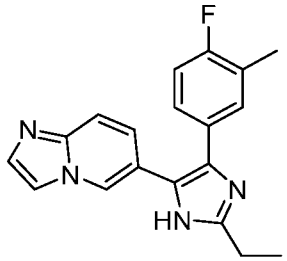
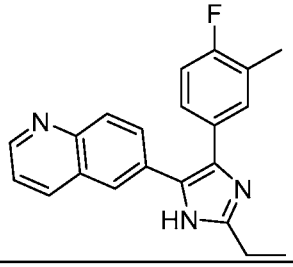
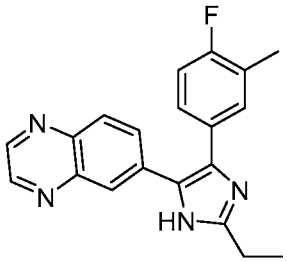
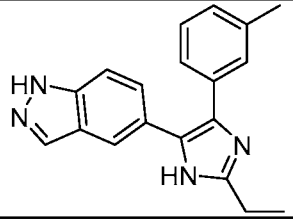
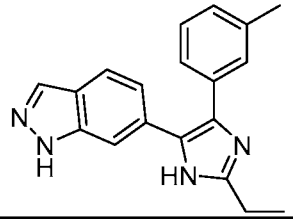
No.	Structure	Name
77		5-(4-(4-Fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
78		6-(4-(4-Fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
79		6-(4-(4-Fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole
80		6-(4-(4-Fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole
81		6-(4-(4-Fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
82		6-(4-(4-Fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)quinoxaline

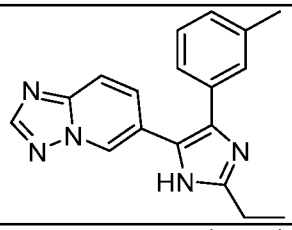
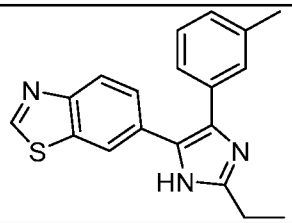
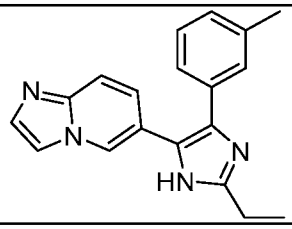
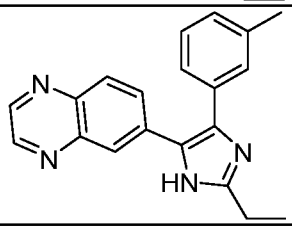
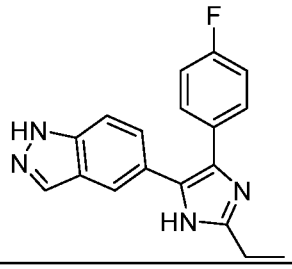
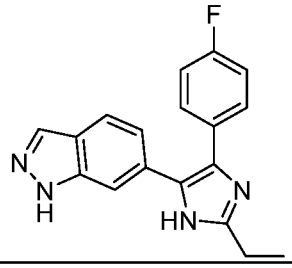
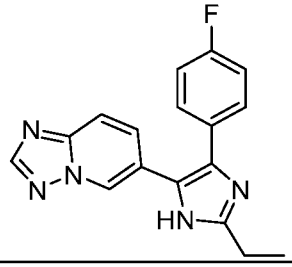
No.	Structure	Name
83		5-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
84		6-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
85		6-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole
86		6-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole
87		6-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
88		6-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)quinoline

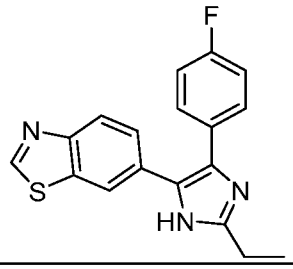
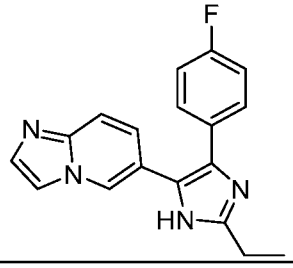
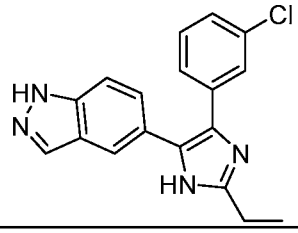
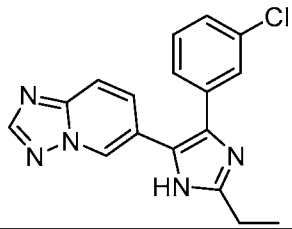
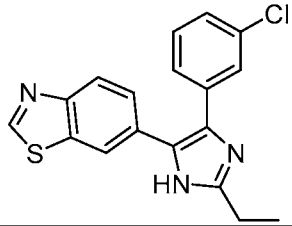
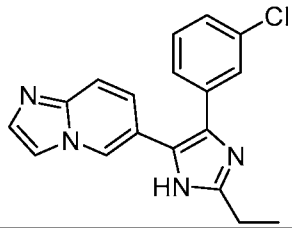
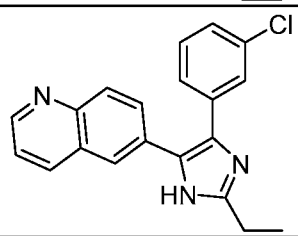
No.	Structure	Name
89		6-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)quinoxaline
90		5-(2-Methyl-4-(3,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
91		6-(2-Methyl-4-(3,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
92		6-(2-Methyl-4-(3,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine
93		6-(2-Methyl-4-(3,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole
94		6-(2-Methyl-4-(3,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine

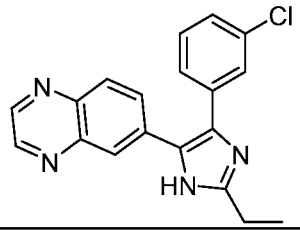
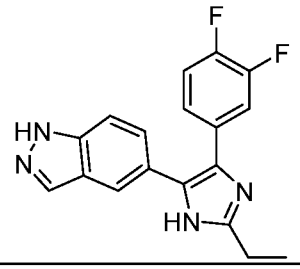
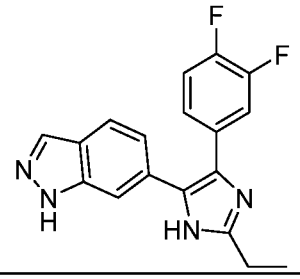
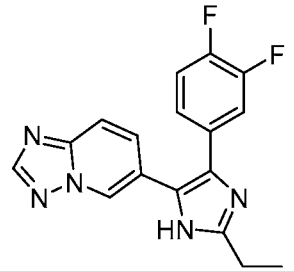
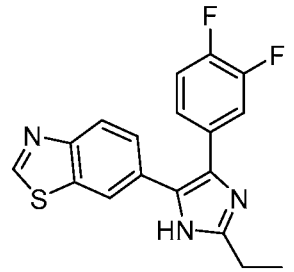
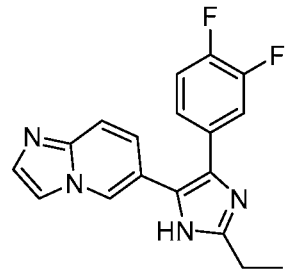
No.	Structure	Name
95		6-(2-Methyl-4-(3,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)quinoline
96		6-(2-Methyl-4-(3,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)quinoxaline
97		5-(2-Methyl-4-(2,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
98		6-(2-Methyl-4-(2,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine
99		6-(2-Methyl-4-(2,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole
100		6-(2-Methyl-4-(2,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)quinoline

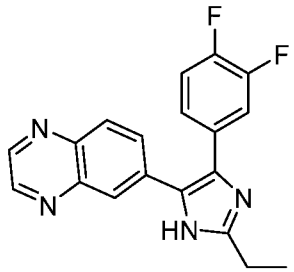
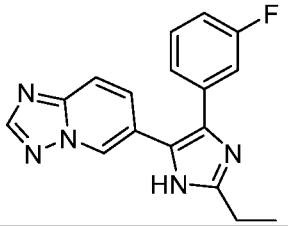
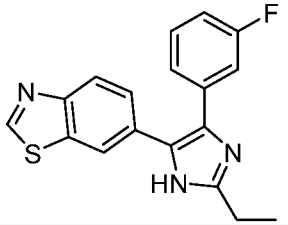
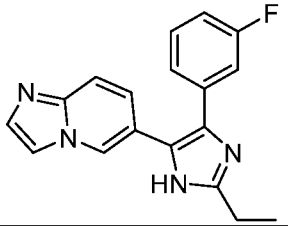
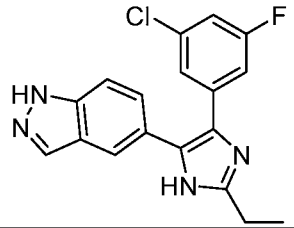
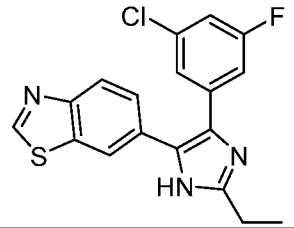
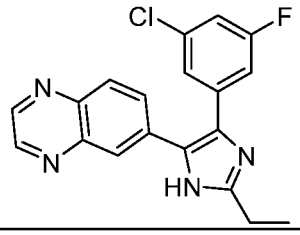
No.	Structure	Name
101		5-(4-(3-Chlorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
102		6-(4-(3-Chlorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
103		6-(4-(3-Chlorophenyl)-2-methyl-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine
104		6-(4-(3-Chlorophenyl)-2-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
105		6-(4-(3-Chlorophenyl)-2-methyl-1*H*-imidazol-5-yl)quinoline
106		5-(2-Ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
107		6-(2-Ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)-1*H*-indazole

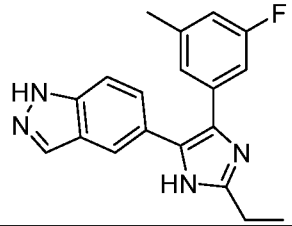
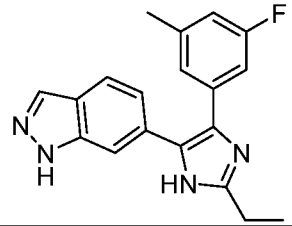
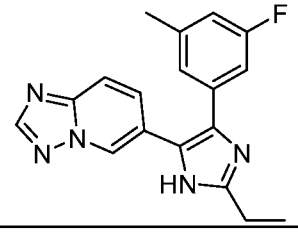
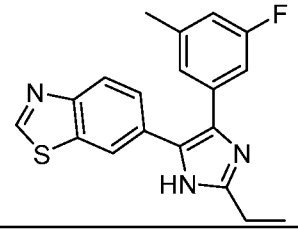
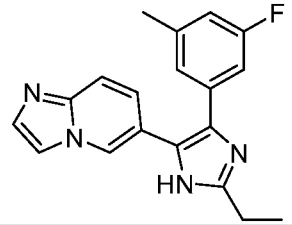
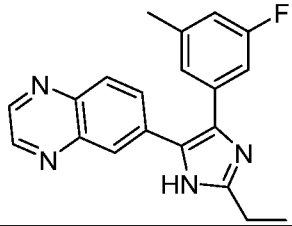
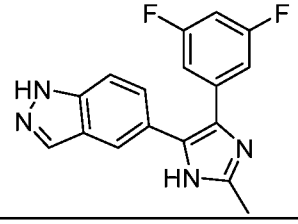
No.	Structure	Name
108		6-(2-Ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine
109		6-(2-Ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole
110		6-(2-Ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
111		6-(2-Ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)quinoline
112		6-(2-Ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)quinoxaline
113		5-(2-Ethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole
114		6-(2-Ethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole

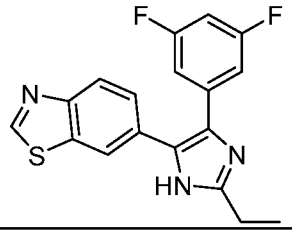
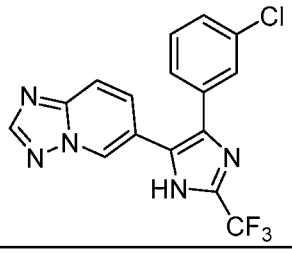
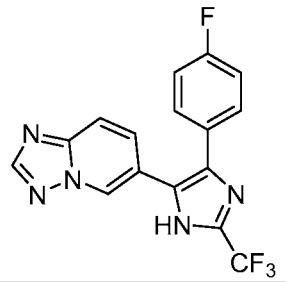
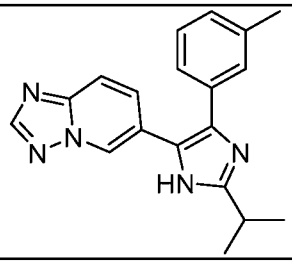
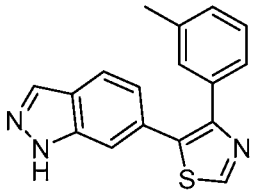
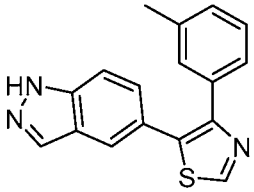
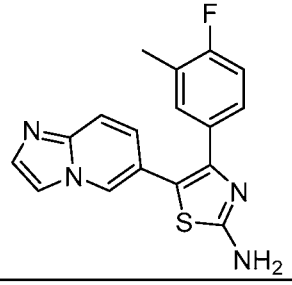
No.	Structure	Name
115		6-(2-Ethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine
116		6-(2-Ethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole
117		6-(2-Ethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
118		6-(2-Ethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)quinoxaline
119		5-(2-Ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
120		6-(2-Ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
121		6-(2-Ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

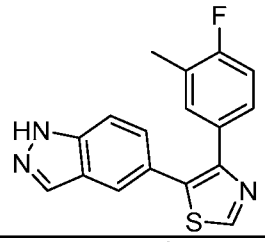
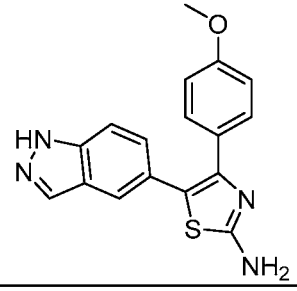
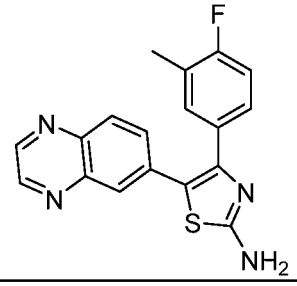
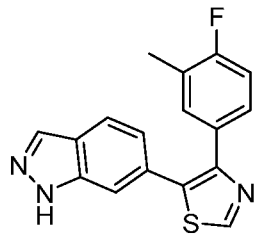
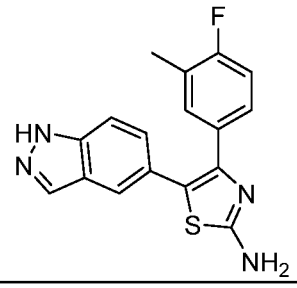
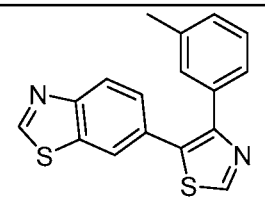
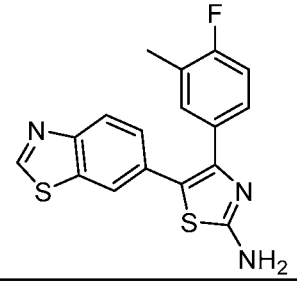
No.	Structure	Name
122		6-(2-Ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole
123		6-(2-Ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
124		5-(4-(3-Chlorophenyl)-2-ethyl-1*H*-imidazol-5-yl)-1*H*-indazole
125		6-(4-(3-Chlorophenyl)-2-ethyl-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine
126		6-(4-(3-Chlorophenyl)-2-ethyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole
127		6-(4-(3-Chlorophenyl)-2-ethyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
128		6-(4-(3-Chlorophenyl)-2-ethyl-1*H*-imidazol-5-yl)quinoline

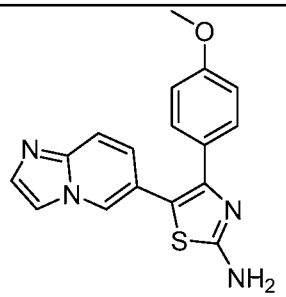
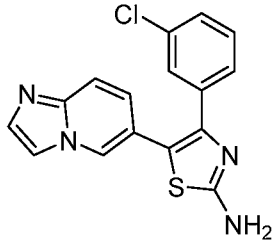
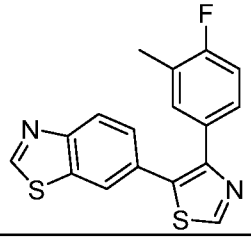
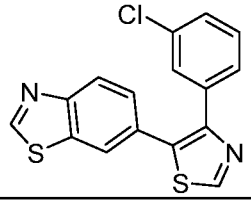
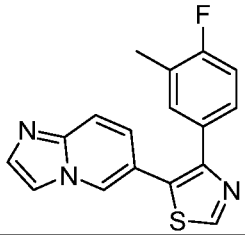
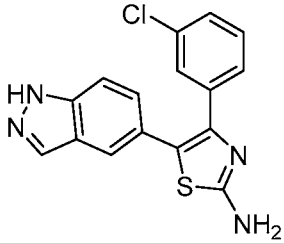
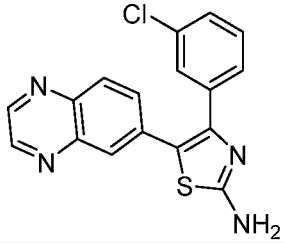
No.	Structure	Name
129		6-(4-(3-Chlorophenyl)-2-ethyl-1*H*-imidazol-5-yl)quinoxaline
130		5-(4-(3,4-Difluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)-1*H*-indazole
131		6-(4-(3,4-Difluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)-1*H*-indazole
132		6-(4-(3,4-Difluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine
133		6-(4-(3,4-Difluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole
134		6-(4-(3,4-Difluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine

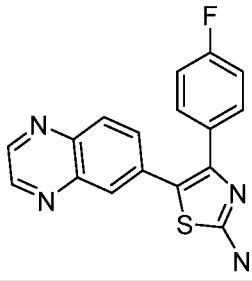
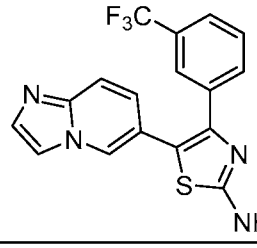
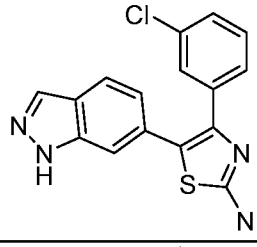
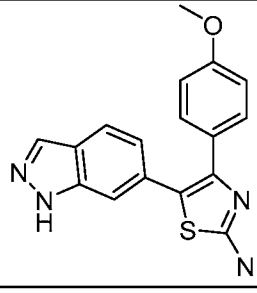
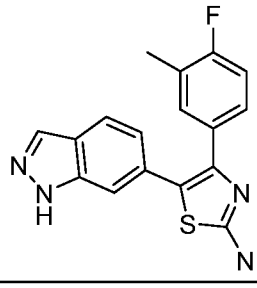
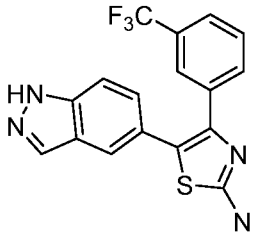
No.	Structure	Name
135		6-(4-(3,4-Difluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)quinoxaline
136		6-(2-Ethyl-4-(3-fluorophenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine
137		6-(2-Ethyl-4-(3-fluorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole
138		6-(2-Ethyl-4-(3-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
139		5-(4-(3-Chloro-5-fluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)-1*H*-indazole
140		6-(4-(3-Chloro-5-fluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole
141		6-(4-(3-Chloro-5-fluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)quinoxaline

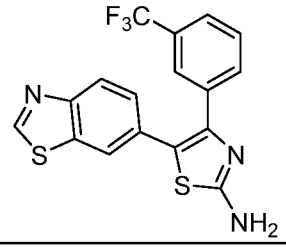
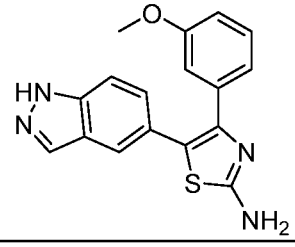
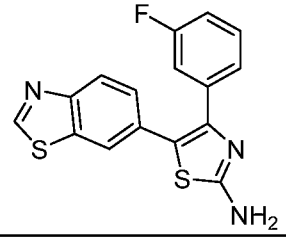
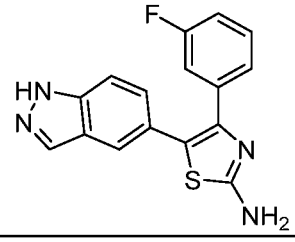
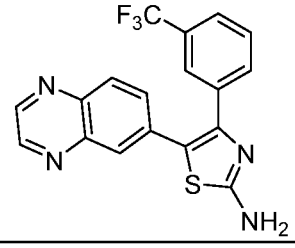
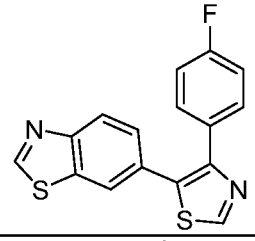
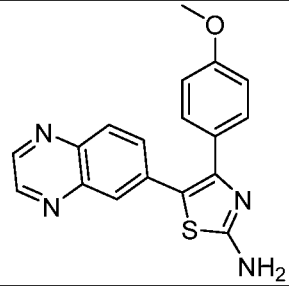
No.	Structure	Name
142		5-(2-Ethyl-4-(3-fluoro-5-methylphenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
143		6-(2-Ethyl-4-(3-fluoro-5-methylphenyl)-1*H*-imidazol-5-yl)-1*H*-indazole
144		6-(2-Ethyl-4-(3-fluoro-5-methylphenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine
145		6-(2-Ethyl-4-(3-fluoro-5-methylphenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole
146		6-(2-Ethyl-4-(3-fluoro-5-methylphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
147		6-(2-Ethyl-4-(3-fluoro-5-methylphenyl)-1*H*-imidazol-5-yl)quinoxaline
148		5-(4-(3,5-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole

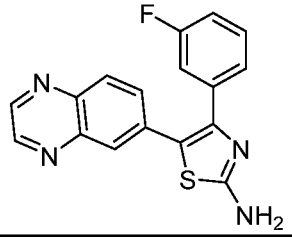
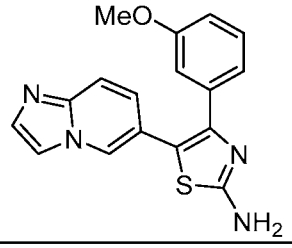
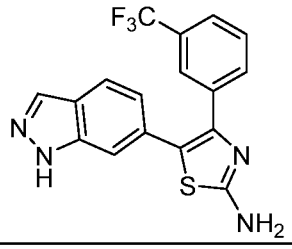
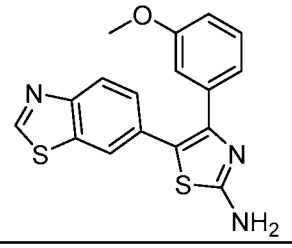
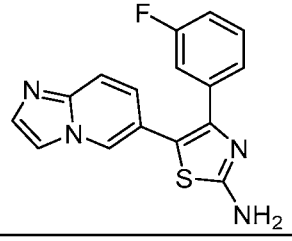
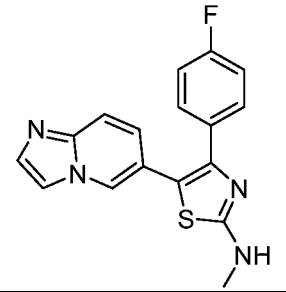
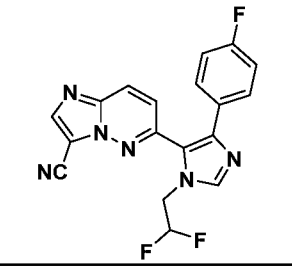
No.	Structure	Name
149		6-(4-(3,5-Difluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole
150		6-(4-(3-Chlorophenyl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine
151		6-(4-(4-Fluorophenyl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine
152		6-(2-Isopropyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine
153		5-(1H-indazol-6-yl)-4-(*m*-tolyl)thiazole
154		5-(1H-indazol-5-yl)-4-(m-tolyl)thiazole
155		4-(4-fluoro-3-methylphenyl)-5-(imidazo[1,2-a]pyridin-6-yl)thiazol-2-amine

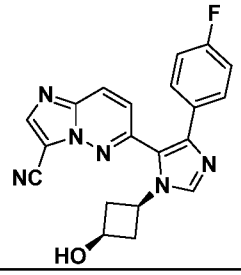
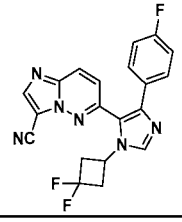
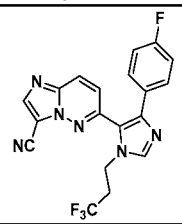
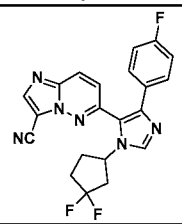
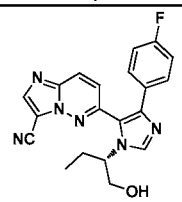
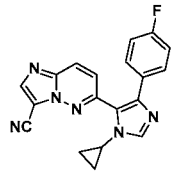
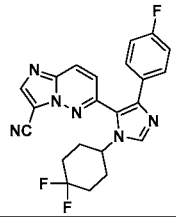
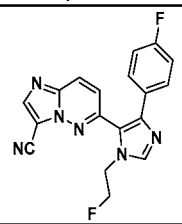
No.	Structure	Name
156		4-(4-fluoro-3-methylphenyl)-5-(1H-indazol-5-yl)thiazole
157		5-(1H-indazol-5-yl)-4-(4-methoxyphenyl)thiazol-2-amine
158		4-(4-fluoro-3-methylphenyl)-5-(quinoxalin-6-yl)thiazol-2-amine
159		4-(4-fluoro-3-methylphenyl)-5-(1H-indazol-6-yl)thiazole
160		4-(4-fluoro-3-methylphenyl)-5-(1H-indazol-5-yl)thiazol-2-amine
161		6-(4-(m-tolyl)thiazol-5-yl)benzo[d]thiazole
162		5-(benzo[d]thiazol-6-yl)-4-(4-fluoro-3-methylphenyl)thiazol-2-amine

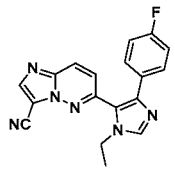
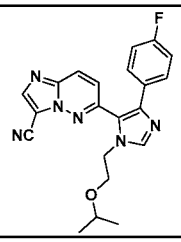
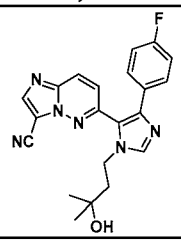
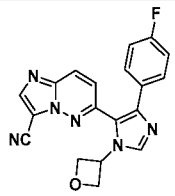
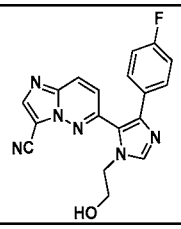
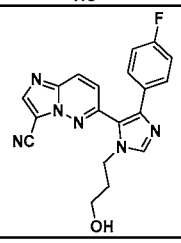
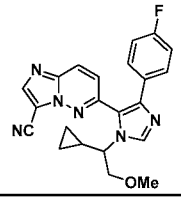
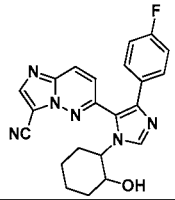
No.	Structure	Name
163		5-(imidazo[1,2-a]pyridin-6-yl)-4-(4-methoxyphenyl)thiazol-2-amine
164		4-(3-chlorophenyl)-5-(imidazo[1,2-a]pyridin-6-yl)thiazol-2-amine
165		6-(4-(4-fluoro-3-methylphenyl)thiazol-5-yl)benzo[d]thiazole
166		6-(4-(3-chlorophenyl)thiazol-5-yl)benzo[d]thiazole
167		4-(4-fluoro-3-methylphenyl)-5-(imidazo[1,2-a]pyridin-6-yl)thiazole
168		4-(3-chlorophenyl)-5-(1H-indazol-5-yl)thiazol-2-amine
169		4-(3-chlorophenyl)-5-(quinoxalin-6-yl)thiazol-2-amine

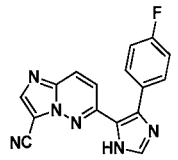
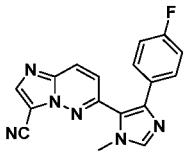
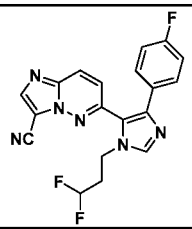
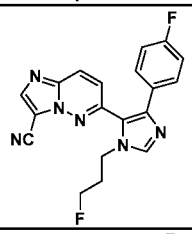
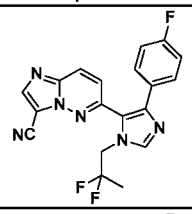
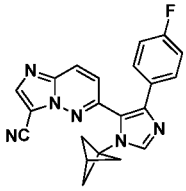
No.	Structure	Name
170		4-(4-fluorophenyl)-5-(quinoxalin-6-yl)thiazol-2-amine
171		5-(imidazo[1,2-a]pyridin-6-yl)-4-(3-(trifluoromethyl)phenyl)thiazol-2-amine
172		4-(3-chlorophenyl)-5-(1H-indazol-6-yl)thiazol-2-amine
173		5-(1H-indazol-6-yl)-4-(4-methoxyphenyl)thiazol-2-amine
174		4-(4-fluoro-3-methylphenyl)-5-(1H-indazol-6-yl)thiazol-2-amine
175		5-(1H-indazol-5-yl)-4-(3-(trifluoromethyl)phenyl)thiazol-2-amine

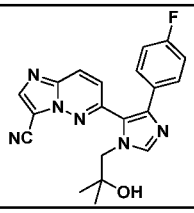
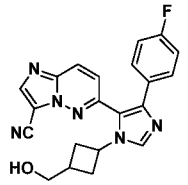
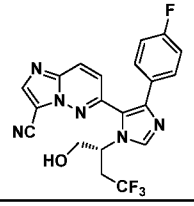
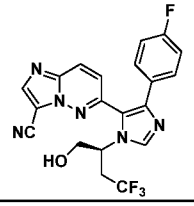
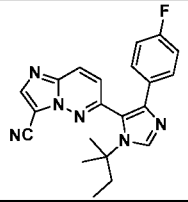
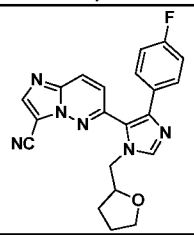
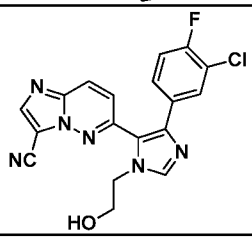
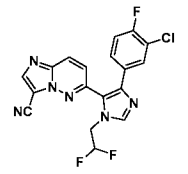
No.	Structure	Name
176		5-(benzo[d]thiazol-6-yl)-4-(3-(trifluoromethyl)phenyl)thiazol-2-amine
177		5-(1H-indazol-5-yl)-4-(3-methoxyphenyl)thiazol-2-amine
178		5-(benzo[d]thiazol-6-yl)-4-(3-fluorophenyl)thiazol-2-amine
179		4-(3-fluorophenyl)-5-(1H-indazol-5-yl)thiazol-2-amine
180		5-(quinoxalin-6-yl)-4-(3-(trifluoromethyl)phenyl)thiazol-2-amine
181		6-(4-(4-fluorophenyl)thiazol-5-yl)benzo[d]thiazole
182		4-(4-methoxyphenyl)-5-(quinoxalin-6-yl)thiazol-2-amine

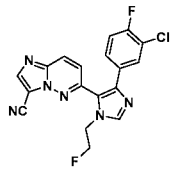
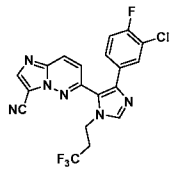
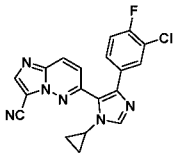
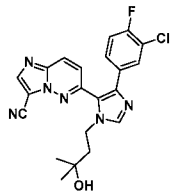
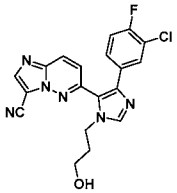
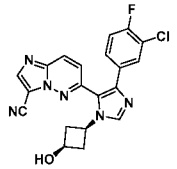
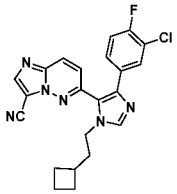
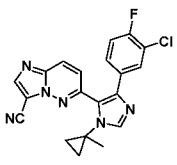
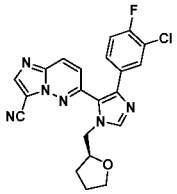
No.	Structure	Name
183		4-(3-fluorophenyl)-5-(quinoxalin-6-yl)thiazol-2-amine
184		5-(imidazo[1,2-a]pyridin-6-yl)-4-(3-methoxyphenyl)thiazol-2-amine
185		5-(1H-indazol-6-yl)-4-(3-(trifluoromethyl)phenyl)thiazol-2-amine
186		5-(benzo[d]thiazol-6-yl)-4-(3-methoxyphenyl)thiazol-2-amine
187		4-(3-fluorophenyl)-5-(imidazo[1,2-a]pyridin-6-yl)thiazol-2-amine
188		4-(4-fluorophenyl)-5-(imidazo[1,2-a]pyridin-6-yl)-N-methylthiazol-2-amine
1′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

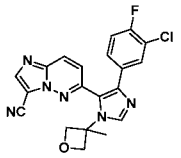
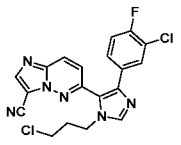
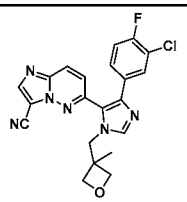
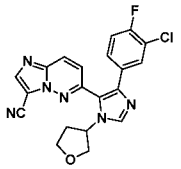
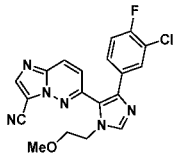
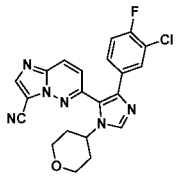
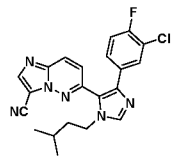
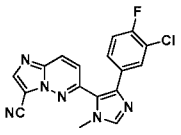
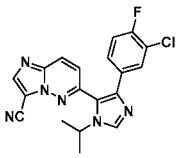
No.	Structure	Name
2′		6-(4-(4-fluorophenyl)-1-*cis*-3-hydroxycyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
3′		6-(1-(3,3-difluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
4′		6-(4-(4-fluorophenyl)-1-(3,3,3-trifluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
5′		6-(1-(3,3-difluorocyclopentyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
6′		(*S*)-6-(4-(4-fluorophenyl)-1-(1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
7′		6-(1-cyclopropyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
8′		6-(1-(4,4-difluorocyclohexyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
9′		6-(1-(2-fluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

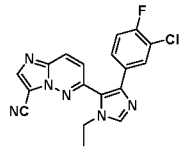
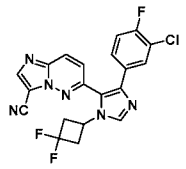
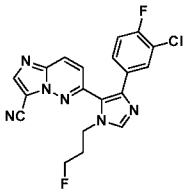
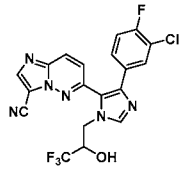
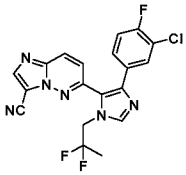
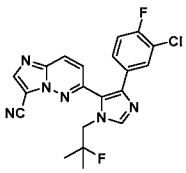
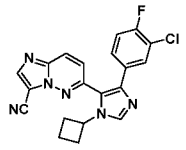
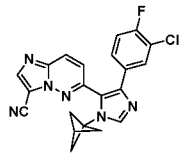
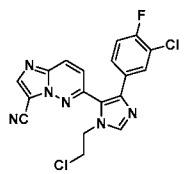
No.	Structure	Name
10′		6-(1-ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
11′		6-(4-(4-fluorophenyl)-1-(2-*iso*propoxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
12′		6-(4-(4-fluorophenyl)-1-(3-hydroxy-3-methylbutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
13′		6-(4-(4-fluorophenyl)-1-(oxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
14′		6-(4-(4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
15′		6-(4-(4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
16′		6-(1-(1-cyclopropyl-2-methoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
17′		6-(4-(4-fluorophenyl)-1-(2-hydroxycyclohexyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

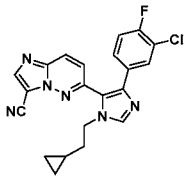
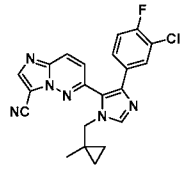
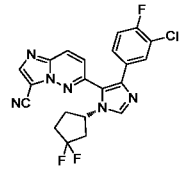
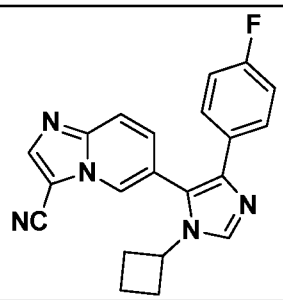
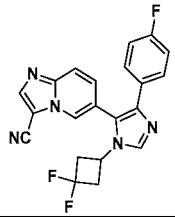
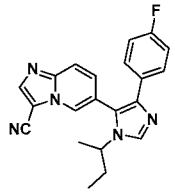
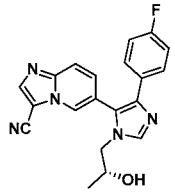
No.	Structure	Name
18′		6-(4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
19′		6-(4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
20′		6-(1-(3,3-difluoropropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
21′		6-(4-(4-fluorophenyl)-1-(3-fluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
22′		6-(1-(2,2-difluoropropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
23′		6-(1-(2-fluoro-2-methylpropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
24′		6-(4-(4-fluorophenyl)-1-isopropyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
25′		6-(1-(bicyclo[1.1.1]pentan-1-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

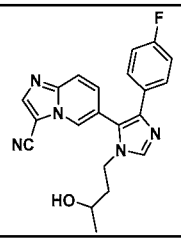
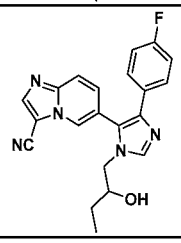
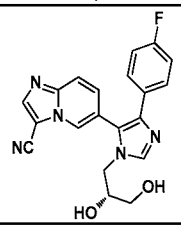
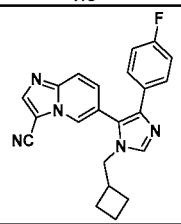
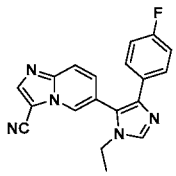
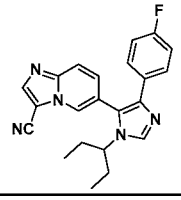
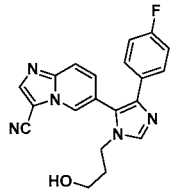
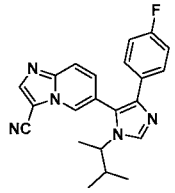
No.	Structure	Name
26′		6-(4-(4-fluorophenyl)-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
27′		6-(4-(4-fluorophenyl)-1-(3-(hydroxymethyl)cyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
28′		(*R*)-6-(4-(4-fluorophenyl)-1-(4,4,4-trifluoro-1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
29′		(*S*)-6-(4-(4-fluorophenyl)-1-(4,4,4-trifluoro-1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
30′		6-(4-(4-fluorophenyl)-1-(*tert*-pentyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
31′		6-(4-(4-fluorophenyl)-1-((tetrahydrofuran-2-yl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
32′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
33′		6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

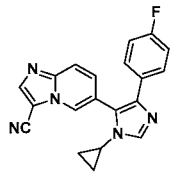
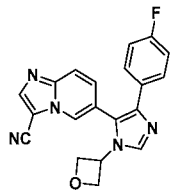
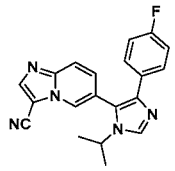
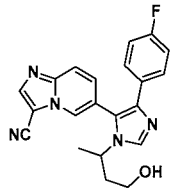
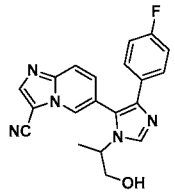
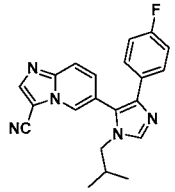
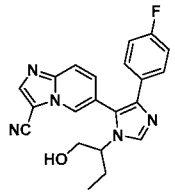
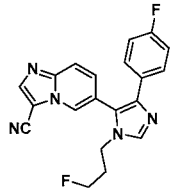
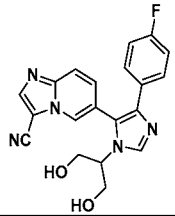
No.	Structure	Name
34′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-fluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
35′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3,3-trifluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
36′		6-(4-(3-chloro-4-fluorophenyl)-1-cyclopropyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
37′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-hydroxy-3-methylbutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
38′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
39′		6-(4-(3-chloro-4-fluorophenyl)-1-((*cis*)-3-hydroxycyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
40′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-cyclobutylethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
41′		6-(4-(3-chloro-4-fluorophenyl)-1-(1-methylcyclopropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
42′		(*S*)-6-(4-(3-chloro-4-fluorophenyl)-1-((tetrahydrofuran-2-yl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

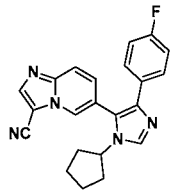
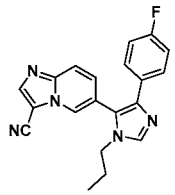
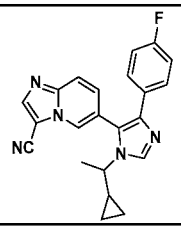
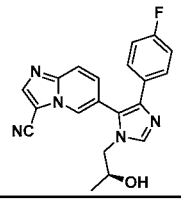
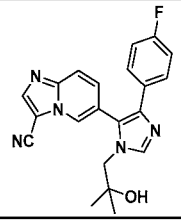
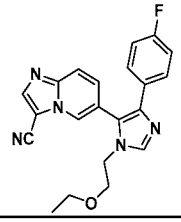
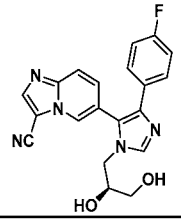
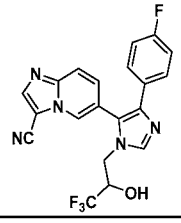
No.	Structure	Name
43′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-methyloxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
44′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-chloropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
45′		6-(4-(3-chloro-4-fluorophenyl)-1-((3-methyloxetan-3-yl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
46′		6-(4-(3-chloro-4-fluorophenyl)-1-(tetrahydrofuran-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
47′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-methoxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
48′		6-(4-(3-chloro-4-fluorophenyl)-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
49′		6-(4-(3-chloro-4-fluorophenyl)-1-*iso*pentyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
50′		6-(4-(3-chloro-4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
51′		6-(4-(3-chloro-4-fluorophenyl)-1-isopropyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

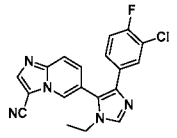
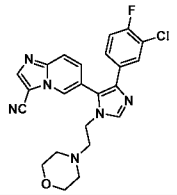
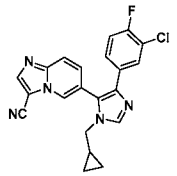
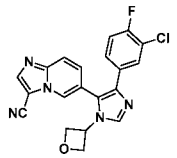
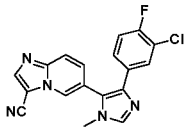
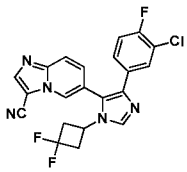
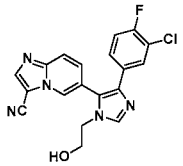
No.	Structure	Name
52′		6-(4-(3-chloro-4-fluorophenyl)-1-ethyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
53′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
54′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-fluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
55′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3,3-trifluoro-2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
56′		6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
57′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-fluoro-2-methylpropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
58′		6-(4-(3-chloro-4-fluorophenyl)-1-cyclobutyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
59′		6-(1-(bicyclo[1.1.1]pentan-1-yl)-4-(3-chloro-4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
60′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-chloroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

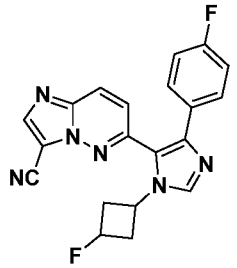
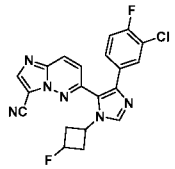
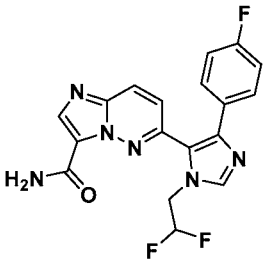
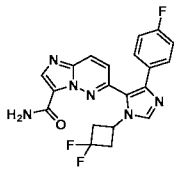
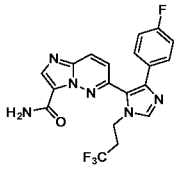
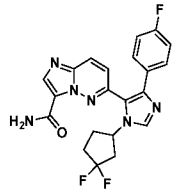
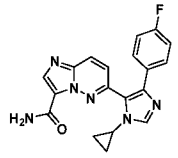
No.	Structure	Name
61′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-cyclopropylethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
62′		6-(4-(3-chloro-4-fluorophenyl)-1-((1-methylcyclopropyl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
63′		(*R*)-6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclopentyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
64′		(*S*)-6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclopentyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
65		6-(1-cyclobutyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
66′		6-(1-(3,3-difluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
67′		6-(1-(sec-butyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
68′		(*R*)-6-(4-(4-fluorophenyl)-1-(2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile

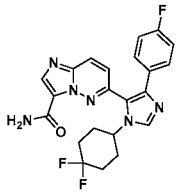
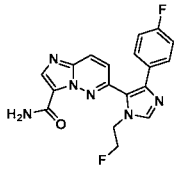
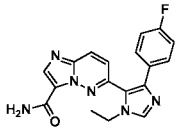
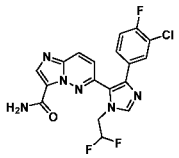
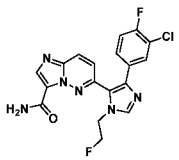
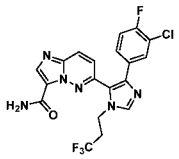
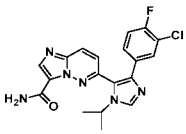
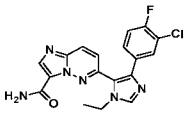
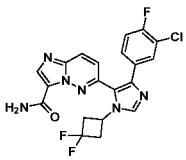
No.	Structure	Name
69′		6-(4-(4-fluorophenyl)-1-(3-hydroxybutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
70′		6-(4-(4-fluorophenyl)-1-(2-hydroxybutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
71′		(*R*)-6-(1-(2,3-dihydroxypropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
72′		6-(1-(cyclobutylmethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
73′		6-(1-ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
74′		6-(4-(4-fluorophenyl)-1-(pentan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
75′		6-(4-(4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
76′		6-(4-(4-fluorophenyl)-1-(3-methylbutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile

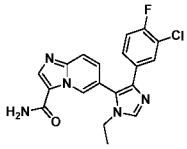
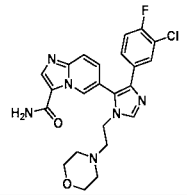
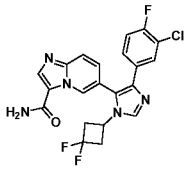
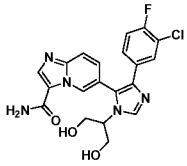
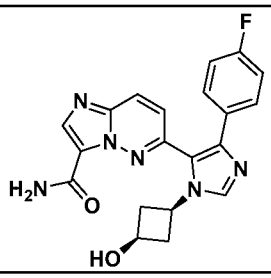
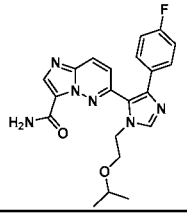
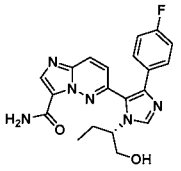
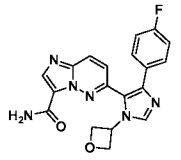
No.	Structure	Name
77′		6-(1-cyclopropyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
78′		6-(4-(4-fluorophenyl)-1-(oxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
79′		6-(4-(4-fluorophenyl)-1-isopropyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
80′		6-(4-(4-fluorophenyl)-1-(4-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
81′		6-(4-(4-fluorophenyl)-1-(1-hydroxypropan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
82′		6-(4-(4-fluorophenyl)-1-isobutyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
83′		6-(4-(4-fluorophenyl)-1-(1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
84′		6-(4-(4-fluorophenyl)-1-(3-fluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
85′		6-(1-(1,3-dihydroxypropan-2-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile

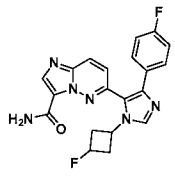
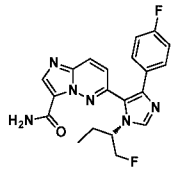
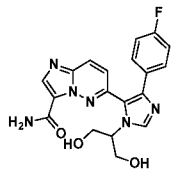
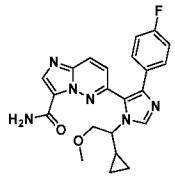
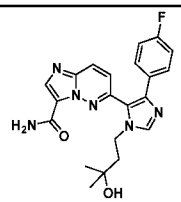
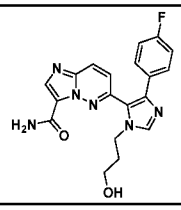
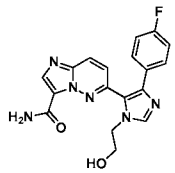
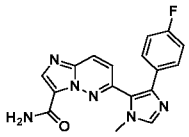
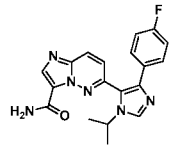
No.	Structure	Name
86′		6-(1-cyclopentyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
87′		6-(4-(4-fluorophenyl)-1-propyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
88′		6-(1-(1-cyclopropylethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
89′		(*S*)-6-(4-(4-fluorophenyl)-1-(2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
90′		6-(4-(4-fluorophenyl)-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
91′		6-(1-(2-ethoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
92′		(*S*)-6-(1-(2,3-dihydroxypropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
93′		6-(4-(4-fluorophenyl)-1-(3,3,3-trifluoro-2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile

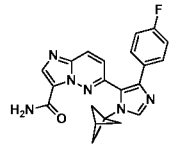
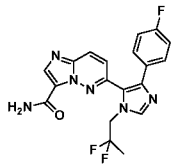
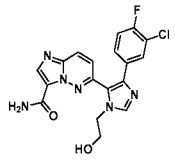
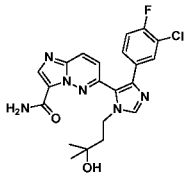
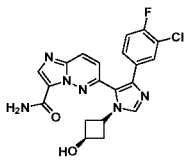
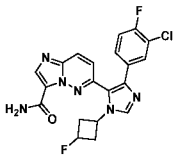
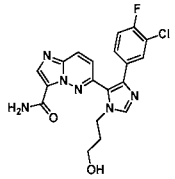
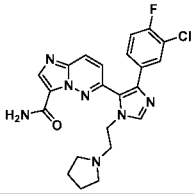
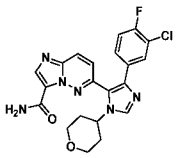
No.	Structure	Name
94′		6-(4-(3-chloro-4-fluorophenyl)-1-ethyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
95′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-morpholinoethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
96′		6-(4-(3-chloro-4-fluorophenyl)-1-(cyclopropylmethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
97′		6-(4-(3-chloro-4-fluorophenyl)-1-(oxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
98′		6-(4-(3-chloro-4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
99′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
100′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
101′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-fluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile

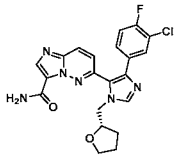
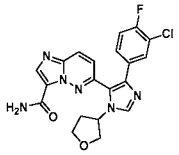
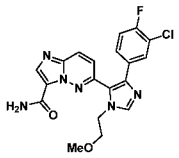
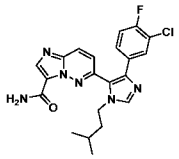
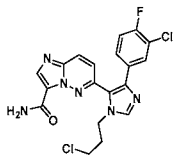
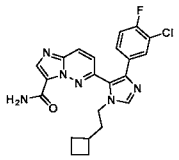
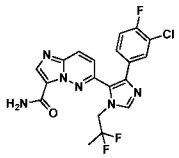
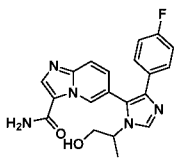
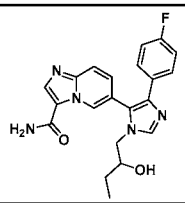
No.	Structure	Name
102		6-(1-(3-fluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
103′		(*S*)-6-(1-(1-fluorobutan-2-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
104′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-fluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
105		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
106′		6-(1-(3,3-difluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
107′		6-(4-(4-fluorophenyl)-1-(3,3,3-trifluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
108′		6-(1-(3,3-difluorocyclopentyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
109′		6-(1-cyclopropyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide

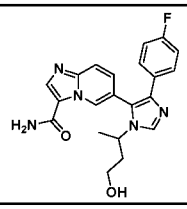
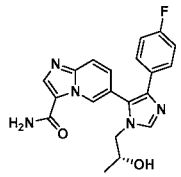
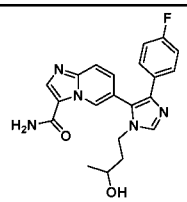
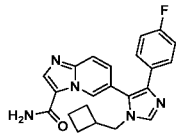
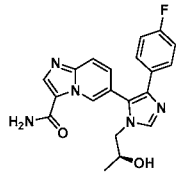
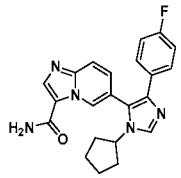
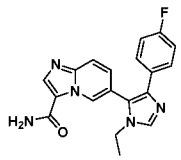
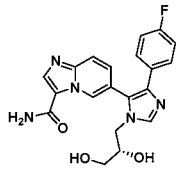
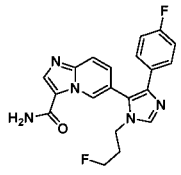
No.	Structure	Name
110′		6-(1-(4,4-difluorocyclohexyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
111′		6-(1-(2-fluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
112′		6-(1-ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
113′		6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
114′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-fluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
115′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3,3-trifluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
116′		6-(4-(3-chloro-4-fluorophenyl)-1-isopropyl-1H-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
117′		6-(4-(3-chloro-4-fluorophenyl)-1-ethyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
118′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide

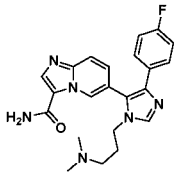
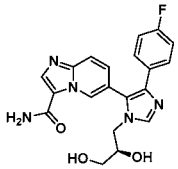
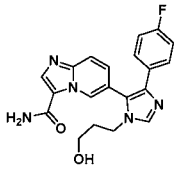
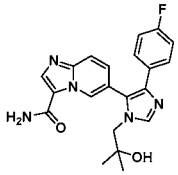
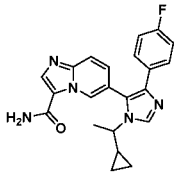
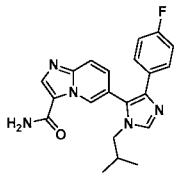
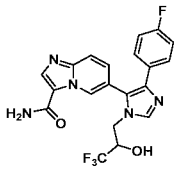
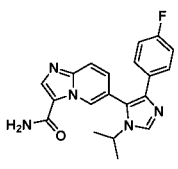
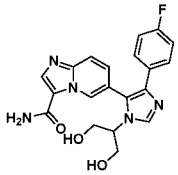
No.	Structure	Name
119′		6-(4-(3-chloro-4-fluorophenyl)-1-ethyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
120′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-morpholinoethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
121′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
122′		6-(4-(3-chloro-4-fluorophenyl)-1-(1,3-dihydroxypropan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
123′		6-(4-(4-fluorophenyl)-1-*cis*-3-hydroxycyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
124′		6-(4-(4-fluorophenyl)-1-(2-*iso*propoxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
125′		(*S*)-6-(4-(4-fluorophenyl)-1-(1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide
126′		6-(4-(4-fluorophenyl)-1-(oxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide

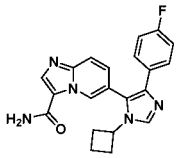
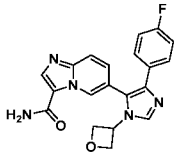
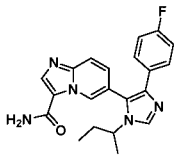
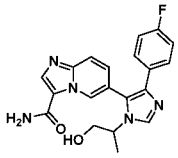
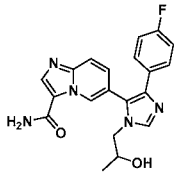
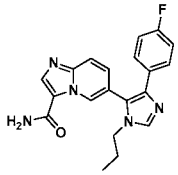
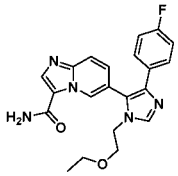
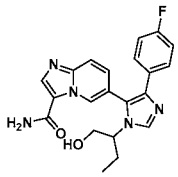
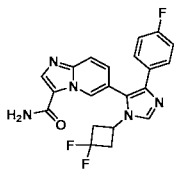
No.	Structure	Name
127′		6-(1-(3-fluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
128′		(*S*)-6-(1-(1-fluorobutan-2-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
129′		6-(1-(1,3-dihydroxypropan-2-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
130′		6-(1-(1-cyclopropyl-2-methoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
131′		6-(4-(4-fluorophenyl)-1-(3-hydroxy-3-methylbutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
132′		6-(4-(4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
133′		6-(4-(4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
134′		6-(4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
135′		6-(4-(4-fluorophenyl)-1-isopropyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide

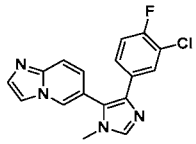
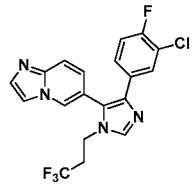
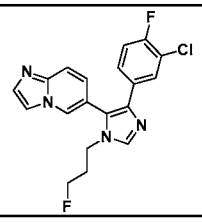
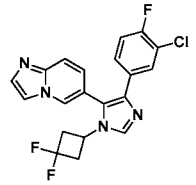
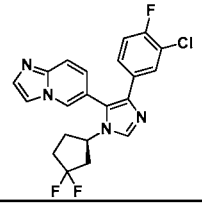
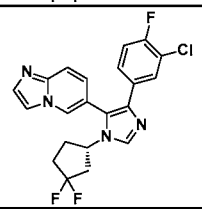
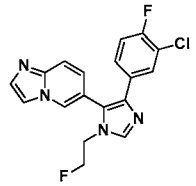
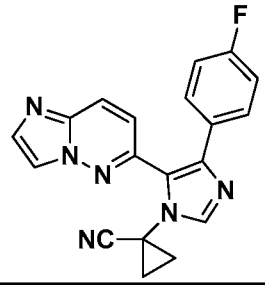
No.	Structure	Name
136′		6-(1-(bicyclo[1.1.1]pentan-1-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
137′		6-(1-(2,2-difluoropropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
138′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
139′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-hydroxy-3-methylbutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
140′		6-(4-(3-chloro-4-fluorophenyl)-1-((*1s,3s*)-3-hydroxycyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
141′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-fluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
142′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
143′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
144′		6-(4-(3-chloro-4-fluorophenyl)-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide

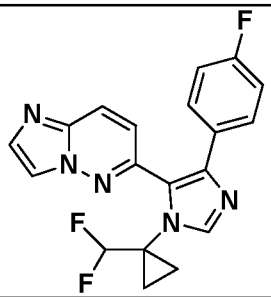
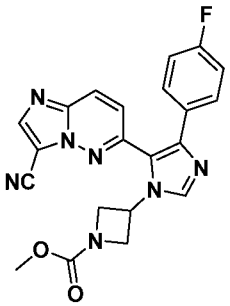
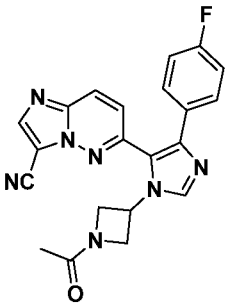
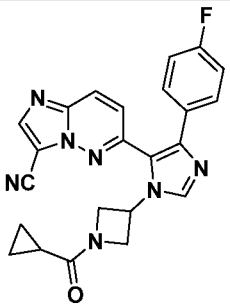
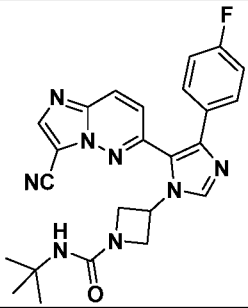
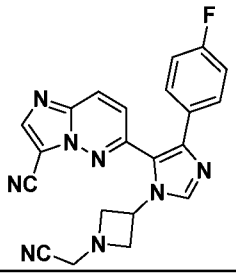
No.	Structure	Name
145′		(*S*)-6-(4-(3-chloro-4-fluorophenyl)-1-((tetrahydrofuran-2-yl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
146′		6-(4-(3-chloro-4-fluorophenyl)-1-(tetrahydrofuran-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
147′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-methoxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
148′		6-(4-(3-chloro-4-fluorophenyl)-1-isopentyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
149′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-chloropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
150′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-cyclobutylethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
151′		6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
152′		6-(4-(4-fluorophenyl)-1-(1-hydroxypropan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
153′		6-(4-(4-fluorophenyl)-1-(2-hydroxybutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

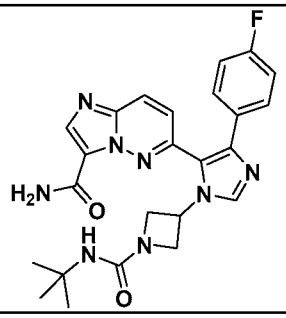
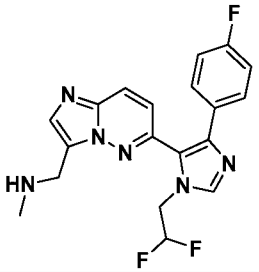
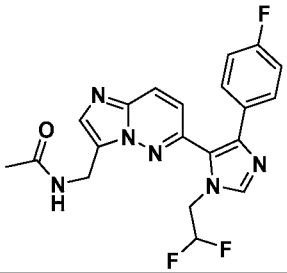
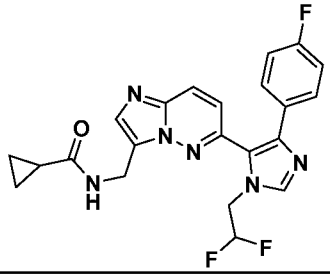
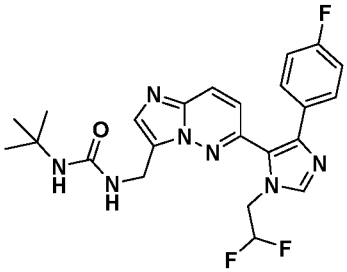
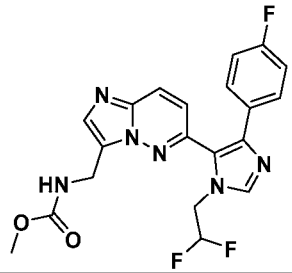
No.	Structure	Name
154′		6-(4-(4-fluorophenyl)-1-(4-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
155′		(*R*)-6-(4-(4-fluorophenyl)-1-(2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
156′		6-(4-(4-fluorophenyl)-1-(3-hydroxybutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
157′		6-(1-(cyclobutylmethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
158′		(*S*)-6-(4-(4-fluorophenyl)-1-(2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
159′		6-(1-cyclopentyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
160′		6-(1-ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
161′		(*S*)-6-(1-(2,3-dihydroxypropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
162′		6-(4-(4-fluorophenyl)-1-(3-fluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

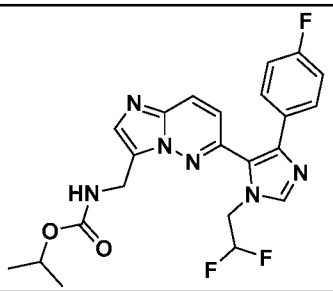
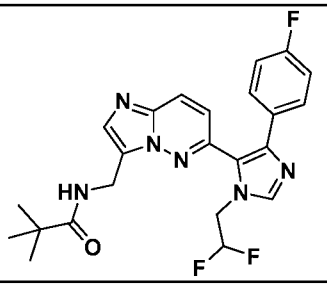
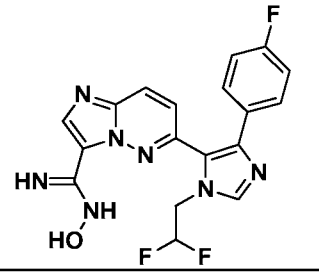
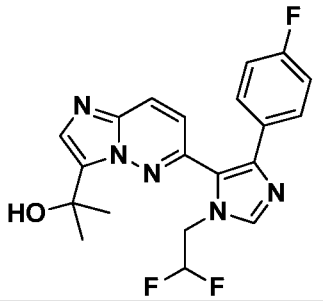
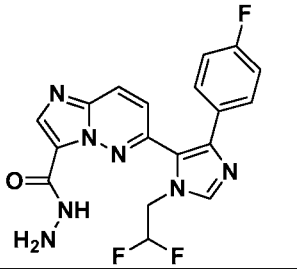
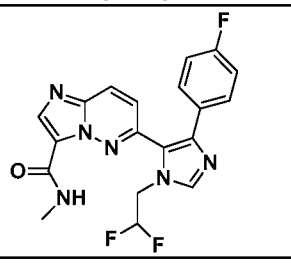
No.	Structure	Name
163′		6-(1-(3-(dimethylamino)propyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
164′		(*R*)-6-(1-(2,3-dihydroxypropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
165′		6-(4-(4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
166′		6-(4-(4-fluorophenyl)-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
167′		6-(1-(1-cyclopropylethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
168′		6-(4-(4-fluorophenyl)-1-*iso*butyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
169′		6-(4-(4-fluorophenyl)-1-(3,3,3-trifluoro-2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
170′		6-(4-(4-fluorophenyl)-1-*iso*propyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
171′		6-(1-(1,3-dihydroxypropan-2-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

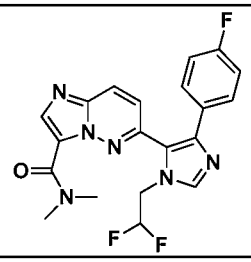
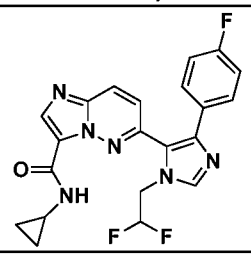
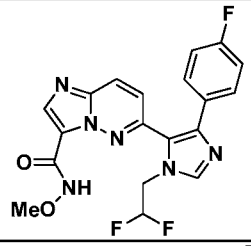
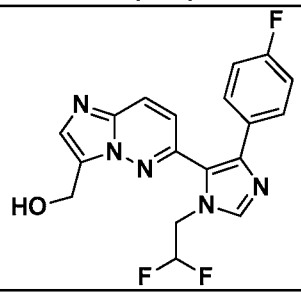
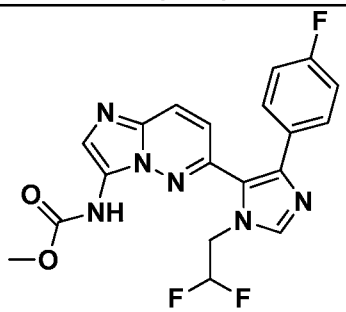
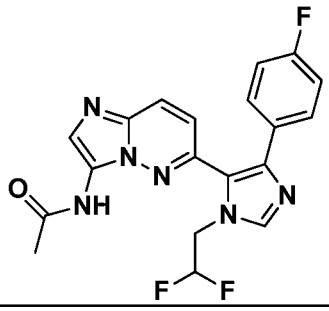
No.	Structure	Name
172′		6-(1-cyclobutyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
173′		6-(4-(4-fluorophenyl)-1-(oxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
174′		6-(1-(sec-butyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
175′		6-(4-(4-fluorophenyl)-1-(1-hydroxypropan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
176′		6-(4-(4-fluorophenyl)-1-(2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
177′		6-(4-(4-fluorophenyl)-1-propyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
178′		6-(1-(2-ethoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
179′		6-(4-(4-fluorophenyl)-1-(1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
180′		6-(1-(3,3-difluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

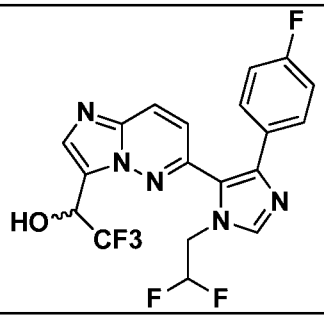
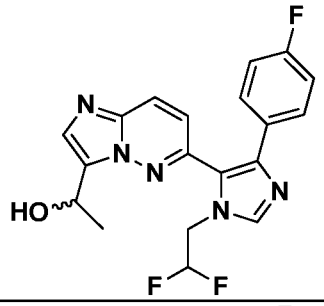
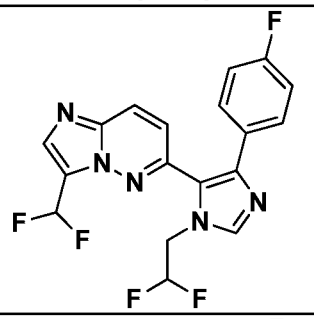
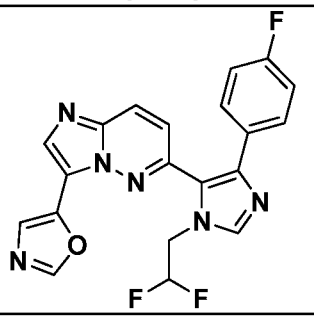
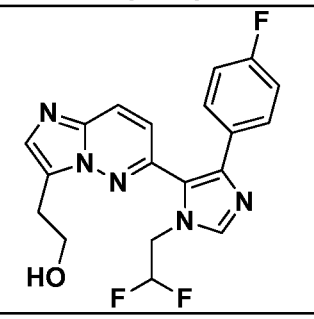
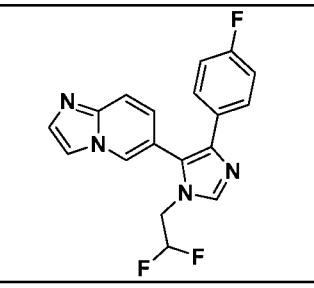
No.	Structure	Name
181′		6-(4-(3-chloro-4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
182′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3,3-trifluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
183′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-fluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
184′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
185′		(*R*)-6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclopentyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
186′		(*S*)-6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclopentyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
187′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-fluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
188′		1-(4-(4-fluorophenyl)-5-(imidazo[1,2-*b*]pyridazin-6-yl)-1*H*-imidazol-1-yl)cyclopropanecarbonitrile

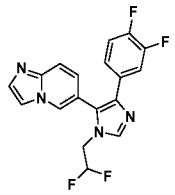
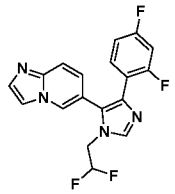
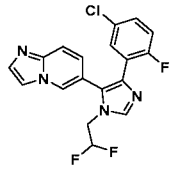
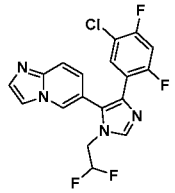
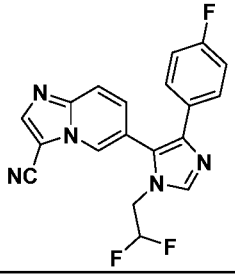
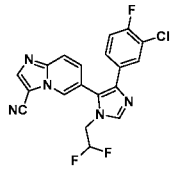
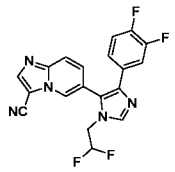
No.	Structure	Name
189′		6-(1-(1-(difluoromethyl)cyclopropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine
190′		methyl 3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-4-(4-fluorophenyl)-1*H*-imidazol-1-yl)azetidine-1-carboxylate
191′		6-(1-(1-acetylazetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
192′		6-(1-(1-(cyclopropanecarbonyl)azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
193′		*N*-(*tert*-butyl)-3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-4-(4-fluorophenyl)-1*H*-imidazol-1-yl)azetidine-1-carboxamide
194′		6-(1-(1-(cyanomethyl)azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

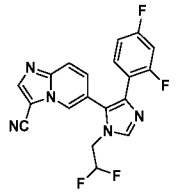
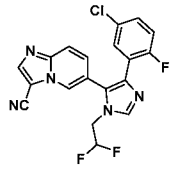
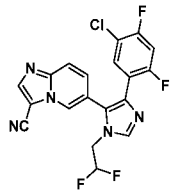
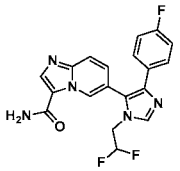
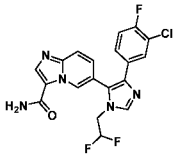
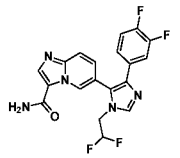
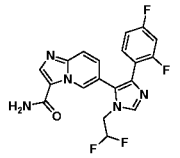
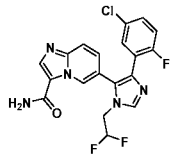
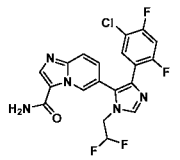
No.	Structure	Name
195′		6-(1-(1-(tert-butylcarbamoyl)azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
196′		(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methanamine
197′		*N*-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)acetamide
198′		*N*-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)cyclopropanecarboxamide
199′		1-(*tert*-butyl)-3-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)urea
200′		methyl ((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)carbamate

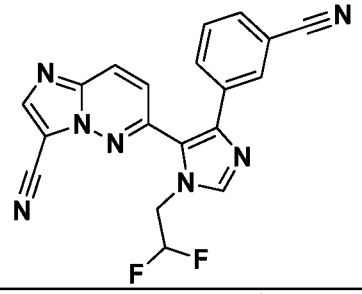
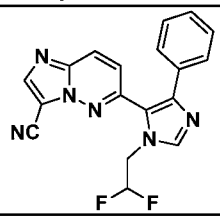
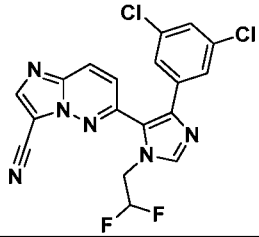
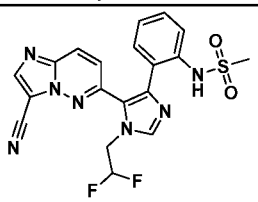
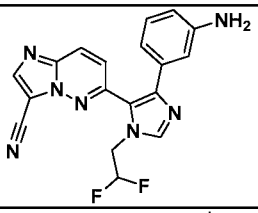
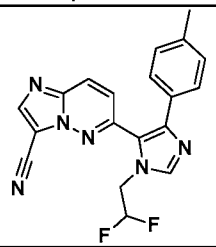
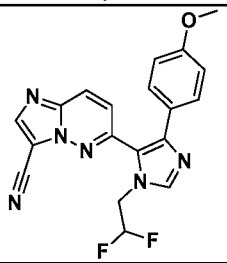
No.	Structure	Name
201′		*iso*propyl ((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)carbamate
202′		*N*-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)pivalamide
203′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-*N*-hydroxyimidazo[1,2-*b*]pyridazine-3-carboximidamide
204′		2-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)propan-2-ol
205′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbohydrazide
206′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-*N*-methylimidazo[1,2-*b*]pyridazine-3-carboxamide

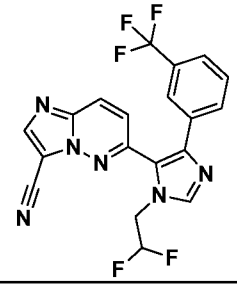
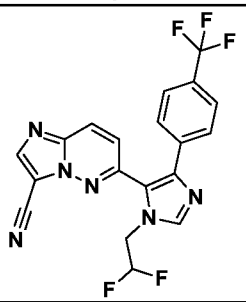
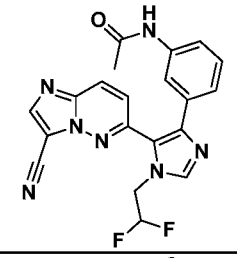
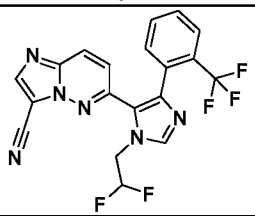
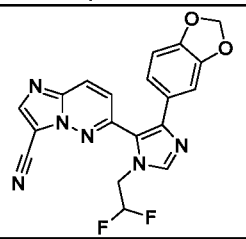
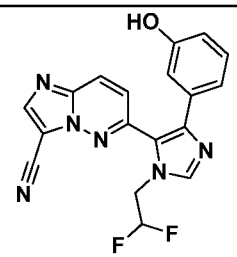
No.	Structure	Name
207′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-N,N-dimethylimidazo[1,2-*b*]pyridazine-3-carboxamide
208′		N-cyclopropyl-6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide
209′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-*N*-methoxyimidazo[1,2-*b*]pyridazine-3-carboxamide
210′		(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methanol
211′		methyl (6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)carbamate
212′		*N*-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)acetamide

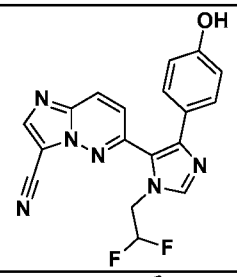
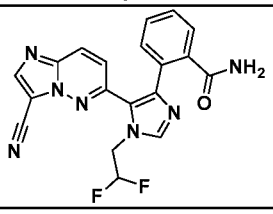
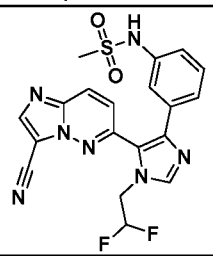
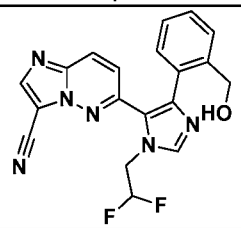
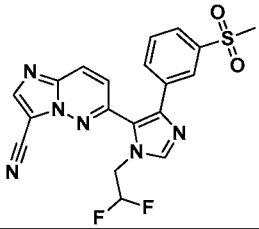
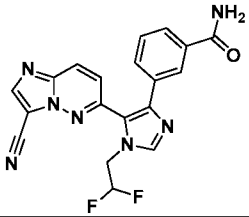
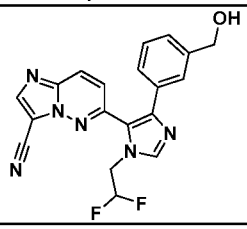
No.	Structure	Name
213′		1-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)-2,2,2-trifluoroethanol
214′		1-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)ethanol
215′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-3-(difluoromethyl) imidazo[1,2-*b*]pyridazine
216′		5-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)oxazole
217′		2-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)ethanol
218′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine

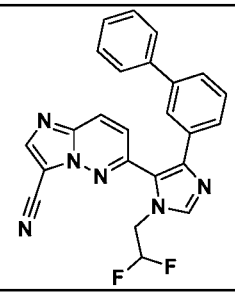
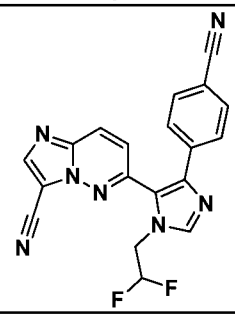
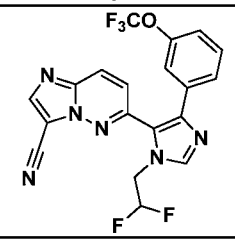
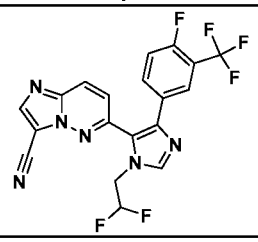
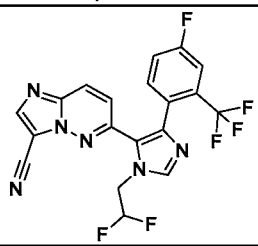
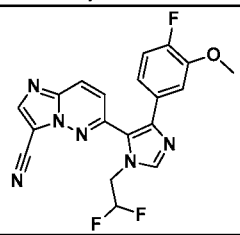
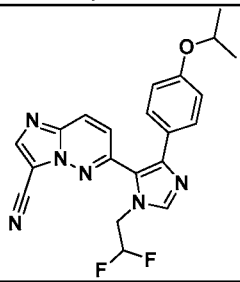
No.	Structure	Name
219′		6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
220′		6-(1-(2,2-difluoroethyl)-4-(3,4-difluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
221′		6-(1-(2,2-difluoroethyl)-4-(2,4-difluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
222′		6-(4-(5-chloro-2-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
223′		6-(4-(5-chloro-2,4-difluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
224′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
225′		6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
226′		6-(1-(2,2-difluoroethyl)-4-(3,4-difluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile

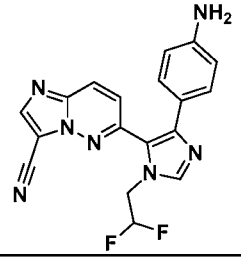
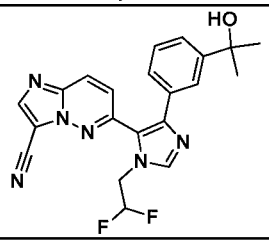
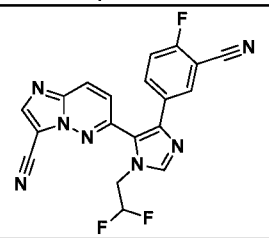
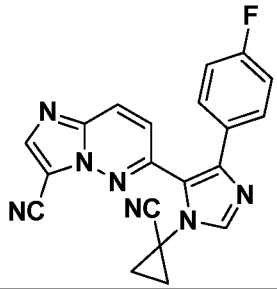
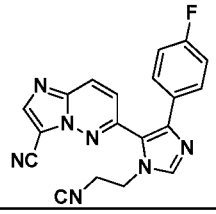
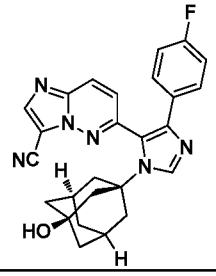
No.	Structure	Name
227′		6-(1-(2,2-difluoroethyl)-4-(2,4-difluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
228′		6-(4-(5-chloro-2-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
229′		6-(4-(5-chloro-2,4-difluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
230′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1H-imidazol-5-yl)imidazo[1,2-a]pyridine-3-carboxamide
231′		6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
232′		6-(1-(2,2-difluoroethyl)-4-(3,4-difluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
233′		6-(1-(2,2-difluoroethyl)-4-(2,4-difluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
234′		6-(4-(5-chloro-2-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
235′		6-(4-(5-chloro-2,4-difluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

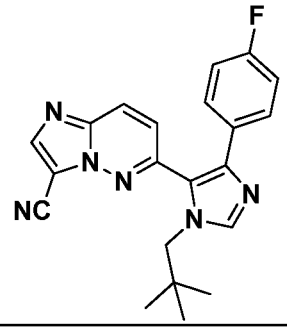
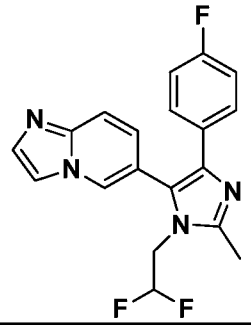
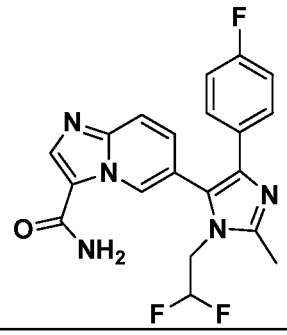
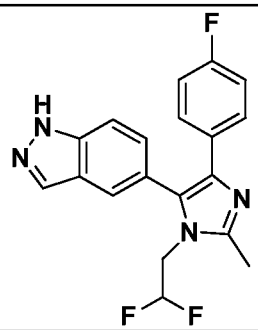
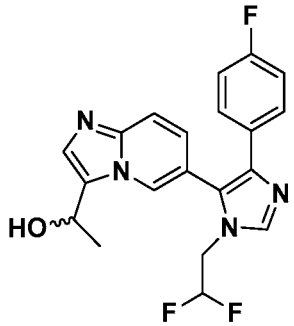
No.	Structure	Name
236		6-(4-(3-cyanophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
237′		6-(1-(2,2-difluoroethyl)-4-phenyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
238′		6-(4-(3,5-dichlorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
239′		*N*-(2-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)phenyl)methanesulfonamide
240′		6-(4-(3-aminophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
241′		6-(1-(2,2-difluoroethyl)-4-(*p*-tolyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
242′		6-(1-(2,2-difluoroethyl)-4-(4-methoxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

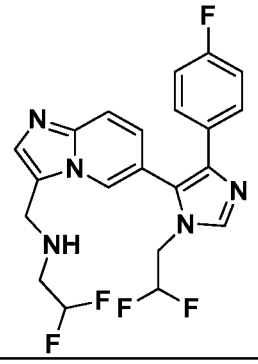
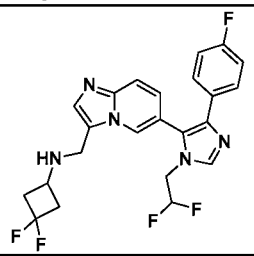
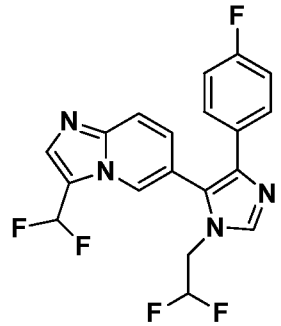
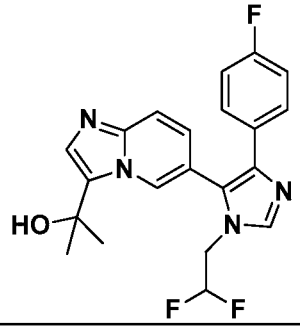
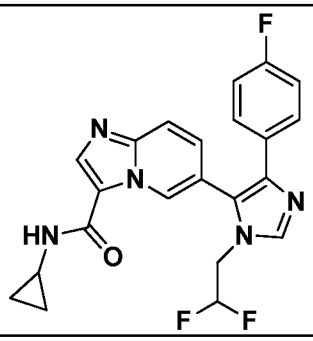
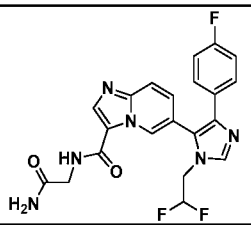
No.	Structure	Name
243′		6-(1-(2,2-difluoroethyl)-4-(3-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
244′		6-(1-(2,2-difluoroethyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
245′		*N*-(3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)phenyl)acetamide
246′		6-(1-(2,2-difluoroethyl)-4-(2-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
247′		6-(4-(benzo[*d*][1,3]dioxol-5-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
248′		6-(1-(2,2-difluoroethyl)-4-(2-hydroxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
249′		6-(1-(2,2-difluoroethyl)-4-(3-hydroxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

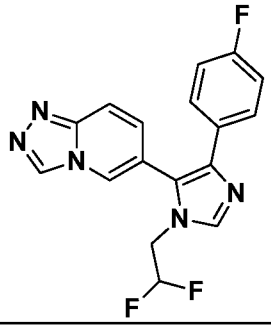
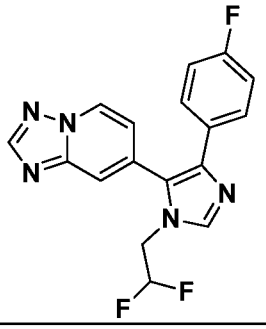
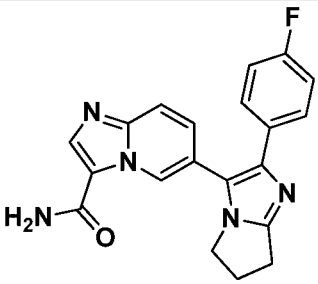
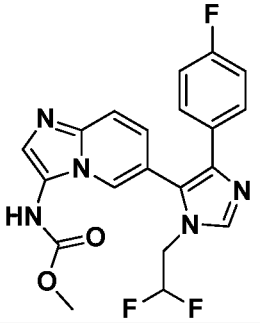
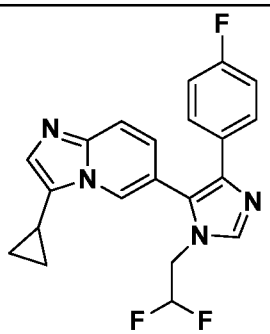
No.	Structure	Name
250′		6-(1-(2,2-difluoroethyl)-4-(4-hydroxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
251′		2-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)benzamide
252′		*N*-(3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)phenyl)methanesulfonamide
253′		6-(1-(2,2-difluoroethyl)-4-(2-(hydroxymethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
254′		6-(1-(2,2-difluoroethyl)-4-(3-(methylsulfonyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
255′		3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)benzamide
256′		6-(1-(2,2-difluoroethyl)-4-(3-(hydroxymethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

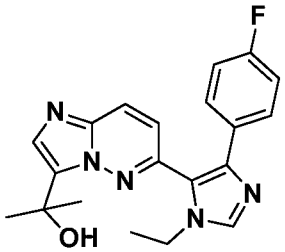
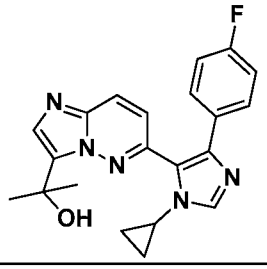
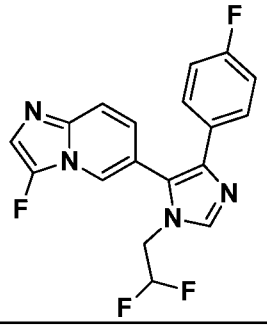
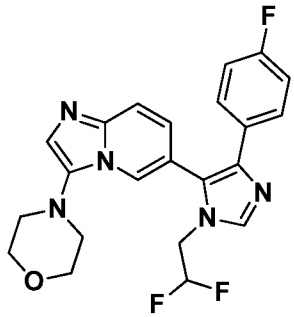
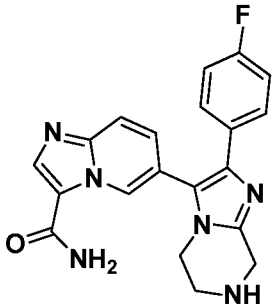
No.	Structure	Name
257′		6-(4-([1,1'-biphenyl]-3-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
258′		6-(4-(4-cyanophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
259′		6-(1-(2,2-difluoroethyl)-4-(3-(trifluoromethoxy)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
260′		6-(1-(2,2-difluoroethyl)-4-(4-fluoro-3-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
261′		6-(1-(2,2-difluoroethyl)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
262′		6-(1-(2,2-difluoroethyl)-4-(4-fluoro-3-methoxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
263′		6-(1-(2,2-difluoroethyl)-4-(4-isopropoxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

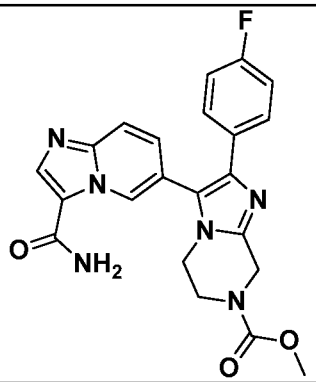
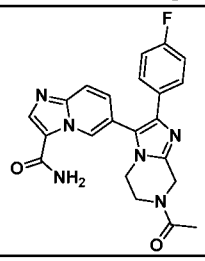
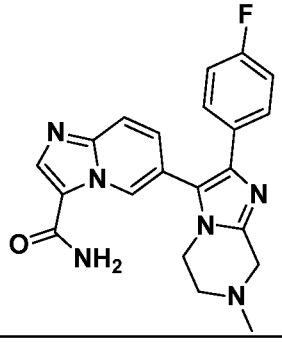
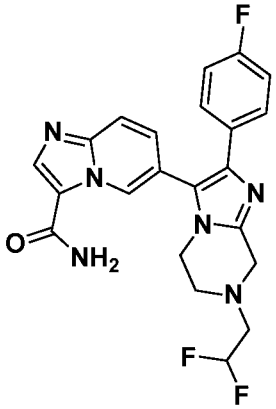
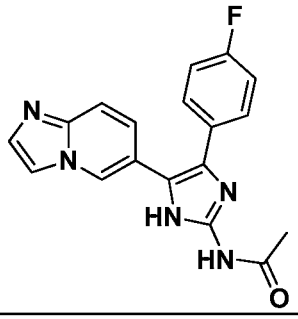
No.	Structure	Name
264′		6-(4-(4-aminophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
265′		6-(1-(2,2-difluoroethyl)-4-(3-(2-hydroxypropan-2-yl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
266′		6-(4-(3-cyano-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
267′		6-(1-(1-cyanocyclopropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
268′		6-(1-(2-cyanoethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
269′		6-(4-(4-fluorophenyl)-1-((*1r,3s,5R,7S*)-3-hydroxyadamantan-1-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

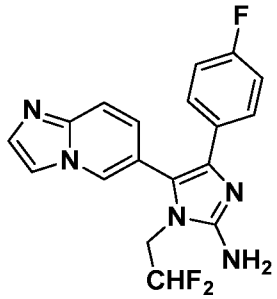
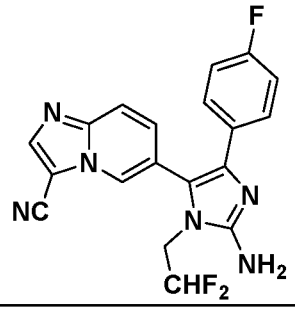
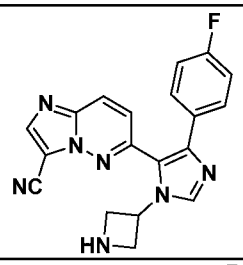
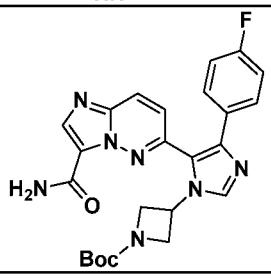
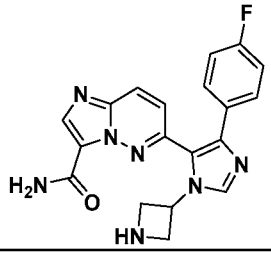
No.	Structure	Name
270′		6-(4-(4-fluorophenyl)-1-neopentyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
271′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine
272′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
273′		5-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole
274′		1-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl)ethanol

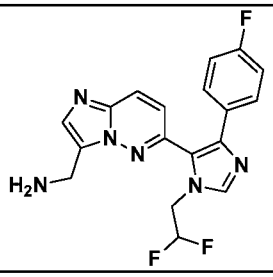
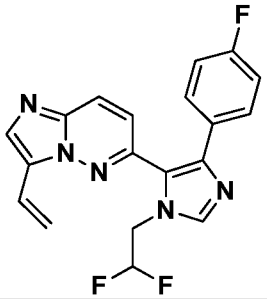
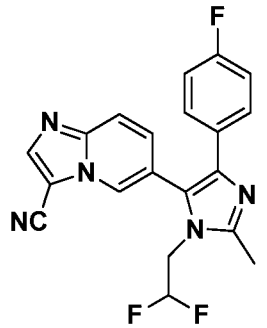
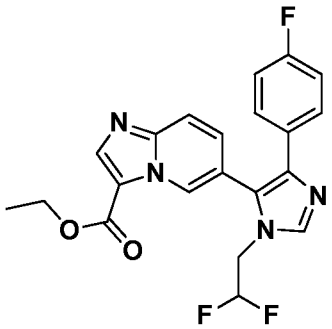
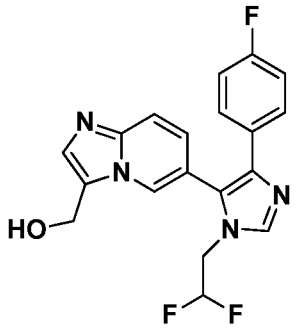
No.	Structure	Name
275′		*N*-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl)methyl)-2,2-difluoroethanamine
276′		*N*-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl)methyl)-3,3-difluorocyclobutanamine
277′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-3-(difluoromethyl)imidazo [1,2-*a*]pyridine
278′		1-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl)ethanol
279′		*N*-cyclopropyl-6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
280′		*N*-(2-amino-2-oxoethyl)-6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

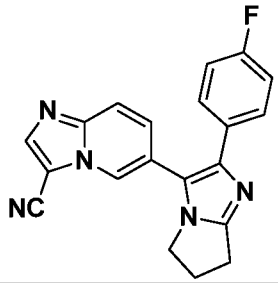
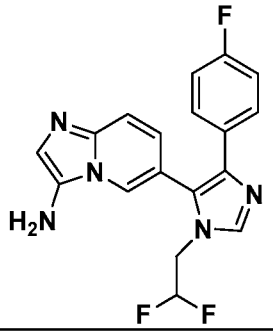
No.	Structure	Name
281′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridine
282′		7-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine
283′		6-(2-(4-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
284′		methyl (6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl)carbamate
285′		3-cyclopropyl-6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine

No.	Structure	Name
286′		2-(6-(1-ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)propan-2-ol
287′		2-(6-(1-cyclopropyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)propan-2-ol
288′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-3-fluoroimidazo[1,2-*a*]pyridine
289′		4-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl)morpholine
290′		6-(2-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

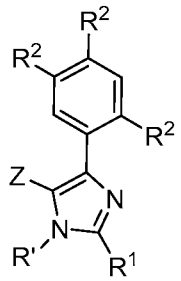
No.	Structure	Name
291′		methyl 3-(3-carbamoylimidazo[1,2-*a*]pyridin-6-yl)-2-(4-fluorophenyl)-5,6-dihydroimidazo[1,2-*a*]pyrazine-7(8*H*)-carboxylate
292′		6-(7-acetyl-2-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
293′		6-(2-(4-fluorophenyl)-7-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
294′		6-(7-(2,2-difluoroethyl)-2-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide
295′		*N*-(4-(4-fluorophenyl)-5-(imidazo[1,2-*a*]pyridin-6-yl)-1*H*-imidazol-2-yl)acetamide

No.	Structure	Name
296′		1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-5-(imidazo[1,2-*a*]pyridin-6-yl)-1*H*-imidazol-2-amine
297′		*N*-(5-(3-cyanoimidazo[1,2-*a*]pyridin-6-yl)-1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)acetamide
298′		6-(2-amino-1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
190C′		6-(1-(azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile
195A′		*tert*-butyl 3-(5-(3-carbamoylimidazo[1,2-*b*]pyridazin-6-yl)-4-(4-fluorophenyl)-1*H*-imidazol-1-yl)azetidine-1-carboxylate
195B′		6-(1-(azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide

No.	Structure	Name
196A′		(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methanamine
213E′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-3-vinylimidazo[1,2-*b*]pyridazine
272A′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
274C′		ethyl 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxylate
274D′		(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl)methanol

No.	Structure	Name
283B′		6-(2-(4-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-3-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile
284D′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-amine

[0049] In embodiment II° of this aspect, the invention comprises compounds having the structure of formula (II°):



(II°)

or a pharmaceutically acceptable salt, prodrug or *N*-oxide thereof, or solvate or hydrate thereof,

wherein

R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_{12}alkyl)-Cak or -(C_0-C_6alkyl)-Hca, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, C_1-C_6alkyl-OR^{S0}, -OR^{S0}, -R^{S0} or cyano;

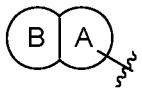
wherein each R^{S0} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

R^1 is hydrogen or C_1-C_6alkyl;

or R′ and R^1 combined with the atoms to which they are attached form a five- to eight-membered Hca;

each R^2 is independently hydrogen, halogen, -C_1-C_6alkyl, -C_1-C_6alkyl-OR^{S2} or -OR^{S2};

Z is

a fused bicyclic ring of the formula, 

, wherein

ring A is 6-membered Het, and

ring B is a 5-membered Het; and

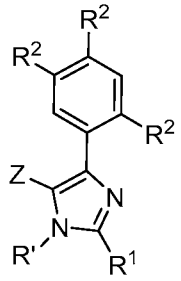
Z is optionally substituted by one or two -R^Z groups that are each independently halogen, cyano, C_{1-6}alkyl, C_{1-6}alkenyl, C_{1-6}haloalkyl, -C_1-C_6alkoxy, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Hca, -OR^{S3}, -SR^{S3}, -$NR^{S3}{}_2$, -$C(O)R^{S3}$, -$C(O)OR^{S3}$, -$C(O)NR^{S3}{}_2$, -$C(NR^{S3})NR^{S3}OR^{S3}$, -$S(O)_2NR^{S3}{}_2$, -$S(O)_2R^{S3}$, -$OC(O)R^{S3}$, -$N(R^{S3})C(O)R^{S3}$, -$OC(O)OR^{S3}$, -$OC(O)NR^{S3}{}_2$, -$N(R^{S3})C(O)OR^{S3}$, -$N(R^{S3})C(O)NR^{S3}{}_2$, -$N(R^{S3f})S(O)_2R^{S3}$, -$OP(O)(OR^{S3})_2$ or -CH_2-$OP(O)(OR^{S3})$, wherein each alkyl, haloalkyl and alkoxy is optionally substituted by one or two -R^{Z2} groups;

wherein each R^{S3} is independently hydrogen, -$NR^{S3}{}_2$, -OR^{S3}, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -$C(O)NR^{S4}{}_2$ or cyano; and

each -R^{Z2} is independently halogen, cyano, C_{1-6}alkyl, C_{1-6}haloalkyl, -C_1-C_6alkoxy, -OR^{S4}, -SR^{S4}, -$NR^{S4}{}_2$, -$C(O)R^{S4}$, -$C(O)OR^{S4}$, -$C(O)NR^{S4}{}_2$, -$S(O)_2NR^{S4}{}_2$, -$S(O)_2R^{S4}$, -$OC(O)R^{S4}$, -$N(R^{S4})C(O)R^{S4}$, -$OC(O)OR^{S4}$, -$OC(O)NR^{S4}{}_2$, -$N(R^{S4})C(O)OR^{S4}$, -$N(R^{S4})C(O)NR^{S4}{}_2$, -$N(R^{S4})S(O)_2R^{S4}$, -$OP(O)(OR^{S4})_2$ or -CH_2-$OP(O)(OR^{S4})$; and

wherein each R^{S4} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with one or two C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

[0050] In embodiment II_1 of this aspect, the invention comprises compounds having the structure of formula (II):



(II)

or a pharmaceutically acceptable salt, prodrug or *N*-oxide thereof, or solvate or hydrate thereof,

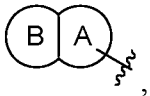
wherein

R′ is hydrogen or C_1-C_6alkyl;

R^1 is hydrogen or C_1-C_6alkyl;

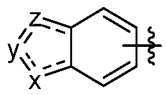
each R^2 is independently hydrogen, halogen or -C_1-C_6alkyl;

Z is

(a) a fused bicyclic ring of the formula,  , wherein

ring A is 6-membered Het, and

ring B is a 5-membered Het; or

(b) 

wherein

z is CH, O, S or N;

y is CH, CH_2, or N; and

x is CH, O, S, N(R^a);

provided that when z is N and x is N(R^a), y is not N;

wherein R^a is hydrogen or -C_1-C_6alkyl.

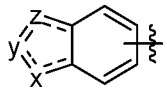
[0051] In embodiment II_2 of this aspect, the invention comprises compounds of embodiment II_1, wherein

Z is a fused bicyclic ring of the formula,  , wherein

ring A is 6-membered Het, and

ring B is a 5-membered Het.

[0052] In embodiment II_3 of this aspect, the invention comprises compounds of embodiment II_1, wherein

Z is a 

wherein

z is CH, O, S or N;

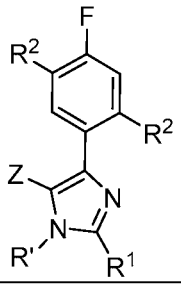
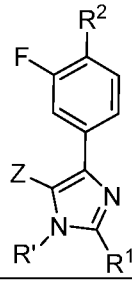
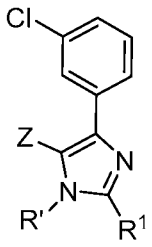
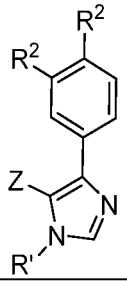
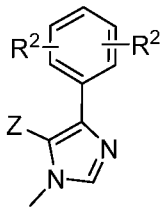
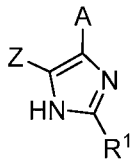
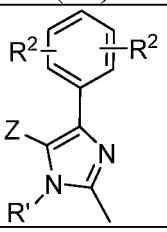
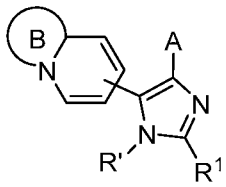
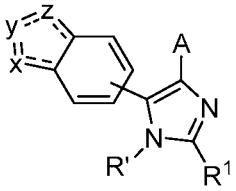
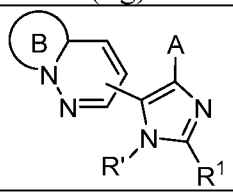
y is CH, CH_2, or N; and

x is CH, O, S, N(R^a);

wherein R^a is hydrogen or -C_1-C_6alkyl;

provided that when z is N and x is N(R^a), y is not N.

[0053] In embodiment II_4, the compounds of the invention are one of formulae (IIa) – (IIj):

		
(IIa)	(IIb)	(IIc)
		
(IId)	(IIe)	(IIf)
		
(IIg)	(IIh)	(IIi)
		
(IIj)		

wherein A, R^1, R^2, R′ and Z are as defined in embodiments II° and II_1 - II_3 above.

[0054] Particular embodiments of this aspect of the invention comprise compounds of any one of the formulae (II°), (II), and (IIa) – (IIj), each as defined in each of the following

rows (or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, or a solvate or hydrate thereof), wherein each entry is a group number as defined above (*e.g.*, **(4z)** refers to R^1 is methyl), and a dash "-" indicates that the variable is as defined in embodiment I_1 or defined according to any one of the applicable variable definitions **(1a)-(1ddd), (2a)-(2ccc), (3a)-(3kk)** and **(4a)-(4gg)** [*e.g.*, when R^1 is a dash, it can be either as defined in any of embodiments II_1 - II_4 or any one of the applicable definitions (**4a**)-(**4gg**)]:

	(II)	A	Z	R′	R^1
(2)-1	(IIa)	(1a)	(2a)	(3a)	(4a)
(2)-2	(IIb)	(1c)	(2b)	(3i)	(4f)
(2)-3	(IIc)	(1d)	(2g)	(3j)	(4j)
(2)-4	(IId)	(1e)	(2i)	(3k)	(4l)
(2)-5	(IIe)	(1h)	(2a)	(3l)	(4r)
(2)-6	(IIf)	(1k)	(2q)	(3m)	(4u)
(2)-7	(IIg)	(1l)	(2r)	(3n)	(4v)
(2)-8	(IIh)	(1n)	(2t)	(3o)	(4x)
(2)-9	(IIi)	(1s)	(2x)	(3p)	(4y)
(2)-10	(IIf)	(1gg)	(2y)	(3i)	(4z)
(2)-11	(IIb)	(1jj)	(2aa)	(3j)	(4r)
(2)-12	(IIc)	(1kk)	(2ff)	(3k)	(4u)
(2)-13	(IId)	(1ll)	(2qq)	(3l)	(4v)
(2)-14	(IIf)	(1mm)	(2tt)	(3j)	(4v)
(2)-15	(IIb)	(1ss)	(2vv)	(3k)	(4a)
(2)-16	(IIc)	(1tt)	(2g)	(3l)	(4f)
(2)-17	(IId)	(1uu)	(2i)	(3m)	(4j)
(2)-18	(IIc)	(1xx)	(2a)	(3n)	(4l)
(2)-19	(IId)	(1aaa)	(2q)	(3o)	(4r)
(2)-20	(IIe)	(1bbb)	(2ff)	(3p)	(4u)
(2)-21	(IIf)	(1ccc)	(2qq)	(3n)	(4v)
(2)-22	(IIg)	(1aaa)	(2qq)	(3o)	(4x)
(2)-23	(IIh)	(1bbb)	(2ff)	(3p)	(4y)
(2)-24	(IIi)	(1ccc)	(2qq)	(3n)	(4z)

	(II)	A	Z	R′	R^1
(2)-25	(IIf)	(1uu)	(2i)	(3o)	(4r)
(2)-26	(IIb)	(1xx)	(2a)	(3p)	(4u)
(2)-27	(IIc)	(1s)	(2q)	(3j)	(4v)
(2)-28	(IId)	(1gg)	(2ff)	(3k)	(4j)
(2)-29	(IIc)	(1d)	(2qq)	(3l)	(4l)
(2)-30	(IId)	(1a)	(2b)	(3m)	(4j)
(2)-31	(IIb)	(1c)	(2g)	(3n)	(4l)
(2)-32	(IIc)	(1d)	(2i)	(3o)	(4r)
(2)-33	(IId)	(1s)	(2a)	(3p)	(4r)
(2)-34	(IIe)	(1bbb)	(2q)	(3n)	(4j)
(2)-35	(IIf)	(1ccc)	(2r)	(3o)	(4l)
(2)-36	(IIg)	(1d)	(2t)	(3p)	(4r)
(2)-37	(IIh)	(1e)	(2x)	(3j)	(4f)
(2)-38	(IIi)	(1h)	(2y)	(3k)	(4j)
(2)-39	(IIc)	(1k)	(2aa)	(3l)	(4l)
(2)-40	(IId)	(1l)	(2ff)	(3a)	(4l)
(2)-41	(IIb)	(1n)	(2vv)	(3i)	(4r)
(2)-42	(IIc)	(1s)	(2g)	(3j)	(4f)
(2)-43	(IId)	(1gg)	(2i)	(3k)	(4j)
(2)-44	(IIc)	(1jj)	(2a)	(3l)	(4l)
(2)-45	(IId)	(1kk)	(2q)	(3m)	(4r)
(2)-46	(IIb)	(1ll)	(2a)	(3n)	(4a)
(2)-47	(IIc)	(1mm)	(2b)	(3o)	(4f)
(2)-48	(IId)	(1ss)	(2g)	(3p)	(4j)

	(II)	A	Z	R′	R^1
(2)-49	(IIe)	(1tt)	(2i)	(3n)	(4l)
(2)-50	(IIf)	(1uu)	(2a)	(3j)	(4r)
(2)-51	(IIg)	(1xx)	(2q)	(3k)	(4u)
(2)-52	(IIh)	(1aaa)	(2r)	(3l)	(4v)
(2)-53	(IIi)	(1bbb)	(2t)	(3m)	(4x)
(2)-54	(IIf)	(1ccc)	(2x)	(3i)	(4y)
(2)-55	(IIb)	(1l)	(2y)	(3j)	(4z)
(2)-56	(IIc)	(1n)	(2aa)	(3k)	(4r)
(2)-57	(IId)	(1s)	(2ff)	(3l)	(4u)
(2)-58	(IIc)	(1a)	(2qq)	(3m)	(4v)
(2)-59	(IId)	(1c)	(2tt)	(3n)	(4r)
(2)-60	(IIb)	(1d)	(2vv)	(3o)	(4u)
(2)-61	(IIc)	(1e)	(2r)	(3p)	(4v)
(2)-62	(IId)	(1h)	(2t)	(3j)	(4j)
(2)-63	(IIe)	(1k)	(2x)	(3k)	(4l)
(2)-64	(IIf)	(1l)	(2y)	(3l)	(4r)
(2)-65	(IIg)	(1n)	(2aa)	(3m)	(4f)
(2)-66	(IIh)	(1s)	(2ff)	(3l)	(4j)
(2)-67	(IIi)	(1gg)	(2qq)	(3a)	(4l)
(2)-68	(IIf)	(1jj)	(2tt)	(3i)	(4v)
(2)-69	(IIb)	(1kk)	(2vv)	(3j)	(4a)
(2)-70	(IIc)	(1ll)	(2ff)	(3i)	(4f)
(2)-71	(IId)	(1mm)	(2qq)	(3j)	(4j)
(2)-72	(IIg)	(1ss)	(2i)	(3k)	(4l)
(2)-73	(IIh)	(1tt)	(2a)	(3l)	(4r)
(2)-74	(IIi)	(1uu)	(2q)	(3m)	(4a)
(2)-75	(IIc)	(1xx)	(2b)	(3n)	(4f)
(2)-76	(IId)	(1aaa)	(2g)	(3o)	(4j)
(2)-77	(IIe)	(1bbb)	(2i)	(3p)	(4l)
(2)-78	(IIf)	(1ccc)	(2a)	(3i)	(4a)

	(II)	A	Z	R′	R^1
(2)-79	(IIg)	(1n)	(2q)	(3j)	(4f)
(2)-80	(IIh)	(1s)	(2r)	(3k)	(4j)
(2)-81	(IIi)	(1gg)	(2t)	(3j)	(4l)
(2)-82	(IIf)	(1aaa)	(2x)	(3k)	(4r)
(2)-83	(IIb)	(1bbb)	(2y)	(3l)	(4u)
(2)-84	(IIc)	(1ccc)	(2aa)	(3m)	(4v)
(2)-85	(IId)	(1l)	(2ff)	(3k)	(4x)
(2)-86	(IIf)	(1n)	(2qq)	(3l)	(4y)
(2)-87	(IIb)	(1s)	(2tt)	(3a)	(4z)
(2)-88	(IIc)	(1d)	(2vv)	(3i)	(4r)
(2)-89	(IId)	(1e)	(2vv)	(3j)	(4u)
(2)-90	(IId)	(1h)	(2g)	(3k)	(4v)
(2)-91	(IIe)	(1k)	(2i)	(3l)	(4j)
(2)-92	(IIf)	(1l)	(2a)	(3m)	(4l)
(2)-93	(IIg)	(1n)	(2q)	(3n)	(4a)
(2)-94	(IIh)	(1s)	(2i)	(3o)	(4f)
(2)-95	(IIi)	(1gg)	(2a)	(3p)	(4l)
(2)-96	(IIf)	(1jj)	(2q)	(3a)	(4r)
(2)-97	(IIb)	(1kk)	(2r)	(3i)	(4u)
(2)-98	(IIc)	(1ll)	(2t)	(3j)	(4v)
(2)-99	(IId)	(1mm)	(2x)	(3i)	(4x)
(2)-100	(IIf)	(1ss)	(2y)	(3j)	(4y)
(2)-101	(IIb)	(1tt)	(2aa)	(3i)	(4z)
(2)-102	(IIc)	(1uu)	(2ff)	(3j)	(4r)
(2)-103	(IId)	(1xx)	(2qq)	(3k)	(4a)
(2)-104	(IId)	(1aaa)	(2tt)	(3l)	(4f)
(2)-105	(IIe)	(1bbb)	(2vv)	(3a)	(4j)
(2)-106	(IIf)	(1ccc)	(2r)	(3i)	(4l)
(2)-107	(IIg)	(1h)	(2vv)	(3j)	(4r)
(2)-108	(IIh)	(1k)	(2g)	(3j)	(4u)

	(II)	A	Z	R′	R^1
(2)-109	(IIi)	(1l)	(2i)	(3k)	(4v)
(2)-110	(IIi)	(1n)	(2a)	(3l)	(4x)
(2)-111	(IIf)	(1s)	(2q)	(3a)	(4y)
(2)-112	(IIb)	(1gg)	(2qq)	(3i)	(4z)
(2)-113	(IIc)	(1jj)	(2tt)	(3j)	(4j)
(2)-114	(IId)	(1kk)	(2vv)	(3j)	(4l)
(2)-115	(IId)	(1ll)	(2ff)	(3k)	(4a)
(2)-116	(IIe)	(1mm)	(2qq)	(3l)	(4f)
(2)-117	(IIf)	(1ss)	(2i)	(3m)	(4v)
(2)-118	(IIg)	(1tt)	(2a)	(3k)	(4j)
(2)-119	(IIh)	(1uu)	(2q)	(3l)	(4l)
(2)-120	(IIi)	(1xx)	(2ff)	(3m)	(4a)
(2)-121	(IIf)	(1aaa)	(2qq)	(3n)	(4f)
(2)-122	(IIb)	(1bbb)	(2b)	(3o)	(4l)
(2)-123	(IIc)	(1ccc)	(2g)	(3p)	(4r)
(2)-124	(IId)	(1l)	(2i)	(3i)	(4u)
(2)-125	(IIb)	(1n)	(2a)	(3j)	(4v)
(2)-126	(IIc)	(1s)	(2q)	(3k)	(4x)
(2)-127	(IId)	(1d)	(2r)	(3l)	(4y)
(2)-128	(IIe)	(1e)	(2t)	(3a)	(4z)
(2)-129	(IIf)	(1h)	(2x)	(3i)	(4j)
(2)-130	(IIg)	(1k)	(2y)	(3j)	(4l)
(2)-131	(IIh)	(1n)	(2aa)	(3k)	(4a)
(2)-132	(IIi)	(1s)	(2ff)	(3l)	(4f)
(2)-133	(IIf)	(1gg)	(2qq)	(3m)	(4v)
(2)-134	(IIb)	(1gg)	(2tt)	(3n)	(4j)
(2)-135	(IIc)	(1jj)	(2vv)	(3o)	(4l)
(2)-136	(IId)	(1kk)	(2g)	(3p)	(4a)
(2)-137	(IIf)	(1ll)	(2i)	(3a)	(4f)
(2)-138	(IIb)	(1mm)	(2a)	(3i)	(4j)

	(II)	A	Z	R′	R^1
(2)-139	(IIc)	(1ss)	(2q)	(3j)	(4l)
(2)-140	(IId)	(1tt)	(2b)	(3a)	(4r)
(2)-141	(IId)	(1uu)	(2g)	(3i)	(4u)
(2)-142	(IIe)	(1xx)	(2i)	(3j)	(4v)
(2)-143	(IIf)	(1aaa)	(2a)	(3i)	(4x)
(2)-144	(IIg)	(1bbb)	(2q)	(3j)	(4y)
(2)-145	(IIh)	(1ccc)	(2r)	(3k)	(4z)
(2)-146	(IIi)	(1l)	(2t)	(3l)	(4j)
(2)-147	(IIf)	(1n)	(2x)	(3m)	(4l)
(2)-148	(IIb)	(1s)	(2y)	(3n)	(4a)
(2)-149	(IIc)	(1n)	(2aa)	(3o)	(4f)
(2)-150	(IId)	(1s)	(2ff)	(3p)	(4a)
(2)-151	(IIb)	(1n)	(2qq)	(3i)	(4f)
(2)-152	(IIc)	(1s)	(2tt)	(3j)	(4u)
(2)-153	(IId)	(1gg)	(2vv)	(3k)	(4v)
(2)-154	(IIe)	(1c)	(2vv)	(3l)	(4j)
(2)-155	(IIf)	(1d)	(2g)	(3i)	(4l)
(2)-156	(IIg)	(1e)	(2i)	(3j)	(4a)
(2)-157	(IIh)	(1h)	(2a)	(3k)	(4f)
(2)-158	(IIi)	(1k)	(2q)	(3l)	(4u)
(2)-159	(IId)	(1l)	(2g)	(3m)	(4v)
(2)-160	(IIe)	(1n)	(2i)	(3n)	(4j)
(2)-161	(IIf)	(1s)	(2a)	(3o)	(4l)
(2)-162	(IIg)	(1gg)	(2q)	(3p)	(4a)
(2)-163	(IIh)	(1jj)	(2g)	(3a)	(4f)
(2)-164	(IIi)	(1kk)	(2i)	(3i)	(4j)
(2)-165	(IIf)	(1ll)	(2a)	(3j)	(4l)
(2)-166	(IIb)	(1mm)	(2q)	(3a)	(4r)
(2)-167	(IIc)	(1ss)	(2r)	(3i)	(4u)
(2)-168	(IId)	(1tt)	(2t)	(3j)	(4v)

	(II)	A	Z	R′	R^1
(2)-169	(IIb)	(1uu)	(2x)	(3k)	(4x)
(2)-170	(IIc)	(1xx)	(2y)	(3l)	(4y)
(2)-171	(IId)	(1aaa)	(2aa)	(3m)	(4z)
(2)-172	(IIe)	(1bbb)	(2ff)	(3n)	(4j)
(2)-173	(IIf)	(1ccc)	(2qq)	(3o)	(4l)
(2)-174	(IIg)	(1n)	(2tt)	(3p)	(4a)
(2)-175	(IIh)	(1s)	(2vv)	(3a)	(4f)
(2)-176	(IIi)	(1gg)	(2g)	(3i)	(4r)
(2)-177	(IId)	(1e)	(2i)	(3j)	(4u)
(2)-178	(IIe)	(1h)	(2a)	(3k)	(4j)
(2)-179	(IIf)	(1k)	(2q)	(3l)	(4l)
(2)-180	(IIb)	(1l)	(2a)	(3a)	(4r)
(2)-181	(IIc)	(1n)	(2b)	(3i)	(4f)
(2)-182	(IId)	(1s)	(2g)	(3j)	(4r)
(2)-183	(IIe)	(1gg)	(2i)	(3k)	(4u)
(2)-184	(IIf)	(1jj)	(2a)	(3l)	(4v)
(2)-185	(IIg)	(1kk)	(2q)	(3m)	(4u)
(2)-186	(IIh)	(1ll)	(2r)	(3n)	(4v)
(2)-187	(IIi)	(1mm)	(2t)	(3o)	(4x)
(2)-188	(IIf)	(1ss)	(2x)	(3p)	(4y)
(2)-189	(IIb)	(1tt)	(2y)	(3i)	(4z)
(2)-190	(IIc)	(1uu)	(2aa)	(3j)	(4r)
(2)-191	(IId)	(1xx)	(2ff)	(3k)	(4u)
(2)-192	(IIg)	(1aaa)	(2qq)	(3l)	(4v)
(2)-193	(IIh)	(1tt)	(2tt)	(3i)	(4j)
(2)-194	(IIi)	(1uu)	(2vv)	(3j)	(4l)
(2)-195	(IIb)	(1xx)	(2vv)	(3k)	(4a)
(2)-196	(IIc)	(1l)	(2y)	(3l)	(4f)
(2)-197	(IId)	(1n)	(2aa)	(3m)	(4f)
(2)-198	(IIe)	(1s)	(2ff)	(3n)	(4j)

	(II)	A	Z	R′	R^1
(2)-199	(IIf)	(1n)	(2g)	(3o)	(4l)
(2)-200	(IIg)	(1s)	(2i)	(3p)	(4r)
(2)-201	(IIh)	(1gg)	(2a)	(3a)	(4u)
(2)-202	(IIi)	(1d)	(2q)	(3i)	(4v)
(2)-203	(IId)	(1a)	(2a)	(3j)	(4x)
(2)-204	(IIe)	(1c)	(2b)	(3n)	(4y)
(2)-205	(IIf)	(1d)	(2g)	(3o)	(4z)
(2)-206	(IIb)	(1e)	(2i)	(3p)	(4j)
(2)-207	(IIc)	(1h)	(2a)	(3k)	(4l)
(2)-208	(IId)	(1k)	(2q)	(3l)	(4r)
(2)-209	(IIe)	(1l)	(2r)	(3a)	(4u)
(2)-210	(IIf)	(1n)	(2t)	(3i)	(4v)
(2)-211	(IIg)	(1n)	(2x)	(3j)	(4x)
(2)-212	(IIh)	(1s)	(2y)	(3k)	(4y)
(2)-213	(IIi)	(1gg)	(2aa)	(3l)	(4z)
(2)-214	(IId)	(1kk)	(2ff)	(3m)	(4j)
(2)-215	(IIe)	(1ll)	(2qq)	(3n)	(4l)
(2)-216	(IIf)	(1mm)	(2tt)	(3o)	(4a)
(2)-217	(IIa)	(1ss)	(2vv)	(3p)	(4f)
(2)-218	(IIb)	(1tt)	(2ff)	(3n)	(4v)
(2)-219	(IIc)	(1uu)	(2qq)	(3o)	(4a)
(2)-220	(IId)	(1xx)	(2i)	(3p)	(4f)
(2)-221	(IIa)	(1aaa)	(2a)	(3a)	(4j)
(2)-222	(IIb)	(1bbb)	(2q)	(3i)	(4l)
(2)-223	(IIc)	(1ccc)	(2ff)	(3j)	(4r)
(2)-224	(IId)	(1tt)	(2qq)	(3k)	(4u)
(2)-225	(IIe)	(1uu)	(2vv)	(3l)	(4v)
(2)-226	(IIf)	(1xx)	(2g)	(3m)	(4x)
(2)-227	(IIg)	(1gg)	(2i)	(3a)	(4y)
(2)-228	(IIh)	(1c)	(2a)	(3i)	(4z)

	(II)	A	Z	R′	R^1
(2)-229	(IIi)	(1d)	(2q)	(3j)	(4j)
(2)-230	(IIg)	(1e)	(2i)	(3k)	(4l)
(2)-231	(IIh)	(1n)	(2a)	(3l)	(4r)
(2)-232	(IIi)	(1s)	(2q)	(3m)	(4j)
(2)-233	(IIf)	(1gg)	(2r)	(3n)	(4l)
(2)-234	(IIa)	(1d)	(2vv)	(3o)	(4r)
(2)-235	(IIb)	(1s)	(2g)	(3p)	(4u)
(2)-236	(IIc)	(1gg)	(2i)	(3a)	(4v)
(2)-237	(IId)	(1jj)	(2a)	(3i)	(4x)
(2)-238	(IIe)	(1kk)	(2q)	(3j)	(4y)
(2)-239	(IIf)	(1n)	(2qq)	(3k)	(4z)
(2)-240	(IIg)	(1s)	(2tt)	(3l)	(4j)
(2)-241	(IIg)	(1gg)	(2vv)	(3m)	(4l)
(2)-242	(IIh)	(1tt)	(2vv)	(3n)	(4r)
(2)-243	(IIi)	(1uu)	(2y)	(3o)	(4u)
(2)-244	(IId)	(1xx)	(2aa)	(3j)	(4v)
(2)-245	(IIe)	(1aaa)	(2ff)	(3k)	(4x)
(2)-246	(IIf)	(1bbb)	(2i)	(3l)	(4y)
(2)-247	(IIg)	(1ccc)	(2a)	(3m)	(4z)
(2)-248	(IIh)	(1tt)	(2q)	(3p)	(4a)
(2)-249	(IIi)	(1uu)	(2r)	(3n)	(4f)
(2)-250	(IIg)	(1xx)	(2vv)	(3o)	(4j)
(2)-251	(IIh)	(1n)	(2g)	(3j)	(4l)
(2)-252	(IIi)	(1s)	(2i)	(3k)	(4r)
(2)-253	(IId)	(1gg)	(2a)	(3l)	(4u)
(2)-254	(IIe)	(1c)	(2q)	(3m)	(4v)
(2)-255	(IIf)	(1d)	(2qq)	(3p)	(4x)
(2)-256	(IId)	(1e)	(2tt)	(3j)	(4y)
(2)-257	(IIe)	(1h)	(2vv)	(3k)	(4z)
(2)-258	(IIf)	(1k)	(2y)	(3l)	(4l)

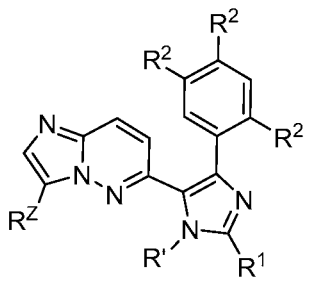
	(II)	A	Z	R′	R^1
(2)-259	(IIa)	(1l)	(2aa)	(3m)	(4r)
(2)-260	(IIb)	(1n)	(2ff)	(3l)	(4u)
(2)-261	(IIc)	(1s)	(2qq)	(3i)	(4v)
(2)-262	(IId)	(1n)	(2tt)	(3j)	(4x)
(2)-263	(IIe)	(1s)	(2vv)	(3k)	(4y)
(2)-264	(IIf)	(1gg)	(2vv)	(3l)	(4z)
(2)-265	(IIg)	(1ll)	(2y)	(3m)	(4l)
(2)-266	(IIh)	(1mm)	(2aa)	(3n)	(4r)
(2)-267	(IIi)	(1ss)	(2ff)	(3o)	(4u)
(2)-268	(IId)	(1tt)	(2a)	(3p)	(4v)
(2)-269	(IIe)	(1n)	(2b)	(3n)	(4x)
(2)-270	(IIf)	(1s)	(2g)	(3o)	(4y)
(2)-271	(IIe)	(1gg)	(2i)	(3p)	(4z)
(2)-272	(IIf)	(1bbb)	(2a)	(3j)	(4j)
(2)-273	(IIg)	(1ccc)	(2q)	(3k)	(4l)
(2)-274	(IIh)	(1n)	(2r)	(3l)	(4a)
(2)-275	(IIi)	(1s)	(2t)	(3m)	(4f)
(2)-276	(IIe)	(1gg)	(2x)	(3k)	(4j)
(2)-277	(IIf)	(1d)	(2a)	(3l)	(4l)
(2)-278	(IIg)	(1xx)	(2b)	(3m)	(4r)
(2)-279	(IIh)	(1n)	(2g)	(3n)	(4j)
(2)-280	(IIi)	(1s)	(2i)	(3o)	(4l)
(2)-281	(IIe)	(1gg)	(2a)	(3p)	(4r)
(2)-282	(IIf)	(1d)	(2q)	(3n)	(4u)
(2)-283	(IIb)	(1e)	(2r)	(3o)	(4v)
(2)-284	(IIc)	(1h)	(2t)	(3p)	(4x)
(2)-285	(IId)	(1k)	(2x)	(3n)	(4y)
(2)-286	(IIe)	(1l)	(2y)	(3o)	(4z)
(2)-287	(IIf)	(1n)	(2aa)	(3p)	(4j)
(2)-288	(IIg)	(1s)	(2ff)	(3j)	(4l)

	(II)	A	Z	R′	R^1
(2)-289	(IIh)	(1gg)	(2qq)	(3k)	(4r)
(2)-290	(IIi)	(1jj)	(2tt)	(3l)	(4j)
(2)-291	(IIc)	(1kk)	(2vv)	(3m)	(4l)
(2)-292	(IId)	(1ll)	(2g)	(3l)	(4r)
(2)-293	(IIe)	(1mm)	(2i)	(3m)	(4j)
(2)-294	(IIf)	(1ss)	(2a)	(3j)	(4l)
(2)-295	(IIg)	(1n)	(2q)	(3k)	(4r)
(2)-296	(IIh)	(1s)	(2r)	(3l)	(4u)
(2)-297	(IIi)	(1gg)	(2t)	(3m)	(4v)
(2)-298	(IId)	(1aaa)	(2x)	(3n)	(4x)
(2)-299	(IIe)	(1bbb)	(2y)	(3o)	(4y)
(2)-300	(IIf)	(1ccc)	(2aa)	(3p)	(4z)
(2)-301	(IIj)	(1e)	(2ww)	(3q)	(4u)
(2)-302	(IIj)	(1h)	(2xx)	(3r)	(4bb)
(2)-303	(IIj)	(1k)	(2yy)	(3s)	(4cc)
(2)-304	(IIj)	(1l)	(2zz)	(3t)	(4dd)

	(II)	A	Z	R′	R^1
(2)-305	(IIj)	(1n)	(2aaa)	(3u)	(4ee)
(2)-306	(IIj)	(1s)	(2bbb)	(3v)	(4ff)
(2)-307	(IIj)	(1gg)	(2ccc)	(3w)	(4gg)
(2)-308	(IIj)	(1jj)	(2ww)	(3x)	(4u)
(2)-309	(IIj)	(1kk)	(2xx)	(3y)	(4bb)
(2)-310	(IIj)	(1ll)	(2yy)	(3z)	(4cc)
(2)-311	(IIj)	(1mm)	(2zz)	(3aa)	(4dd)
(2)-312	(IIj)	(1ss)	(2aaa)	(3bb)	(4ee)
(2)-313	(IIj)	(1n)	(2bbb)	(3cc)	(4ff)
(2)-314	(IIj)	(1s)	(2ccc)	(3dd)	(4gg)
(2)-315	(IIj)	(1gg)	(2ww)	(3ee)	(4u)
(2)-316	(IIj)	(1aaa)	(2xx)	(3ff)	(4bb)
(2)-317	(IIj)	(1bbb)	(2yy)	(3gg)	(4cc)
(2)-318	(IIj)	(1s)	(2zz)	(3hh)	(4dd)
(2)-319	(IIj)	(1a)	(2aaa)	(3ii)	(4ee)
(2)-320	(IIj)	(1c)	(2bbb)	(3jj)	(4ff)

[0055] In some embodiments, the compound of formulae (II) or (IIa) - (IIj) is one of the following compounds (or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, or a solvate or hydrate thereof): 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 15, 16, 17, 18, 22, 23, 24, 25, 27, 28, 31, 32, 33, 34, 41, 42, 48, 60, 61, 62, 63, 64, 71, 98, 99, 102, 104, 108, 125, 126.

[0056] In embodiment III° of this aspect, the invention comprises compounds having the structure of formula (III°):



(III°)

or a pharmaceutically acceptable salt, prodrug or *N*-oxide thereof, or solvate or hydrate thereof,

wherein

R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_{12}alkyl)-Cak or -(C_0-C_6alkyl)-Hca, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, C_1-C_6alkyl-OR^{S0}, -OR^{S0}, -R^{S0} or cyano;

wherein each R^{S0} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

R^1 is hydrogen or C_1-C_6alkyl;

or R′ and R^1 combined with the atoms to which they are attached form a five- to eight-membered Hca;

each R^2 is independently hydrogen, halogen, -C_1-C_6alkyl, -C_1-C_6alkyl-OR^{S2} or -OR^{S2}; and

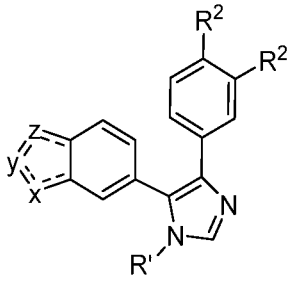
R^Z is halogen, cyano, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$alkenyl, $C_{1\text{-}6}$haloalkyl, -C_1-C_6alkoxy, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Hca, -OR^{S3}, -SR^{S3}, -$NR^{S3}{}_2$, -$C(O)R^{S3}$, -$C(O)OR^{S3}$, -$C(O)NR^{S3}{}_2$, -$C(NR^{S3})NR^{S3}OR^{S3}$, -$S(O)_2NR^{S3}{}_2$, -$S(O)_2R^{S3}$, -$OC(O)R^{S3}$, -$N(R^{S3})C(O)R^{S3}$, -$OC(O)OR^{S3}$, -$OC(O)NR^{S3}{}_2$, -$N(R^{S3})C(O)OR^{S3}$, -$N(R^{S3})C(O)NR^{S3}{}_2$, -$N(R^{S3f})S(O)_2R^{S3}$, -$OP(O)(OR^{S3})_2$ or -CH_2-$OP(O)(OR^{S3})$, wherein each alkyl, haloalkyl and alkoxy is optionally substituted by one or two -R^{Z2} groups;

wherein each R^{S3} is independently hydrogen, -$NR^{S3}{}_2$, -OR^{S3}, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -$C(O)NR^{S4}{}_2$ or cyano; and

each -R^{Z2} is independently halogen, cyano, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, -C_1-C_6alkoxy, -OR^{S4}, -SR^{S4}, -$NR^{S4}{}_2$, -$C(O)R^{S4}$, -$C(O)OR^{S4}$, -$C(O)NR^{S4}{}_2$, -$S(O)_2NR^{S4}{}_2$, -$S(O)_2R^{S4}$, -$OC(O)R^{S4}$, -$N(R^{S4})C(O)R^{S4}$, -$OC(O)OR^{S4}$, -$OC(O)NR^{S4}{}_2$, -$N(R^{S4})C(O)OR^{S4}$, -$N(R^{S4})C(O)NR^{S4}{}_2$, -$N(R^{S4})S(O)_2R^{S4}$, -$OP(O)(OR^{S4})_2$ or -CH_2-$OP(O)(OR^{S4})$; and

wherein each R^{S4} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with one or two C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

[0057] In embodiment III_1 of this aspect, the invention comprises compounds having the structure of formula (III):



(III)

or a pharmaceutically acceptable salt, prodrug or *N*-oxide thereof, or solvate or hydrate thereof,

wherein

R′ is hydrogen or C_1-C_6alkyl;

each R^2 is independently hydrogen, halogen or -C_1-C_6alkyl;

z is CH, O, S or N;

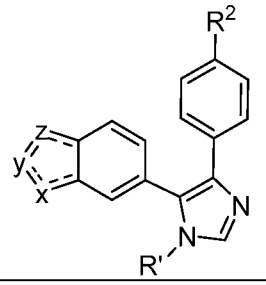
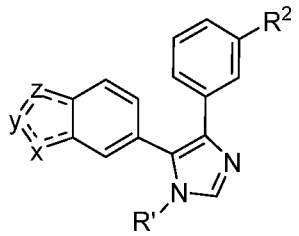
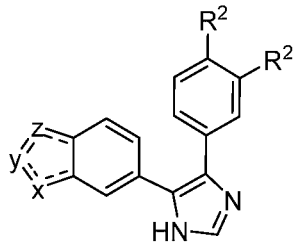
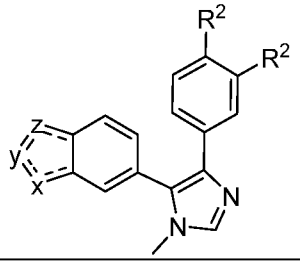
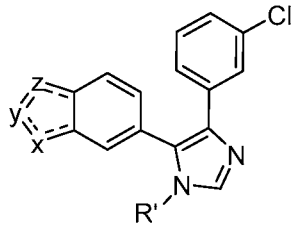
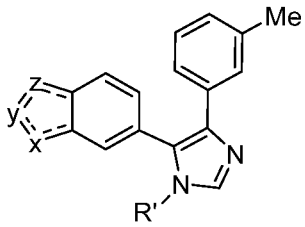
y is CH, CH_2, or N; and

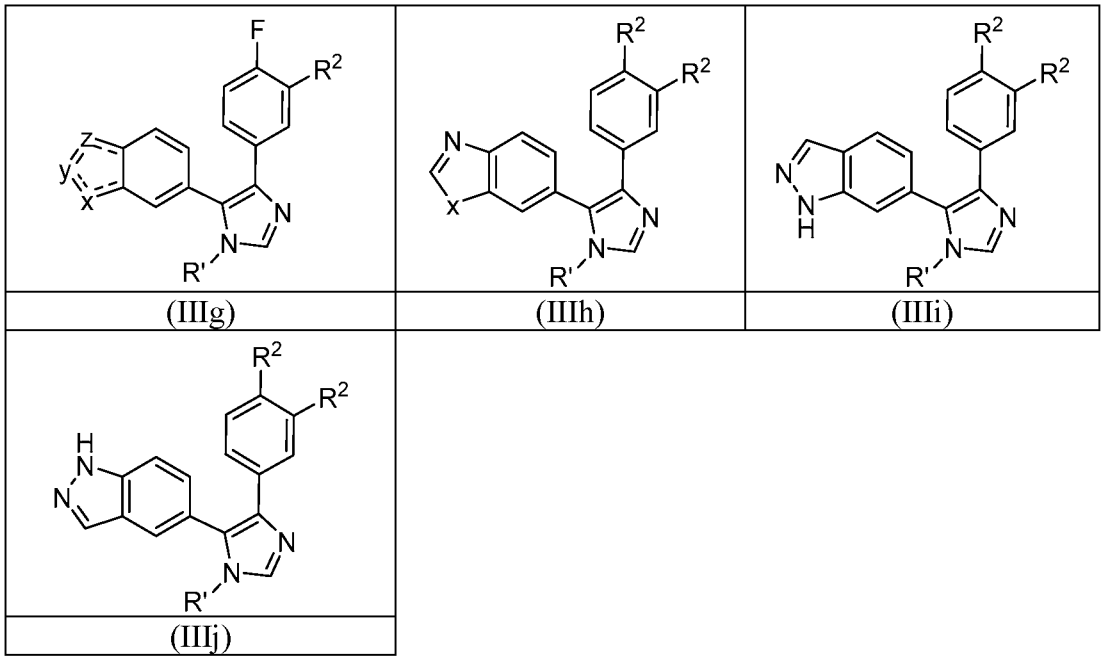
x is CH, O, S, N(R^a);

wherein R^a is hydrogen or -C_1-C_6alkyl.

provided that when z is N and x is N(R^a), y is not N.

[0058] In embodiment III_2, the compounds of the invention are of one of formulae (IIIa) - (IIIj):

		
(IIIa)	(IIIb)	(IIIc)
		
(IIId)	(IIIe)	(IIIf)



wherein R^2, R′, x, y, z and R^a are as defined in embodiment III_1 above.

[0059] Particular embodiments of this aspect of the invention comprise compounds of any one of the formulae (III°), (III), and (IIIa) – (IIIj), each as defined in each of the following rows (or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, or a solvate or hydrate thereof), wherein each entry is a group number as defined above (*e.g.*, **(3o)** refers to R′ is methyl), an "X" indicates that the variable is defined by another group in the embodiment (*e.g.*, in embodiment **(3)-9** below, Z is defined in (IIIi)) and a dash "-" indicates that the variable is as defined in embodiment I_1 or defined according to any one of the applicable variable definitions **(1a)-(1ddd), (2a)-(2ccc), (3a)-(3kk)** and **(4a)-(4gg)** [*e.g.*, when R′ is a dash, it can be either as defined in embodiment III_1 or III_2, or any one of the applicable definitions (**3a**)-(**3kk**)]:

	(III)	**A**	**Z**	**R′**
(3)-1	(IIIa)	(1a)	(2i)	(3a)
(3)-2	(IIIb)	(1c)	(2cc)	(3i)
(3)-3	(IIIc)	(1d)	-	X
(3)-4	(IIId)	(1e)	(2i)	X
(3)-5	(IIIe)	X	(2cc)	(3l)
(3)-6	(IIIf)	X	(2i)	(3m)
(3)-7	(IIIg)	(1l)	(2cc)	(3n)

	(III)	**A**	**Z**	**R′**
(3)-8	(IIIh)	(1n)	(2mm)	(3o)
(3)-9	(IIIi)	(1s)	X	(3p)
(3)-10	(IIIj)	(1gg)	X	(3j)
(3)-11	(IIIa)	(1xx)	-	(3k)
(3)-12	(IIIb)	(1kk)	(2i)	(3l)
(3)-13	(IIIc)	(1d)	(2cc)	X
(3)-14	(IIId)	(1mm)	-	X

	(III)	A	Z	R′
(3)-15	(IIIa)	(1aaa)	(2i)	(3a)
(3)-16	(IIIb)	(1tt)	(2cc)	(3i)
(3)-17	(IIIc)	(1uu)	-	X
(3)-18	(IIId)	(1xx)	-	X
(3)-19	(IIIe)	X	(2i)	-
(3)-20	(IIIf)	X	(2cc)	(3j)
(3)-21	(IIIg)	(1ccc)	-	(3k)
(3)-22	(IIIh)	(1k)	(2mm)	(3l)
(3)-23	(IIIi)	(1ss)	X	(3a)
(3)-24	(IIIj)	(1tt)	X	(3i)
(3)-25	(IIIa)	(1xx)	-	(3j)
(3)-26	(IIIb)	(1aaa)	-	(3k)
(3)-27	(IIIc)	(1h)	(2i)	X
(3)-28	(IIId)	-	(2cc)	X
(3)-29	(IIIc)	-	-	X
(3)-30	(IIIe)	X	(2i)	-
(3)-31	(IIIf)	X	-	(3n)
(3)-32	(IIIa)	(1aaa)	-	(3o)
(3)-33	(IIId)	-	(2cc)	X
(3)-34	(IIIe)	X	(2i)	-
(3)-35	(IIIf)	X	(2cc)	(3j)
(3)-36	(IIIg)	(1ss)	-	(3k)
(3)-37	(IIIh)	(1tt)	(2mm)	(3l)
(3)-38	(IIIi)	(1k)	X	(3a)
(3)-39	(IIIj)	(1uu)	X	(3i)
(3)-40	(IIIa)	(1bbb)	-	(3j)
(3)-41	(IIIb)	(1aaa)	(2i)	(3k)

	(III)	A	Z	R′
(3)-42	(IIIc)	(1n)	(2cc)	X
(3)-43	(IIId)	(1k)	-	X
(3)-44	(IIId)	(1uu)	(2i)	X
(3)-45	(IIIe)	X	(2cc)	-
(3)-46	(IIIf)	X	(2i)	(3a)
(3)-47	(IIIg)	(1ss)	(2cc)	(3j)
(3)-48	(IIIh)	(1ss)	(2mm)	(3k)
(3)-49	(IIIi)	(1tt)	X	(3l)
(3)-50	(IIIj)	(1k)	X	(3i)
(3)-51	(IIId)	(1uu)	-	X
(3)-52	(IIIe)	X	(2i)	-
(3)-53	(IIIf)	X	(2cc)	(3n)
(3)-54	(IIIg)	(1k)	-	(3o)
(3)-55	(IIIh)	(1uu)	(2mm)	(3p)
(3)-56	(IIIi)	(1ss)	X	(3i)
(3)-57	(IIIa)	(1xx)	(2i)	(3j)
(3)-58	(IIIb)	(1e)	(2cc)	(3i)
(3)-59	(IIIc)	(1l)	-	X
(3)-60	(IIId)	(1k)	-	X
(3)-61	(IIIc)	(1n)	-	X
(3)-62	(IIId)	(1uu)	-	X
(3)-63	(IIIe)	X	(2i)	-
(3)-64	(IIIf)	X	(2cc)	(3i)
(3)-65	(IIIg)	(1uu)	-	(3j)
(3)-66	(IIIh)	(1tt)	(2mm)	(3j)
(3)-67	(IIIi)	(1k)	X	(3k)
(3)-68	(IIIj)	(1k)	X	(3l)

	(III)	A	Z	R′
(3)-69	(IIIc)	(1uu)	-	(3k)
(3)-70	(IIIe)	X	-	-
(3)-71	(IIIf)	X	(2i)	(3a)
(3)-72	(IIIa)	(1ccc)	(2cc)	(3i)
(3)-73	(IIIc)	(1k)	-	X
(3)-74	(IIId)	(1uu)	-	-
(3)-75	(IIIe)	X	(2i)	-
(3)-76	(IIIf)	X	(2cc)	(3j)
(3)-77	(IIIg)	(1ss)	-	(3k)
(3)-78	(IIIh)	(1tt)	(2rr)	(3l)
(3)-79	(IIIi)	(1k)	X	(3a)
(3)-80	(IIIj)	(1uu)	X	(3i)
(3)-81	(IIIb)	(1bbb)	(2cc)	(3j)
(3)-82	(IIIc)	(1m)	-	X
(3)-83	(IIIe)	X	(2i)	-
(3)-84	(IIIf)	X	(2cc)	(3i)
(3)-85	(IIIg)	(1ss)	(2i)	(3k)
(3)-86	(IIIg)	(1tt)	(2cc)	(3a)
(3)-87	(IIIh)	(1k)	(2mm)	(3k)
(3)-88	(IIIe)	X	-	-
(3)-89	(IIIf)	X	(2i)	(3i)
(3)-90	(IIIg)	(1ss)	(2cc)	(3j)
(3)-91	(IIIh)	(1tt)	(2mm)	(3k)
(3)-92	(IIIi)	(1k)	X	(3l)
(3)-93	(IIIj)	(1uu)	X	(3n)
(3)-94	(IIIb)	(1aaa)	-	(3o)
(3)-95	(IIIc)	(1k)	(2i)	X

	(III)	A	Z	R′
(3)-96	(IIIe)	X	(2cc)	-
(3)-97	(IIIf)	X	-	(3n)
(3)-98	(IIIg)	(1n)	-	(3o)
(3)-99	(IIIg)	(1k)	-	(3p)
(3)-100	(IIIh)	(1ss)	(2qq)	(3k)
(3)-101	(IIIg)	(1tt)		(3l)
(3)-102	(IIIh)	(1k)	(2mm)	(3a)
(3)-103	(IIIi)	(1uu)	X	(3a)
(3)-104	(IIIj)	(1k)	X	(3i)
(3)-105	(IIIb)	(1ccc)	-	(3j)
(3)-106	(IIIc)	(1k)	-	X
(3)-107	(IIIe)	X	(2i)	-
(3)-108	(IIIf)	X	(2cc)	(3i)
(3)-109	(IIIg)	(1k)	-	(3j)
(3)-110	(IIIg)	(1tt)	-	(3i)
(3)-111	(IIIh)	(1ss)	(2mm)	(3a)
(3)-112	(IIIf)	X	-	(3i)
(3)-113	(IIIg)	(1k)	(2i)	(3j)
(3)-114	(IIIh)	(1n)	(2cc)	(3j)
(3)-115	(IIIi)	(1x)	X	(3k)
(3)-116	(IIIj)	(1k)	X	(3n)
(3)-117	(IIIb)	(1bbb)	-	(3o)
(3)-118	(IIIc)	(1uu)	-	X
(3)-119	(IIIe)	X	(2i)	-
(3)-120	(IIIf)	X	(2cc)	(3k)
(3)-121	(IIIg)	(1ss)	(2i)	(3a)
(3)-122	(IIIg)	(1tt)	(2cc)	(3i)

	(III)	A	Z	R′
(3)-123	(IIIh)	(1k)	(2mm)	(3j)
(3)-124	(IIIf)	X	(2i)	(3a)
(3)-125	(IIIg)	(1uu)	(2i)	(3j)
(3)-126	(IIIa)	(1aaa)	(2cc)	(3k)
(3)-127	(IIIb)	(1xx)	-	(3l)
(3)-128	(IIIc)	(1k)	-	X
(3)-129	(IIId)	(1n)	(2i)	X
(3)-130	(IIIe)	X	(2cc)	-
(3)-131	(IIIf)	X	-	(3a)
(3)-132	(IIIg)	(1k)	-	(3j)
(3)-133	(IIIh)	(1n)	(2mm)	(3k)
(3)-134	(IIIi)	(1l)	X	(3l)
(3)-135	(IIIj)	(1uu)	X	(3k)
(3)-136	(IIIa)	(1xx)	(2i)	(3a)
(3)-137	(IIIb)	(1aaa)	(2cc)	(3i)
(3)-138	(IIIc)	(1ss)	-	X
(3)-139	(IIId)	(1tt)	-	X
(3)-140	(IIIc)	(1k)	(2i)	X
(3)-141	(IIIe)	X	(2cc)	-
(3)-142	(IIIf)	X	-	(3i)
(3)-143	(IIIa)	(1bbb)	(2i)	(3j)
(3)-144	(IIIb)	(1aaa)	(2cc)	(3k)
(3)-145	(IIIc)	(1uu)	-	X
(3)-146	(IIId)	(1c)	-	X
(3)-147	(IIIe)	X	(2i)	-
(3)-148	(IIIf)	X	(2cc)	(3a)
(3)-149	(IIIb)	(1xx)	-	(3i)

	(III)	A	Z	R′
(3)-150	(IIIc)	(1uu)	(2i)	X
(3)-151	(IIIe)	X	(2cc)	-
(3)-152	(IIIf)	X	(2i)	(3n)
(3)-153	(IIIg)	(1d)	(2cc)	(3o)
(3)-154	(IIIg)	(1k)	-	(3p)
(3)-155	(IIIh)	(1d)	(2pp)	(3a)
(3)-156	(IIIg)	(1n)	(2i)	(3i)
(3)-157	(IIIh)	(1k)	(2cc)	(3j)
(3)-158	(IIIi)	(1d)	X	(3k)
(3)-159	(IIIj)	(1n)	X	(3n)
(3)-160	(IIIb)	(1ccc)	-	(3o)
(3)-161	(IIIc)	(1uu)	(2i)	X
(3)-162	(IIIe)	X	(2i)	-
(3)-163	(IIIf)	X	(2cc)	(3i)
(3)-164	(IIIa)	(1aaa)	(2i)	(3j)
(3)-165	(IIIb)	(1xx)	(2cc)	(3k)
(3)-166	(IIIc)	(1d)	-	X
(3)-167	(IIId)	(1k)	(2i)	X
(3)-168	(IIIa)	(1ccc)	(2i)	(3k)
(3)-169	(IIIb)	(1e)	(2cc)	(3a)
(3)-170	(IIIa)	(1aaa)	(2i)	(3j)
(3)-171	(IIIb)	(1e)	(2cc)	(3k)
(3)-172	(IIIc)	(1uu)	-	(3l)
(3)-173	(IIIa)	(1xx)	-	(3a)
(3)-174	(IIIb)	(1ccc)	(2i)	(3i)
(3)-175	(IIIc)	(1k)	(2cc)	X
(3)-176	(IIId)	(1d)	(2i)	-

	(III)	A	Z	R′
(3)-177	(IIIc)	(1n)	(2cc)	X
(3)-178	(IIIe)	X	-	-
(3)-179	(IIIf)	X	(2i)	(3n)
(3)-180	(IIIg)	(1ss)	(2cc)	(3o)
(3)-181	(IIIg)	(1tt)	-	(3p)
(3)-182	(IIIh)	(1k)	(2oo)	(3k)
(3)-183	(IIIi)	(1uu)	X	(3l)
(3)-184	(IIIj)	(1k)	X	(3i)
(3)-185	(IIIa)	(1e)	(2i)	(3j)
(3)-186	(IIIb)	(1aaa)	(2cc)	(3k)
(3)-187	(IIIc)	(1ss)	-	(3l)
(3)-188	(IIId)	(1tt)	(2i)	X
(3)-189	(IIId)	(1k)	(2i)	X
(3)-190	(IIIe)	X	(2cc)	-
(3)-191	(IIIf)	X	(2i)	(3j)
(3)-192	(IIIg)	(1ss)	(2cc)	(3k)
(3)-193	(IIIb)	(1xx)	(2i)	(3n)
(3)-194	(IIIb)	(1bbb)	(2cc)	(3o)
(3)-195	(IIIc)	(1ss)	(2i)	(3p)
(3)-196	(IIIe)	X	(2cc)	-
(3)-197	(IIIf)	X	(2i)	(3a)
(3)-198	(IIIg)	(1ss)	(2cc)	(3j)

	(III)	A	Z	R′
(3)-199	(IIIg)	(1tt)	-	(3k)
(3)-200	(IIIh)	(1k)	(2nn)	(3l)
(3)-201	(III°)	(1f)	(2zz)	(3q)
(3)-202	(III°)	(1jj)	(2aaa)	(3r)
(3)-203	(III°)	(1kk)	(2bbb)	(3s)
(3)-204	(III°)	(1ll)	(2ccc)	(3t)
(3)-205	(III°)	(1mm)	(2zz)	(3u)
(3)-206	(III°)	(1nn)	(2aaa)	(3v)
(3)-207	(III°)	(1rr)	(2bbb)	(3w)
(3)-208	(III°)	(1ss)	(2ccc)	(3x)
(3)-209	(III°)	(1tt)	(2zz)	(3y)
(3)-210	(III°)	(1uu)	(2aaa)	(3z)
(3)-211	(III°)	(1vv)	(2bbb)	(3aa)
(3)-212	(III°)	(1zz)	(2ccc)	(3bb)
(3)-213	(III°)	(1aaa)	(2zz)	(3q)
(3)-214	(III°)	(1bbb)	(2aaa)	(3r)
(3)-215	(III°)	(1ccc)	(2bbb)	(3s)
(3)-216	(III°)	(1ddd)	(2ccc)	(3t)
(3)-217	(III°)	(1f)	(2zz)	(3u)
(3)-218	(III°)	(1jj)	(2aaa)	(3v)
(3)-219	(III°)	(1rr)	(2bbb)	(3w)
(3)-220	(III°)	(1zz)	(2ccc)	(3x)

[0060] In some embodiments, the compound of formulae (I), (Ia) - (Iv), (II), (IIa) - (IIi), (III) and (IIIa) - (IIIj) is one of the following compounds (or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, or a solvate or hydrate thereof): 3, 4, 5, 7, 10, 11, 15, 16, 18, 22, 23, 24, 25, 27, 28, 31, 41, 42, 60, 61, 153, 154, 155, 156, 157, 158, 159, 160, 161.

[0061] In some embodiments, the compound of formulae (III) or (IIIa) - (IIIj) is one of the following compounds (or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof,

or a solvate or hydrate thereof): 3, 4, 5, 7, 10, 11, 15, 16, 18, 22, 23, 24, 25, 27, 28, 31, 41, 42, 60, 61.

[0062] In some embodiments, the compound of formulae (III) or (IIIa) - (IIIj) is one of the following compounds (or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, or a solvate or hydrate thereof): 3, 4, 5, 22, 23, 24.

[0063] In some embodiments, the compound of formula (I°), (Iw) - (Ix), (II°), (IIj) and (III°) is one of the following compounds (or a pharmaceutically acceptable salt, prodrug, or *N*-oxide thereof, or a solvate or hydrate thereof): 2′, 12′, 14′, 24′, 32′, 105′ and 204′.

[0064] In another aspect, the present invention comprises pharmaceutical compositions comprising a compound according to any one of the preceding aspects of the invention or any embodiment thereof, together with a pharmaceutically acceptable excipient, diluent, or carrier.

[0065] In another aspect, the invention comprises the use of a compound described by any one of the preceding aspects of the invention or any embodiment thereof, for the preparation of a medicament for the treatment of medical diseases or conditions that benefit from the inhibition of cytokine signaling. Medical conditions contemplated in this aspect include all diseases and conditions described herein.

[0066] The compounds of formulae (I°), (I), (Ia) - (Ix), (II°), (II), (IIa) - (IIj), (III°), (III) and (IIIa) - (IIIj) described above are useful as kinase inhibitors and/or inhibitors of cytokine signaling. Exemplary kinases inhibited by the presently disclosed compounds include, without limitation, ACVR1; ACVR1B (ALK-4); ACVR1C; ACVR2A; ACVR2B; ACVRL1; BMPR1A; BMPR1B; BMPR2; TGFBR1 (ALK-5), PI3K and MAP4K4 (HGK). Exemplary cytokines, the signaling of which is inhibited by the present compounds include, without limitation, TGF-β superfamily, including Activin, Nodal, TGF-β1, and GDF-8. In one aspect the present compounds are selective for one or more kinase and/or cytokine signaling pathway. For example, exemplary compounds inhibit TGF-β1 signaling, GDF-8 signaling, or both. In one aspect the present compounds inhibit GDF-8 signaling preferentially to TGF-β1 signaling, such that GDF8 signaling is inhibited at least about 1.5-fold more potently or from about 1.1-fold to about 25-fold more potently. In one embodiment certain compounds inhibit GDF8 signaling at least about 5-fold more potently, such as from about 8-fold to about 50-fold, or at least about 10-fold more potently, such as from about 15-fold to about 300-fold more potently.

[0067] In particular, the present compounds can be use to treat disorders, such as pulmonary hypertension, chronic renal disease, acute renal disease, wound healing, arthritis,

osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, kidney fibrosis, lung fibrosis, including idiopathic pulmonary fibrosis, and liver fibrosis, hepatitis B, hepatitis C, alcohol-induced hepatitis, cancer, haemochromatosis, primary biliary cirrhosis, restenosis, retroperitoneal fibrosis, mesenteric fibrosis, endometriosis, keloids, cancer, abnormal bone function, inflammatory disorders, scarring and photoaging of the skin.

[0068] Particular proliferative diseases that can be treated with the present compounds include those selected from a benign or malignant tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina or thyroid, sarcoma, glioblastomas, multiple myeloma or gastrointestinal cancer, especially colon carcinoma or colorectal adenoma or a tumor of the neck and head, an epidermal hyperproliferation, melanoma, psoriasis, prostate hyperplasia, a neoplasia, a neoplasia of epithelial character, leukemias and lymphomas, a mammary carcinoma or a leukemia. Other diseases include Cowden syndrome, Lhermitte-Dudos disease and Bannayan-Zonana syndrome, or diseases in which the PI3K/PKB pathway is aberrantly activated.

[0069] The compounds described herein also include isotopically labeled compounds where one or more atoms have an atomic mass different from the atomic mass conventionally found in nature. Examples of isotopes that may be incorporated into the compounds disclosed herein include, but are not limited to, ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{18}F etc. Thus, the disclosed compounds may be enriched in one or more of these isotopes relative to the natural abundance of such isotope. As is known to those of skill in the art, such isotopically enriched compounds are useful for a variety of purposes. For example, substitution with heavier isotopes such as deuterium (^{2}H) may afford certain therapeutic advantages that result from greater metabolic stability. Substitution with positron emitting isotopes, such as 18F can be useful in Positron Emission Tomography (PET) studies. By way of example, deuterium (^{2}H) has a natural abundance of about 0.015%. Accordingly, for approximately every 6,500 hydrogen atoms occurring in nature, there is one deuterium atom. Specifically contemplated herein are compounds enriched in deuterium at one or more positions. Thus, deuterium containing compounds of the disclosure have deuterium at one or more positions (as the case may be) in an abundance of greater than 0.015%.

[0070] In another aspect, the invention comprises combination therapies for the treatment of cancer, including both pre-malignant and malignant neoplasms. In this aspect, the

invention comprises a method of treating cancer comprising administering to a subject a compound disclosed herein in conjunction with a therapeutic treatment of cancer. In some embodiments of the invention, the compounds disclosed herein are used in combination of standard of care anti-proliferative treatments of cancer. The amount of a compound disclosed herein for use in the combination therapy is an amount sufficient to inhibit signaling by members of the TGF-β superfamily, such as Nodal and Activin, which promote the survival and/or differentiation of cancer stem cells and thereby enhance the efficacy of the therapeutic treatment. Treatment with the present compounds thus blocks the ability of cancer stem cells to recapitulate a tumor destroyed by treatment with standard of care. Efficacy of treatment can be determined by any art recognized method generally empolyed for the particular cancer being treated and includes, for example, retardation, inhibition, or regression of tumor growth.

[0071] Reference to "combination therapy" and treatment with a compound dislcosed herein "in conjunction with" another therapeutic treatment means that the compound and other therapeutic treatment can be administered simultaneously or sequentially such that the resultant treatment is more efficacious than either treatment alone.

[0072] One embodiment of treating cancer in a subject comprises administering to a subject in need thereof an amount described above of a compound disclosed herein in combination with the administration of a therapeutically effective amount of one or more chemotherapeutic agents, wherein the one or more chemotherapeutic agents is selected from the group consisting of antimetabolites, alkylating agents, coordination compounds, platinum complexes, DNA cross-linking compounds, inhibitors of transcription enzymes, tyrosine kinase inhibitors, protein kinase inhibitors, topoisomerase inhibitors, DNA minor-groove binding compounds, vinca alkyloids, taxanes, antitumor antibiotics, hormones, aromatase inhibitors, enzymes, growth factor receptors antibodies, cytokines, cell surface markers antibodies, HDAC inhibitors, HSP 90 inhibitors, BCL-2 inhibitors, B-raf inhibitors, MEK inhibitors, mTOR inhibitors, proteasome inhibitors and monoclonal antibodies.

[0073] Among the BCL-2 inhibitors useful in the invention is ABT-199.

[0074] Another embodiment of methods for treating a subject comprises administering to the subject an amount (as described above) of a compound disclosed herein in combination with the administration of a therapeutically effective amount of one or more chemotherapeutic agents, the one or more chemotherapeutic agents being independently selected from the group consisting of mechlorothamine, cyclophosphamide, ifosfamide, melphalan, chlorambucil, ethyleneimines, methylmelamines, procarbazine, dacarbazine,

temozolomide, busulfan, carmustine, lomustine, methotrexate, fluorouracil, capecitabine, cytarabine, gemcitabine, cytosine arabinoside, mecaptopurine, fludarabine, cladribine, thioguanine, azathioprine, vinblastine, vincristine, paclitaxel, docetaxel, colchicine, actinomycin D, daunorubicin, bleomycin,L-asparaginase, cisplatin, carboplatin, oxaliplatin, prednisone, dexamethasone, amino glutethimide, formestane, anastrozole, hydroxyprogesterone caproate, medroxyprogesterone, tamoxifen, amsacrine, mitoxantrone, topotecan, irinotecan, camptothecin, afatinib, axitinib, bosutinib, bortezomib, carfilzomib, cabozantinib, cediranib, crizotinib, dasatinib, dabrafenib, evorolimus, ibrutinib, LDK378, LGX818, MEK162, regorafenib, ruxolitinib, selumetinib, sorafenib, trametinib, vemurafenib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, nilotinib, palbociclib, pazopanib, pomatinib, semaxanib, sirolimus, sunitinib, temsirolimus, vatalanib, vandetanib, anti Her2 antibodies, interferon-α , interferon-γ, interleukin 2, GM CSF, anti CTLA 4 antibodies, rituximab, anti CD33 antibodies, MGCD0103, vorinostat, 17-AAG, thalidomide, lenalidomide, rapamycin, CCI-779, doxorubicine, gemcitabine, melphalan, NPI052, gemtuzumab, alemtuzumab, cetuximab, ibritumomab tiuxaetan, tositumomab, iodine-131 tositumomab, trastuzumab, ado-trastuzumab emtansine, obinutuzumab, bevacizumab, rituximab, and anti-TRAIL death receptor antibodies.

[0075] Among the CTLA 4 antibodies that can be used in the present invention is ipilimumab, marketed as YERVOY® by Bristol-Myers Squibb.

[0076] Other chemotherapeutic agents include checkpoint pathway inhibitors, *e.g.*, PD-1 inhibitors, such as nivolumab and lambrolizumab, and PD-L1 inhibitors, such as pembrolizumab, MEDI-4736 and MPDL3280A/RG7446. Additional checkpoint inhibitors for combination with the compounds disclosed herein include, Anti-LAG-3 agents, such as BMS-986016 (MDX-1408).

[0077] Further chemotherapeutic agents for combination with the presently disclosed TGF-β signalling inhibitors include Anti-SLAMF7 agents, such as the humanized monoclonal antibody elotuzumab (BMS-901608), anti-KIR agents, such as the anti-KIR monoclonal antibody lirilumab (BMS-986015), and anti-CD137 agents, such as the fully human monoclonal antibody urelumab (BMS-663513).

[0078] The following table displays exemplary cancers treatable in the combination therapies of the invention and the therapeutic drug and/or other treatment for use with the compounds disclosed herein:

Cancer	Drug or Treatment
Glioma	lomustine, temozolide and/or radiation
hepatocellular carcinoma	sorafenib, regorafenib
myelodysplastic syndromes	decitabine or azacytidine
pancreatic cancer	Gemcitabine
ovarian cancer, such as epithelial ovarian carcinoma	carboplatin, cisplatin, doxorubicin, gemcitabine, paclitaxel
breast cancer	Trastuzumab
basal and squamous skin carcinomas	5-fluorouracil, imiquimod, photodynamic therapy (*e.g.* with 5-aminolevulinic acid),
head and neck carcinoma	bleomycin, cisplatin, cetuximab, docetaxel, fluorouracil, methotrexate
triple negative breast cancer	Paclitaxel
Prostate	abiraterone, enzalutamide

[0079] Further provided herein are methods of treatment wherein compounds of the invention are administered with one or more immuno-oncology agents. The immuno-oncology agents used herein, also known as cancer immunotherapies, are effective to enhance, stimulate, and/or up-regulate immune responses in a subject. In one aspect, the administration of a compound of the invention with an immuno-oncology agent has a synergic effect in inhibiting tumor growth.

[0080] In one aspect, the compound(s) of the invention are sequentially administered prior to administration of the immuno-oncology agent. In another aspect, compound(s) of the invention are administered concurrently with the immunology-oncology agent. In yet another aspect, compound(s) of the invention are sequentially administered after administration of the immuno-oncology agent.

[0081] In another aspect, compounds of the invention may be co-formulated with an immuno-oncology agent.

[0082] Immuno-oncology agents include, for example, a small molecule drug, antibody, or other biologic or small molecule. Examples of biologic immuno-oncology agents include, but are not limited to, cancer vaccines, antibodies, and cytokines. In one aspect, the antibody is a monoclonal antibody. In another aspect, the monoclonal antibody is humanized or human.

[0083] In one aspect, the immuno-oncology agent is (i) an agonist of a stimulatory (including a co-stimulatory) receptor or (ii) an antagonist of an inhibitory (including a co-

inhibitory) signal on T cells, both of which result in amplifying antigen-specific T cell responses (often referred to as immune checkpoint regulators).

[0084] Certain of the stimulatory and inhibitory molecules are members of the immunoglobulin super family (IgSF). One important family of membrane-bound ligands that bind to co-stimulatory or co-inhibitory receptors is the B7 family, which includes B7-1, B7-2, B7-H1 (PD-L1), B7-DC (PD-L2), B7-H2 (ICOS-L), B7-H3, B7-H4, B7-H5 (VISTA), and B7-H6. Another family of membrane bound ligands that bind to co-stimulatory or co-inhibitory receptors is the TNF family of molecules that bind to cognate TNF receptor family members, which includes CD40 and CD40L, OX-40, OX-40L, CD70, CD27L, CD30, CD30L, 4-1BBL, CD137 (4-1BB), TRAIL/Apo2-L, TRAILR1/DR4, TRAILR2/DR5, TRAILR3, TRAILR4, OPG, RANK, RANKL, TWEAKR/Fn14, TWEAK, BAFFR, EDAR, XEDAR, TACI, APRIL, BCMA, LTβR, LIGHT, DcR3, HVEM, VEGI/TL1A, TRAMP/DR3, EDAR, EDA1, XEDAR, EDA2, TNFR1, Lymphotoxin α/TNFβ, TNFR2, TNFα, LTβR, Lymphotoxin α 1β2, FAS, FASL, RELT, DR6, TROY, NGFR.

[0085] In another aspect, the immuno-oncology agent is a cytokine that inhibits T cell activation (*e.g.*, IL-6, IL-10, TGF-ß, VEGF, and other immunosuppressive cytokines) or a cytokine that stimulates T cell activation, for stimulating an immune response.

[0086] In one aspect, T cell responses can be stimulated by a combination of a compound of the invention and one or more of (i) an antagonist of a protein that inhibits T cell activation (*e.g.*, immune checkpoint inhibitors) such as CTLA-4, PD-1, PD-L1, PD-L2, LAG-3, TIM-3, Galectin 9, CEACAM-1, BTLA, CD69, Galectin-1, TIGIT, CD113, GPR56, VISTA, 2B4, CD48, GARP, PD1H, LAIR1, TIM-1, and TIM-4, and (ii) an agonist of a protein that stimulates T cell activation such as B7-1, B7-2, CD28, 4-1BB (CD137), 4-1BBL, ICOS, ICOS-L, OX40, OX40L, GITR, GITRL, CD70, CD27, CD40, DR3 and CD28H.

[0087] Other agents that can be combined with compounds of the invention for the treatment of cancer include antagonists of inhibitory receptors on NK cells or agonists of activating receptors on NK cells. For example, compounds of the invention can be combined with antagonists of KIR, such as lirilumab.

[0088] Yet other agents for combination therapies include agents that inhibit or deplete macrophages or monocytes, including but not limited to CSF-1R antagonists such as CSF-1R antagonist antibodies including RG7155 (WO11/70024, WO11/107553, WO11/131407, WO13/87699, WO13/119716, WO13/132044) or FPA-008 (WO11/140249; WO13169264; WO14/036357).

[0089] In another aspect, compounds of the invention can be used with one or more of agonistic agents that ligate positive costimulatory receptors, blocking agents that attenuate signaling through inhibitory receptors, antagonists, and one or more agents that increase systemically the frequency of anti-tumor T cells, agents that overcome distinct immune suppressive pathways within the tumor microenvironment (*e.g.*, block inhibitory receptor engagement (*e.g.*, PD-L1/PD-1 interactions), deplete or inhibit Tregs (*e.g.*, using an anti-CD25 monoclonal antibody (*e.g.*, daclizumab) or by ex vivo anti-CD25 bead depletion), inhibit metabolic enzymes such as IDO, or reverse/prevent T cell anergy or exhaustion) and agents that trigger innate immune activation and/or inflammation at tumor sites.

[0090] In one aspect, the immuno-oncology agent is a CTLA-4 antagonist, such as an antagonistic CTLA-4 antibody. Suitable CTLA-4 antibodies include, for example, YERVOY (ipilimumab) or tremelimumab.

[0091] In another aspect, the immuno-oncology agent is a PD-1 antagonist, such as an antagonistic PD-1 antibody. Suitable PD-1 antibodies include, for example, OPDIVO (nivolumab), KEYTRUDA (pembrolizumab), or MEDI-0680 (AMP-514; WO2012/145493). The immuno-oncology agent may also include pidilizumab (CT-011), though its specificity for PD-1 binding has been questioned. Another approach to target the PD-1 receptor is the recombinant protein composed of the extracellular domain of PD-L2 (B7-DC) fused to the Fc portion of IgG1, called AMP-224

[0092] In another aspect, the immuno-oncology agent is a PD-L1 antagonist, such as an antagonistic PD-L1 antibody. Suitable PD-L1 antibodies include, for example, MPDL3280A (RG7446; WO2010/077634), durvalumab (MEDI4736), BMS-936559 (WO2007/005874), and MSB0010718C (WO2013/79174).

[0093] In another aspect, the immuno-oncology agent is a LAG-3 antagonist, such as an antagonistic LAG-3 antibody. Suitable LAG3 antibodies include, for example, BMS-986016 (WO10/19570, WO14/08218), or IMP-731 or IMP-321 (WO08/132601, WO09/44273).

[0094] In another aspect, the immuno-oncology agent is a CD137 (4-1BB) agonist, such as an agonistic CD137 antibody. Suitable CD137 antibodies include, for example, urelumab and PF-05082566 (WO12/32433).

[0095] In another aspect, the immuno-oncology agent is a GITR agonist, such as an agonistic GITR antibody. Suitable GITR antibodies include, for example, BMS-986153, BMS-986156, TRX-518 (WO06/105021, WO09/009116) and MK-4166 (WO11/028683).

[0096] In another aspect, the immuno-oncology agent is an IDO antagonist. Suitable IDO antagonists include, for example, INCB-024360 (WO2006/122150, WO07/75598,

WO08/36653, WO08/36642), indoximod, or NLG-919 (WO09/73620, WO09/1156652, WO11/56652, WO12/142237).

[0097] In another aspect, the immuno-oncology agent is an OX40 agonist, such as an agonistic OX40 antibody. Suitable OX40 antibodies include, for example, MEDI-6383 or MEDI-6469.

[0098] In another aspect, the immuno-oncology agent is an OX40L antagonist, such as an antagonistic OX40 antibody. Suitable OX40L antagonists include, for example, RG-7888 (WO06/029879).

[0099] In another aspect, the immuno-oncology agent is a CD40 agonist, such as an agonistic CD40 antibody. In yet another embodiment, the immuno-oncology agent is a CD40 antagonist, such as an antagonistic CD40 antibody. Suitable CD40 antibodies include, for example, lucatumumab or dacetuzumab.

[0100] In another aspect, the immuno-oncology agent is a CD27 agonist, such as an agonistic CD27 antibody. Suitable CD27 antibodies include, for example, varlilumab.

[0101] In another aspect, the immuno-oncology agent is MGA271 (to B7H3) (WO11/109400).

[0102] In another aspect, the invention comprises a method for treating a subject afflicted with cancer comprising administering to the subject a therapeutically effective amount of:

a) a TGF-Beta inhibitor; and

b) an anti-cancer agent which is an antibody or an antigen-binding portion thereof that binds specifically to a Programmed Death-1 (PD-1) receptor and inhibits PD-1 activity.

[0103] In some embodiments, the PD-1 inhibitor is administered by infusion.

[0104] In some embodiments, the anti-PD-1 antibody is nivolumab.

[0105] In another aspect, the invention comprises a method of determining and measuring the ability of the compounds disclosed herein to inhibit signaling by members of the TGF-β superfamily, such as Nodal and Activin, in order to identify cancers and, more specifically, tumors. In one embodiment, neoplasms susceptible to such combination therapy can be identified by testing for Nodal and Activin signaling activity using techniques known to those skilled in the art, including, for example, assays described in Lonardo, E. et al. (2011) Cell Stem Cell 9, 433-446 (which is hereby incorporated by reference in its entirety). Optionally in this embodiment, where the tested compound is found to inhibit signalling of a member of the TGF-β superfamily, such as Nodal and Activin, in the tested neoplasm, the compound is

subsequently used in a combination therapy for treatment of the neoplasm, as described herein.

Definitions

[0106] Terms used herein may be preceded and/or followed by a single dash, "-", or a double dash, "=", to indicate the bond order of the bond between the named substituent and its parent moiety; a single dash indicates a single bond and a double dash indicates a double bond or a pair of single bonds in the case of a spiro-substituent. In the absence of a single or double dash it is understood that a single bond is formed between the substituent and its parent moiety; further, substituents are intended to be read "left to right" unless a dash indicates otherwise. For example, arylalkyl, arylalkyl-, and –alkylaryl indicate the same functionality.

[0107] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (*e.g.*, alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an "alkyl" moiety can refer to a monovalent radical (*e.g.* CH_3-CH_2-), in some circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (*e.g.*, -CH_2-CH_2-), which is equivalent to the term "alkylene." (Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene). All atoms are understood to have their normal number of valences for bond formation (*i.e.*, 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). Nitrogens in the presently disclosed compounds can be hypervalent, *e.g.*, an N-oxide or tetrasubstituted ammonium salt. On occasion a moiety may be defined, for example, as $(A)_a$-B-, wherein a is 0 or 1. In such instances, when a is 0 the moiety is B- and when a is 1 the moiety is A-B-.

[0108] As used herein, the term "alkyl" includes alkyl, alkenyl and alkynyl groups of a designed number of carbon atoms, such as 1 to 6 carbons (*i.e.*, inclusive of 1 and 6), 1 to 6 carbons, 1 to 3 carbons, or 1, 2, 3, 4, 5 or 6. The term "C_m-$C_n$alkyl" means an alkyl group having from m to n carbon atoms (*i.e.*, inclusive of m and n). The term "C_m-$C_n$alkyl" means an alkyl group having from m to n carbon atoms. For example, "C_1-C_6alkyl" is an alkyl group having from one to six carbon atoms. Alkyl and alkyl groups may be straight or branched and depending on context, may be a monovalent radical or a divalent radical (*i.e.*, an alkylene

group). In the case of an alkyl or alkyl group having zero carbon atoms (*i.e.*, "C_0alkyl"), the group is simply a single covalent bond if it is a divalent radical or is a hydrogen atom if it is a monovalent radical. For example, the moiety "-(C_0-C_6alkyl)-Ar" signifies connection of an optionally substituted aryl through a single bond or an alkylene bridge having from 1 to 6 carbons. Examples of "alkyl" include, for example, methyl, ethyl, propyl, isopropyl, butyl, iso-, sec- and tert-butyl, pentyl, hexyl, heptyl, 3-ethylbutyl, 3-hexenyl and propargyl. If the number of carbon atoms is not specified, the subject "alkyl" or "alkyl" moiety has from 1 to 6 carbons.

[0109] The term "haloalkyl" is an alkyl group substituted with one or more halogen atoms, *e.g.* F, Cl, Br and I. A more specific term, *e.g.*, "fluoroalkyl" is an alkyl group substituted with one or more fluorine atoms. Examples of "fluoroalkyl" include fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, hexafluoroisopropyl and the like. In certain embodiments of the compounds disclosed herein, each haloalkyl is a fluoroalkyl.

[0110] The term "aryl" or "Ar" represents an aromatic ring system having a single ring (*e.g.*, phenyl) which is optionally fused to other aromatic hydrocarbon rings or non-aromatic hydrocarbon rings. "Aryl" includes ring systems having multiple condensed rings and in which at least one is carbocyclic and aromatic, (*e.g.*, 1,2,3,4-tetrahydronaphthyl, naphthyl). Examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, fluorenyl, tetralinyl, and 6,7,8,9-tetrahydro-5*H*-benzo[a]cycloheptenyl. In certain examples, aryl groups include those having a first carbocyclic, aromatic ring fused to an aromatic or aliphatic heterocycle, for example, 2,3-dihydrobenzofuranyl.. The aryl groups herein are unsubstituted or, when specified as "optionally substituted", can unless stated otherwise be substituted in one or more substitutable positions with various groups, as described below.

[0111] The term "heteroaryl" or "Het" refers to an aromatic ring system containing at least one heteroatom selected from nitrogen, oxygen and sulfur in an aromatic ring. Most commonly, the heteroaryl groups will have 1, 2, 3, or 4 heteroatoms. The heteroaryl may be fused to one or more non-aromatic ring, for example, cycloalkyl or heterocycloalkyl rings, wherein the cycloalkyl (Cak) and heterocycloalkyl (Hca) rings are described herein. In one embodiment of the present compounds the heteroaryl group is bonded to the remainder of the structure through an atom in a heteroaryl group aromatic ring. In another embodiment, the heteroaryl group is bonded to the remainder of the structure through a non-aromatic ring atom. Examples of heteroaryl groups include, for example, pyridyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl,

quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, benzo[1,4]oxazinyl, triazolyl, tetrazolyl, isothiazolyl, naphthyridinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, chromonyl, chromanonyl, pyridinyl-*N*-oxide, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl *N*-oxide, pyrimidinyl *N*-oxide, pyridazinyl *N*-oxide, pyrazinyl *N*-oxide, quinolinyl *N*-oxide, indolyl *N*-oxide, indolinyl *N*-oxide, isoquinolyl *N*-oxide, quinazolinyl *N*-oxide, quinoxalinyl *N*-oxide, phthalazinyl *N*-oxide, imidazolyl *N*-oxide, isoxazolyl *N*-oxide, oxazolyl *N*-oxide, thiazolyl *N*-oxide, indolizinyl *N*-oxide, indazolyl *N*-oxide, benzothiazolyl *N*-oxide, benzimidazolyl *N*-oxide, pyrrolyl *N*-oxide, oxadiazolyl *N*-oxide, thiadiazolyl *N*-oxide, triazolyl *N*-oxide, tetrazolyl *N*-oxide, benzothiopyranyl S-oxide, benzothiopyranyl S,S-dioxide. Preferred heteroaryl groups include pyridyl, pyrimidyl, quinolinyl, indolyl, pyrrolyl, furanyl, thienyl and imidazolyl, pyrazolyl, indazolyl, thiazolyl and benzothiazolyl. In certain embodiments, each heteroaryl is selected from pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, isothiazolyl, pyridinyl-*N*-oxide, pyrrolyl *N*-oxide, pyrimidinyl *N*-oxide, pyridazinyl *N*-oxide, pyrazinyl *N*-oxide, imidazolyl *N*-oxide, isoxazolyl *N*-oxide, oxazolyl *N*-oxide, thiazolyl *N*-oxide, pyrrolyl *N*-oxide, oxadiazolyl *N*-oxide, thiadiazolyl *N*-oxide, triazolyl *N*-oxide, and tetrazolyl *N*-oxide. Preferred heteroaryl groups include pyridyl, pyrimidyl, quinolinyl, indolyl, pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, indazolyl, thiazolyl and benzothiazolyl. The heteroaryl groups herein are unsubstituted or, when specified as "optionally substituted", can unless stated otherwise be substituted in one or more substitutable positions with various groups, as described below.

[0112] The term "heterocycloalkyl" or "Hca" refers to a non-aromatic ring or ring system containing at least one heteroatom that is preferably selected from nitrogen, oxygen and sulfur, wherein said heteroatom is in a non-aromatic ring. The heterocycloalkyl may have 1, 2, 3 or 4 heteroatoms. The heterocycloalkyl may be saturated (*i.e.*, a heterocycloalkyl) or partially unsaturated (*i.e.*, a heterocycloalkenyl). Heterocycloalkyl includes monocyclic

groups of three to eight annular atoms as well as bicyclic and polycyclic ring systems, including bridged and fused systems, wherein each ring includes three to eight annular atoms. The heterocycloalkyl ring is optionally fused to other heterocycloalkyl rings and/or non-aromatic hydrocarbon rings and/or phenyl rings. In certain embodiments, the heterocycloalkyl groups have from 3 to 7 members in a single ring. In other embodiments, heterocycloalkyl groups have 5 or 6 members in a single ring. In some embodiments, the heterocycloalkyl groups have 3, 4, 5, 6 or 7 members in a single ring. Examples of heterocycloalkyl groups include, for example, azabicyclo[2.2.2]octyl (in each case also "quinuclidinyl" or a quinuclidine derivative), azabicyclo[3.2.1]octyl, 2,5-diazabicyclo[2.2.1]heptyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, 2-oxazolidonyl, piperazinyl, homopiperazinyl, piperazinonyl, pyrrolidinyl, azepanyl, azetidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, 3,4-dihydroisoquinolin-2(1*H*)-yl, isoindolindionyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, imidazolidonyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-oxide. Especially desirable heterocycloalkyl groups include morpholinyl, 3,4-dihydroisoquinolin-2(1*H*)-yl, tetrahydropyranyl, piperidinyl, aza-bicyclo[2.2.2]octyl, γ-butyrolactonyl (*i.e.*, an oxo-substituted tetrahydrofuranyl), γ-butryolactamyl (*i.e.*, an oxo-substituted pyrrolidine), pyrrolidinyl, piperazinyl, azepanyl, azetidinyl, thiomorpholinyl, thiomorpholinyl S,S-dioxide, 2-oxazolidonyl, imidazolidonyl, isoindolindionyl, piperazinonyl. The heterocycloalkyl groups herein are unsubstituted or, when specified as "optionally substituted", can unless stated otherwise be substituted in one or more substitutable positions with various groups, as described below.

[0113] The term "cycloalkyl" or "Cak" refers to a non-aromatic carbocyclic ring or ring system, which may be saturated (*i.e.*, a cycloalkyl) or partially unsaturated (*i.e.*, a cycloalkenyl). The cycloalkyl ring optionally fused to or otherwise attached (*e.g.*, bridged systems) to other cycloalkyl rings. Certain examples of cycloalkyl groups present in the disclosed compounds have from 3 to 7 members in a single ring, such as having 5 or 6 members in a single ring. In some embodiments, the cycloalkyl groups have 3, 4, 5, 6 or 7 members in a single ring. Examples of cycloalkyl groups include, for example, cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, tetrahydronaphthyl and bicyclo[2.2.1]heptane. The

cycloalkyl groups herein are unsubstituted or, when specified as "optionally substituted", may be substituted in one or more substitutable positions with various groups.

[0114] The term "ring system" encompasses monocycles, as well as fused and/or bridged polycycles.

[0115] The term "oxa" means a divalent oxygen radical in a chain, sometimes designated as -O-.

[0116] The term "oxo" means a doubly bonded oxygen, sometimes designated as =O or for example in describing a carbonyl "C(O)" may be used to show an oxo substituted carbon.

[0117] The term "electron withdrawing group" means a group that withdraws electron density from the structure to which it is attached than would a similarly-attached hydrogen atom. For example, electron withdrawing groups can be selected from the group consisting of halo (*e.g.*, fluoro, chloro, bromo, and iodo), cyano, -(C_1-C_4 fluoroalkyl), -O-(C_1-C_4 fluoroalkyl), -C(O)-(C_0-C_4alkyl), -C(O)O-(C_0-C_4alkyl), -C(O)N(C_0-C_4alkyl)(C_0-C_4alkyl), -$S(O)_2$O-(C_0-C_4alkyl), NO_2 and -C(O)-Hca in which the Hca includes a nitrogen atom to which the -C(O)- is bound, in which no alkyl, fluoroalkyl or heterocycloalkyl is substituted with an aryl, heteroaryl, cycloalkyl or heterocycloalkyl-containing group.

[0118] The term "substituted," when used to modify a specified group or radical, means that one or more hydrogen atoms of the specified group or radical are each, independently of one another, replaced with the same or different substituent groups as defined below, unless specified otherwise.

[0119] Substituent groups for substituting for hydrogens on saturated carbon atoms in the specified group or radical are, unless otherwise specified, -R^{60}, halo, -O^-M^+, =O, -OR^{70}, -SR^{70}, -S^-M^+, =S, -$NR^{80}R^{80}$, =NR^{70}, =N-OR^{70}, trihalomethyl, -CF_3, -CN, -OCN, -SCN, -NO, -NO_2, =N_2, -N_3, -SO_2R^{70}, -$SO_2O^-M^+$, -SO_2OR^{70}, -OSO_2R^{70}, -$OSO_2O^-M^+$, -OSO_2OR^{70}, -$P(O)(O^-)_2(M^+)_2$, -$P(O)(OR^{70})O^-M^+$, -$P(O)(OR^{70})_2$, -$C(O)R^{70}$, -$C(S)R^{70}$, -$C(NR^{70})R^{70}$, -$C(O)O^-M^+$, -$C(O)OR^{70}$, -$C(S)OR^{70}$, -$C(O)NR^{80}R^{80}$, -$C(NR^{70})NR^{80}R^{80}$, -$OC(O)R^{70}$, -$OC(S)R^{70}$, -$OC(O)O^-M^+$, -$OC(O)OR^{70}$, -$OC(S)OR^{70}$, -$NR^{70}C(O)R^{70}$, -$NR^{70}C(S)R^{70}$, -$NR^{70}CO_2^-M^+$, -$NR^{70}CO_2R^{70}$, -$NR^{70}C(S)OR^{70}$, -$NR^{70}C(O)NR^{80}R^{80}$, -$NR^{70}C(NR^{70})R^{70}$ and -$NR^{70}C(NR^{70})NR^{80}R^{80}$. Each R^{60} is independently selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl, each of which is optionally substituted with 1, 2, 3, 4 or 5 groups selected from the group consisting of halo, -O^-M^+, =O, -OR^{71}, -SR^{71}, -S^-M^+, =S, -$NR^{81}R^{81}$, =NR^{71}, =N-OR^{71}, trihalomethyl, -CF_3, -CN, -OCN, -SCN, -NO, -NO_2, =N_2, -N_3, -SO_2R^{71}, -$SO_2O^-M^+$, -SO_2OR^{71}, -OSO_2R^{71}, -$OSO_2O^-M^+$, -OSO_2OR^{71}, -$P(O)(O^-)_2(M^+)_2$,

-P(O)(OR^{71})O$^-$M$^+$, -P(O)(OR^{71})$_2$, -C(O)R^{71}, -C(S)R^{71}, -C(NR^{71})R^{71}, -C(O)O$^-$M$^+$, -C(O)OR^{71}, -C(S)OR^{71}, -C(O)NR^{81}R^{81}, -C(NR^{71})NR^{81}R^{81}, -OC(O)R^{71}, -OC(S)R^{71}, -OC(O)O$^-$M$^+$, -OC(O)OR^{71}, -OC(S)OR^{71}, -NR^{71}C(O)R^{71}, -NR^{71}C(S)R^{71}, -NR^{71}CO$_2^-$M$^+$, -NR^{71}CO$_2$R^{71}, -NR^{71}C(S)OR^{71}, -NR^{71}C(O)NR^{81}R^{81}, -NR^{71}C(NR^{71})R^{71} and -NR^{71}C(NR^{71})NR^{81}R^{81}. Each R^{70} is independently hydrogen or R^{60}; each R^{80} is independently R^{70} or alternatively, two R^{80}'s, taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered heterocycloalkyl which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S, of which N may have -H or C_1-C_3alkyl substitution; and each M$^+$ is a counter ion with a net single positive charge. Each R^{71} is independently hydrogen or R^{61}, in which R^{61} is alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl, each of which is optionally substituted with 1, 2, 3, 4 or 5 groups selected from the group consisting of halo, -O$^-$M$^+$, =O, -OR^{72}, -SR^{72}, -S$^-$M$^+$, =S, -NR^{82}R^{82}, =NR^{72}, =N-OR^{72}, trihalomethyl, -CF_3, -CN, -OCN, -SCN, -NO, -NO_2, =N_2, -N_3, -SO_2R^{71}, -SO_2O$^-$M$^+$, -SO_2OR^{72}, -OSO$_2$R^{72}, -OSO$_2$O$^-$M$^+$, -OSO$_2$OR^{72}, -P(O)(O$^-$)$_2$(M$^+$)$_2$, -P(O)(OR^{72})O$^-$M$^+$, -P(O)(OR^{72})$_2$, -C(O)R^{72}, -C(S)R^{72}, -C(NR^{72})R^{72}, -C(O)O$^-$M$^+$, -C(O)OR^{72}, -C(S)OR^{72}, -C(O)NR^{82}R^{82}, -C(NR^{72})NR^{82}R^{82}, -OC(O)R^{72}, -OC(S)R^{72}, -OC(O)O$^-$M$^+$, -OC(O)OR^{72}, -OC(S)OR^{72}, -NR^{72}C(O)R^{72}, -NR^{72}C(S)R^{72}, -NR^{72}CO$_2^-$M$^+$, -NR^{72}CO$_2$R^{72}, -NR^{72}C(S)OR^{72}, -NR^{72}C(O)NR^{82}R^{82}, -NR^{72}C(NR^{72})R^{72} and -NR^{72}C(NR^{72})NR^{82}R^{82}; and each R^{81} is independently R^{71} or alternatively, two R^{81}s, taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered heterocycloalkyl which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S, of which N may have -H or C_1-C_3 alkyl substitution. Each R^{72} is independently hydrogen, (C_1-C_6alkyl) or (C_1-C_6fluoroalkyl); each R^{82} is independently R^{72} or alternatively, two R^{82}s, taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered heterocycloalkyl which may optionally include 1, 2, 3 or 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S, of which N may have -H or C_1-C_3alkyl substitution. Each M$^+$ may independently be, for example, an alkali ion, such as K$^+$, Na$^+$, Li$^+$; an ammonium ion, such as $^+$N(R^{60})$_4$; or an alkaline earth ion, such as [Ca^{2+}]$_{0.5}$, [Mg^{2+}]$_{0.5}$, or [Ba^{2+}]$_{0.5}$ ("subscript 0.5 means *e.g.* that one of the counter ions for such divalent alkali earth ions can be an ionized form of a presently disclosed compound and the other a typical counter ion such as chloride, or two ionized presently disclosed molecules can serve as counter ions for such divalent alkali earth ions, or a doubly ionized compound can serve as the counter ion for such divalent alkali earth ions).

As specific examples, $-NR^{80}R^{80}$ is meant to include $-NH_2$, -NH-alkyl, *N*-pyrrolidinyl, *N*-piperazinyl, 4-methyl-piperazin-1-yl and *N*-morpholinyl.

[0120] Substituent groups for hydrogens on unsaturated carbon atoms in "substituted" alkene, alkyne, aryl and heteroaryl groups are, unless otherwise specified, $-R^{60}$, halo, $-O^-M^+$, $-OR^{70}$, $-SR^{70}$, $-S^-M^+$, $-NR^{80}R^{80}$, trihalomethyl, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-SO_2R^{70}$, $-SO_3^-M^+$, $-SO_3R^{70}$, $-OSO_2R^{70}$, $-OSO_3^-M^+$, $-OSO_3R^{70}$, $-PO_3^{-2}(M^+)_2$, $-P(O)(OR^{70})O^-M^+$, $-P(O)(OR^{70})_2$, $-C(O)R^{70}$, $-C(S)R^{70}$, $-C(NR^{70})R^{70}$, $-CO_2^-M^+$, $-CO_2R^{70}$, $-C(S)OR^{70}$, $-C(O)NR^{80}R^{80}$, $-C(NR^{70})NR^{80}R^{80}$, $-OC(O)R^{70}$, $-OC(S)R^{70}$, $-OCO_2^-M^+$, $-OCO_2R^{70}$, $-OC(S)OR^{70}$, $-NR^{70}C(O)R^{70}$, $-NR^{70}C(S)R^{70}$, $-NR^{70}CO_2^-M^+$, $-NR^{70}CO_2R^{70}$, $-NR^{70}C(S)OR^{70}$, $-NR^{70}C(O)NR^{80}R^{80}$, $-NR^{70}C(NR^{70})R^{70}$ and $-NR^{70}C(NR^{70})NR^{80}R^{80}$, where R^{60}, R^{70}, R^{80} and M^+ are as previously defined.

[0121] Substituent groups for hydrogens on nitrogen atoms in "substituted" heteroalkyl and heterocycloalkyl groups are, unless otherwise specified, $-R^{60}$, $-O^-M^+$, $-OR^{70}$, $-SR^{70}$, $-S^-M^+$, $-NR^{80}R^{80}$, trihalomethyl, $-CF_3$, -CN, -NO, $-NO_2$, $-S(O)_2R^{70}$, $-S(O)_2O^-M^+$, $-S(O)_2OR^{70}$, $-OS(O)_2R^{70}$, $-OS(O)_2O^-M^+$, $-OS(O)_2OR^{70}$, $-P(O)(O^-)_2(M^+)_2$, $-P(O)(OR^{70})O^-M^+$, $-P(O)(OR^{70})(OR^{70})$, $-C(O)R^{70}$, $-C(S)R^{70}$, $-C(NR^{70})R^{70}$, $-C(O)OR^{70}$, $-C(S)OR^{70}$, $-C(O)NR^{80}R^{80}$, $-C(NR^{70})NR^{80}R^{80}$, $-OC(O)-R^{70}$, $-OC(S)R^{70}$, $-OC(O)OR^{70}$, $-OC(S)OR^{70}$, $-NR^{70}C(O)R^{70}$, $-NR^{70}C(S)R^{70}$, $-NR^{70}C(O)OR^{70}$, $-NR^{70}C(S)OR^{70}$, $-NR^{70}C(O)NR^{80}R^{80}$, $-NR^{70}C(NR^{70})R^{70}$ and $-NR^{70}C(NR^{70})NR^{80}R^{80}$, where R^{60}, R^{70}, R^{80} and M^+ are as previously defined.

[0122] In certain embodiments of the compounds disclosed herein, a group that is substituted has 1, 2, 3, or 4 substituents, 1, 2, or 3 substituents, 1 or 2 substituents, or 1 substituent.

[0123] In certain embodiments, substituent groups on "substituted" alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups are -halo, -OH, -O-(C_1-C_4alkyl), -O-(C_1-C_4haloalkyl), -N(C_0-C_4 alkyl)(C_0-C_4alkyl), -SH, -S(O)$_{0\text{-}2}$-(C_1-C_4alkyl), -(C_1-C_4alkyl), -(C_1-C_4haloalkyl), -C(O)-(C_0-C_4alkyl), -C(O)N(C_0-C_4alkyl)(C_0-C_4alkyl), -N(C_0-C_4alkyl)C(O)(C_0-C_4alkyl)(C_0-C_4alkyl), -C(O)O-(C_0-C_4alkyl), -OC(O)-(C_0-C_4alkyl), S(O)$_2$-O(C_0-C_4alkyl), and $-NO_2$, in which no alkyl is further substituted.

[0124] The compounds disclosed herein can also be provided as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases and organic acids and bases. If the compound is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids.

Such salts may be, for example, acid addition salts of at least one of the following acids: benzenesulfonic acid, citric acid, α-glucoheptonic acid, D-gluconic acid, glycolic acid, lactic acid, malic acid, malonic acid, mandelic acid, phosphoric acid, propanoic acid, succinic acid, sulfuric acid, tartaric acid (d, l, or dl), tosic acid (toluenesulfonic acid), valeric acid, palmitic acid, pamoic acid, sebacic acid, stearic acid, lauric acid, acetic acid, adipic acid, carbonic acid, 4-chlorobenzenesulfonic acid, ethanedisulfonic acid, ethylsuccinic acid, fumaric acid, galactaric acid (mucic acid), D-glucuronic acid, 2-oxo-glutaric acid, glycerophosphoric acid, hippuric acid, isethionic acid (ethanolsulfonic acid), lactobionic acid, maleic acid, 1,5-naphthalene-disulfonic acid, 2-naphthalene-sulfonic acid, pivalic acid, terephthalic acid, thiocyanic acid, cholic acid, n-dodecyl sulfate, 3-hydroxy-2-naphthoic acid, 1-hydroxy-2-naphthoic acid, oleic acid, undecylenic acid, ascorbic acid, (+)-camphoric acid, d-camphorsulfonic acid, dichloroacetic acid, ethanesulfonic acid, formic acid, hydriodic acid, hydrobromic acid, hydrochloric acid, methanesulfonic acid, nicotinic acid, nitric acid, orotic acid, oxalic acid, picric acid, L-pyroglutamic acid, saccharine, salicylic acid, gentisic acid, and/or 4-acetamidobenzoic acid.

[0125] The compounds described herein can also be provided in prodrug form. "Prodrug" refers to a derivative of an active compound (drug) that undergoes a transformation under the conditions of use, such as within the body, to release the active drug. Prodrugs are frequently, but not necessarily, pharmacologically inactive until converted into the active drug. Prodrugs are typically obtained by masking a functional group in the drug believed to be in part required for activity with a progroup (defined below) to form a promoiety which undergoes a transformation, such as cleavage, under the specified conditions of use to release the functional group, and hence the active drug. The cleavage of the promoiety can proceed spontaneously, such as by way of a hydrolysis reaction, or it can be catalyzed or induced by another agent, such as by an enzyme, by light, by acid, or by a change of or exposure to a physical or environmental parameter, such as a change of temperature. The agent can be endogenous to the conditions of use, such as an enzyme present in the cells to which the prodrug is administered or the acidic conditions of the stomach, or it can be supplied exogenously. A wide variety of progroups, as well as the resultant promoieties, suitable for masking functional groups in the active drugs to yield prodrugs are well-known in the art. For example, a hydroxyl functional group can be masked as a sulfonate, ester or carbonate promoiety, which can be hydrolyzed *in vivo* to provide the hydroxyl group. An amino functional group can be masked as an amide, carbamate, imine, urea, phosphenyl, phosphoryl or sulfenyl promoiety, which can be hydrolyzed *in vivo* to provide the amino group. A

carboxyl group can be masked as an ester (including silyl esters and thioesters), amide or hydrazide promoiety, which can be hydrolyzed *in vivo* to provide the carboxyl group. Specific examples of suitable progroups and their respective promoieties will be apparent to those of skill in the art.

[0126] The compounds disclosed herein can also be provided as *N*-oxides.

[0127] The presently disclosed compounds, salts, prodrugs and *N*-oxides can be provided, for example, in solvate or hydrate form.

[0128] One of ordinary skill in the art of medicinal chemistry also will appreciate that the disclosed structures are intended to include isotopically enriched forms of the present compounds. As used herein "isotopes" includes those atoms having the same atomic number but different mass numbers. As is known to those of skill in the art, certain atoms, such as hydrogen occur in different isotopic forms. For example, hydrogen includes three isotopic forms, protium, deuterium and tritium. As will be apparent to those of skill in the art upon consideration of the present compounds, certain compounds can be enriched at a given position with a particular isotope of the atom at that position. For example, compounds having a fluorine atom, may be synthesized in a form enriched in the radioactive fluorine isotope ^{18}F. Similarly, compounds may be enriched in the heavy isotopes of hydrogen: deuterium and tritium; and similarly can be enriched in a radioactive isotope of carbon, such as ^{13}C. Such isotopic variant compounds undergo different metabolic pathways and can be useful, for example, in studying the ubiquitination pathway and its role in disease.

[0129] As used herein, the term "cell" is meant to refer to a cell that is *in vitro*, ex vivo or *in vivo*. In some embodiments, an ex vivo cell can be part of a tissue sample excised from an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal.

[0130] As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" an enzyme with a compound includes the administration of a compound described herein to an individual or patient, such as a human, as well as, for example, introducing a compound into a sample containing a cellular or purified preparation containing the enzyme.

[0131] As used herein, the terms "individual," "patient," or "subject" are used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

[0132] As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

[0133] In certain embodiments, a therapeutically effective amount can be an amount suitable for

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed or otherwise susceptible to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder; or

(3) ameliorating the disease (including a symptom thereof); for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

[0134] As used here, the terms "treatment" and "treating" means (i) ameliorating the referenced disease state, condition, or disorder (or a symptom thereof), such as, for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing or improving the pathology and/or symptomatology) such as decreasing the severity of disease or symptom thereof; or (ii) eliciting the referenced biological effect (*e.g.*, modulation or inhibition of GDF-8 or TGF-β1).

[0135] Manifestation of amelioration of a disease condition by inhibiting GDF-8 or TGF-β1 may require the concomitant or sequential administration of additional therapeutic agents, such as antineoplastic agents in the case of cancer, or antiretroviral agents in the case of viral diseases. For example, administration of GDF-8 and TGF-β1inhibitors for the treatment of cancer does not always produce a direct antitumor effect when used as a single agent. However, when combined with chemotherapeutic drugs (antineoplastic) the antitumor effect observed is higher than the sum of effects of each agent alone.

[0136] As used herein, the terms "catalytic pocket", "catalytic site", "active site" collectively and indistinctly refer to a region of the enzyme that contains amino acid residues responsible for the substrate binding (charge, hydrophobicity, steric hindrance) and catalytic

amino acid residues which act as proton donors or acceptors or are responsible for binding a cofactor and participate in the catalysis of a chemical reaction.

[0137] As used herein, the phrase "pharmaceutically acceptable salt" refers to both pharmaceutically acceptable acid and base addition salts and solvates. Such pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

Pharmaceutical Formulations and Dosage Forms

[0138] The compounds of structural formulae (I) – (III) can be administered, for example, orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing one or more pharmaceutically acceptable carriers, diluents or excipients. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (*e.g.*, intravenous), intramuscular, or intrathecal injection or infusion techniques and the like.

[0139] Pharmaceutical compositions can be made using the presently disclosed compounds. For example, in one embodiment, a pharmaceutical composition includes a pharmaceutically acceptable carrier, diluent or excipient, and compound as described above with reference to structural formulae (I) – (III).

[0140] In the pharmaceutical compositions disclosed herein, one or more compounds of structural formulae (I) – (III) may be present in association with one or more pharmaceutically acceptable carriers, diluents or excipients, and, if desired, other active ingredients. The pharmaceutical compositions containing compounds of structural formulae (I) – (III) may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

[0141] Compositions intended for oral use can be prepared according to any suitable method for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of

tablets. These excipients can be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by suitable techniques to delay disintegration and absorption 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 can be employed.

[0142] Formulations for oral use can also be presented as hard gelatin capsules, wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[0143] Formulations for oral use can also be presented as lozenges.

[0144] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0145] Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0146] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

[0147] Pharmaceutical compositions can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

[0148] In some embodiments, the pharmaceutically acceptable carrier, diluent, or excipient is not water. In other embodiments, the water comprises less than 50% of the composition. In some embodiments, composiitons comprising less than 50% water have at least 1%, 2%, 3%, 4% or 5% water. In other embodiments, the water content is present in the composition in a trace amount.

[0149] In some embodiments, the pharmaceutically acceptable carrier, diluent, or excipient is not alcohol. In other embodiments, the alcohol comprises less than 50% of the composition. In some embodiments, composiitons comprising less than 50% alcohol have at least 1%, 2%, 3%, 4% or 5% alcohol. In other embodiments, the alcohol content is present in the composition in a trace amount.

[0150] Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a demulcent, a preservative, flavoring, and coloring agents. The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils can be employed as a solvent

or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0151] Compounds of structural formulae (I) – (III) can also be administered in the form of suppositories, *e.g.*, for rectal administration of the drug. These compositions can be prepared by mixing the compound with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

[0152] Compounds of structural formula (I) – (III) can also be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

[0153] The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[0154] The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0155] For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of a compound described herein.

[0156] The tablets or pills can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0157] The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

[0158] The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

[0159] The therapeutic dosage of the compounds can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound described herein in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds described herein can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 µg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight

per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0160] The compounds described herein can also be formulated in combination with one or more additional active ingredients which can include any pharmaceutical agent such as anti-viral agents, vaccines, antibodies, immune enhancers, immune suppressants, anti-inflammatory agents and the like.

Examples

General Synthetic Methodologies

[0161] Many general references providing commonly known chemical synthetic schemes and conditions useful for synthesizing the disclosed compounds are available (see, *e.g.*, Smith and March, March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Fifth Edition, Wiley-Interscience, 2001; or Vogel, A Textbook of Practical Organic Chemistry, Including Qualitative Organic Analysis, Fourth Edition, New York: Longman, 1978).

[0162] Compounds as described herein can be purified by any of the means known in the art, including chromatographic means, such as HPLC, preparative thin layer chromatography, flash column chromatography and ion exchange chromatography. Any suitable stationary phase can be used, including normal and reversed phases as well as ionic resins. Most typically the disclosed compounds are purified via silica gel and/or alumina chromatography. See, *e.g.*, Introduction to Modern Liquid Chromatography, 2nd Edition, ed. L. R. Snyder and J. J. Kirkland, John Wiley and Sons, 1979; and Thin Layer Chromatography, ed E. Stahl, Springer-Verlag, New York, 1969.

[0163] During any of the processes for preparation of the subject compounds, it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups as described in standard works, such as J. F. W. McOmie, "Protective Groups in Organic Chemistry," Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis," Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie," Houben-Weyl, 4.sup.th edition, Vol. 15/l,

Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosauren, Peptide, Proteine," Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and/or in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide and Derivate," Georg Thieme Verlag, Stuttgart 1974. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

[0164] The compounds disclosed herein can be made using procedures familiar to the person of ordinary skill in the art and as described herein. For example, compounds of structural formula (I) can be prepared according to Schemes 1-3, or analogous synthetic schemes.

[0165] One of skill in the art can adapt the reaction sequences of Schemes 1 and 2 to fit the desired target molecule. Of course, in certain situations one of skill in the art will use different reagents to affect one or more of the individual steps or to use protected versions of certain of the substituents. Additionally, one skilled in the art would recognize that compounds of structural formulae (I) – (III) can be synthesized using different routes altogether.

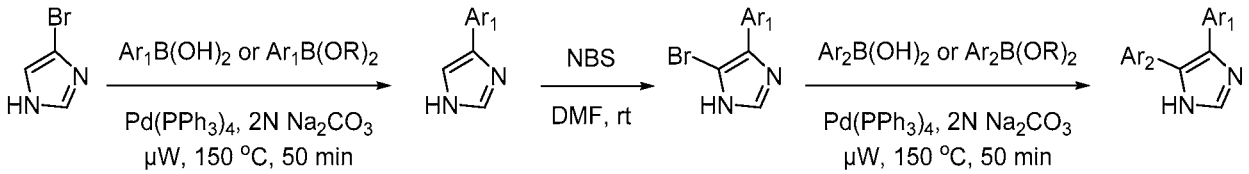
[0166] Compounds suitable for use in the presently disclosed pharmaceutical compositions include compounds of Table A, above. These compounds can be made according to the general schemes described above, for example using a procedure similar to that described below in the Examples.

[0167] The following examples are intended to further illustrate certain embodiments and are not intended to limit the scope of the presently disclosed compounds.

EXAMPLES

Example 1: Synthesis and Characterization

Scheme 1: General Synthesis of 4,5-Diarylimidazoles



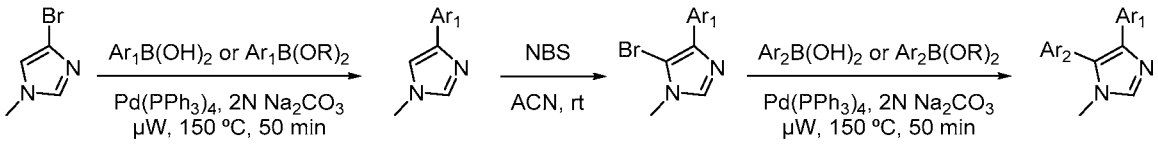
[0168] **Step 1:** A solution of 4-bromo-1*H*-imidazole (1.0 g, 6.8 mmol), (4-fluoro-3-methylphenyl)boronic acid (1.1 g, 7.1 mmol), tetrakis(triphenylphosphine)palladium(0) (0.63 g, 0.55 mmol) and aqueous Na_2CO_3 (2 M, 4 mL, 8.0 mmol) in a mixture of DME/EtOH/H_2O (7:3:2, 10 mL) was evacuated and then refilled with nitrogen (three cycles). Resulting

reaction mixture was then irradiated in the microwave at 150 °C for 50 min., dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black residue. The residue was purified by column chromatography eluting with MeOH/DCM to provide 4-(4-fluoro-3-methylphenyl)-1*H*-imidazole (1.1g, 92%). MS *m/e*: 177 $(M+H)^+$.

[0169] **Step 2:**To a solution of 4-(4-fluoro-3-methylphenyl)-1*H*-imidazole (1.1 g, 6.2 mmol) in DMF (10 mL), *N*-bromosuccinimide (1.2 g, 6.7 mmol) was added at room temperature. The resulting reaction mixture was allowed to stir at room temperature for 1h, and then transferred dropwise into a stirred solution of ice-water (50 mL). The resulting yellow precipitate was filtered, washed with water and dried under vacuum overnight to give 5-bromo-4-(4-fluoro-3-methylphenyl)-1*H*-imidazole (1.2 g, 74%). MS *m/e*: 255 $(M+H)^+$.

[0170] **Step 3:**A degassed solution of 5-bromo-4-(4-fluoro-3-methylphenyl)-1*H*-imidazole (50 mg, 0.2 mmol), indazole-5-boronic acid pinacol ester (60 mg,0.25 mmol), tetrakis(triphenylphosphine)palladium(0) (25mg, 0.02 mmol) and aqueous Na_2CO_3 (2 M, 0.3 mL) in a mixture of DME/EtOH/H_2O (7:3:2, 1.0 mL) was irradiated in the microwave at 150 °C for 50 min. The reaction mixture was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black residue, which was purified by HPLC to provide 5-(4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 293 $(M+H)^+$.

[0171] **Scheme 2: General Synthesis of 1-Methyl-4,5-diarylimidazoles**



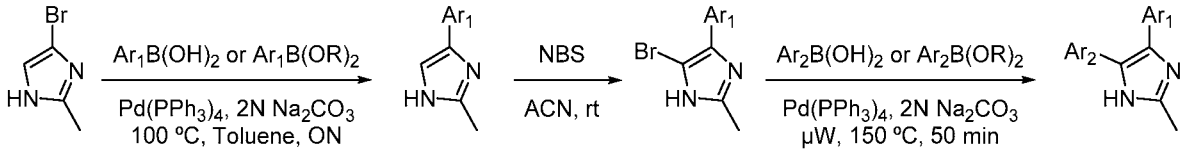
[0172] **Step 1:** A solution of 4-bromo-1-methyl-1*H*-imidazole (1.0 g, 6.2mmol), (4-fluoro-3-methylphenyl)boronic acid (1.0 g, 6.5 mmol), tetrakis(triphenylphosphine)-palladium(0) (0.6 g, 0.52 mmol) and aqueous Na_2CO_3 (2 M,4 mL, 8.0 mmol) in a mixture of DME/EtOH/H_2O (7:3:2, 10 mL) was evacuated and then refilled with nitrogen (three cycles). Resulting reaction mixture was then irradiated in the microwave at 150 °C for 50 min., dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black residue, which was purified by column chromatography eluting with MeOH/DCM to provide 4-(4-fluoro-3-methylphenyl)-1-methyl-1*H*-imidazole (0.6 g, 51%). MS *m/e*: 191 $(M+H)^+$.

[0173] **Step 2:** To a solution of 4-(4-fluoro-3-methylphenyl)-1-methyl-1*H*-imidazole (0.6 g, 3.2 mmol) in acetonitrile (10 mL), *N*-bromosuccinimide (0.62 g, 3.5 mmol) was added at room temperature. The resulting reaction mixture was allowed to stir at room temperature for 1h, and then transferred dropwise into a stirred solution of ice-water (50 mL). The resulting

yellow precipitate was filtered, washed with water and dried under vacuum overnight to give 5-bromo-4-(4-fluoro-3-methylphenyl)-1-methyl-1*H*-imidazole (0.6 g, 71%). MS *m/e*: 269 $(M+H)^+$.

[0174] **Step 3:** A degassed solution of 5-bromo-4-(4-fluoro-3-methylphenyl)-1-methyl-1*H*-imidazole (50 mg, 0.2 mmol), indazole-5-boronic acid pinacol ester (60 mg, 0.25 mmol), tetrakis(triphenylphosphine)palladium(0) (25 mg, 0.02 mmol) and aqueous Na_2CO_3 (2 M, 0.3 mL) in a mixture of DME/EtOH/H_2O (7:3:2, 1.0 mL) was irradiated in the microwave at 150 °C for 50 min. The reaction mixture was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black residue, which was purified by HPLC to provide 5-(4-(4-fluoro-3-methylphenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 307 $(M+H)^+$.

Scheme 3: General Synthesis of 2-Methyl-4,5-diarylimidazoles



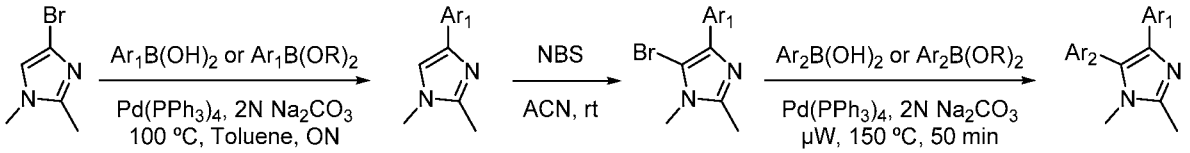
[0175] **Step 1:** A solution of 4-bromo-2-methyl-1*H*-imidazole (1.0 g, 6.2 mmol), (4-fluoro-3-methylphenyl)boronic acid (1.1 g, 7.1 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.33 g, 0.3 mmol) in a mixture of aqueous Na_2CO_3 solution (2 M, 10 mL, 20 mmol) and toluene (10 mL) was evacuated and then refilled with nitrogen (three cycles). Resulting reaction mixture was then allowed to stir at 100 °C overnight, cooled down to room temperature, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black residue. Purification by column chromatography eluting with MeOH/DCM provided 4-(4-fluoro-3-methylphenyl)-2-methyl-1*H*-imidazole (1.1 g, 93%). MS *m/e*: 191 $(M+H)^+$.

[0176] **Step 2:** To a solution of 4-(4-fluoro-3-methylphenyl)-2-methyl-1*H*-imidazole (1.1 g, 5.8 mmol) in acetonitrile (10 mL), *N*-bromosuccinimide (0.62 g, 3.5 mmol) was added. The resulting reaction mixture was allowed to stir at room temperature for 1h, and then transferred dropwise into a stirred solution of ice-water (50 mL). The resulting yellow precipitate was filtered, washed with water and dried under vacuum overnight to give 5-bromo-4-(4-fluoro-3-methylphenyl)-2-methyl-1*H*-imidazole as a yellow solid (0.89 g, 57%). MS *m/e*: 269 $(M+H)^+$.

[0177] **Step 3:** A degassed solution of 5-bromo-4-(4-fluoro-3-methylphenyl)-2-methyl-1*H*-imidazole (50 mg, 0.2 mmol), indazole-5-boronic acid pinacol ester (60 mg, 0.25 mmol), tetrakis(triphenylphosphine)palladium(0) (25 mg, 0.02 mmol) and aqueous Na_2CO_3 (2 M, 0.3

mL) in a mixture of DME/EtOH/H_2O (7:3:2, 1.0 mL) was irradiated in the microwave at 150 °C for 50 min. The reaction mixture was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black residue, which was purified by HPLC to provide 5-(4-(4-fluoro-3-methylphenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 307 $(M+H)^+$.

Scheme 4: General Synthesis of 1,2-Dimethyl-4,5-diarylimidazoles

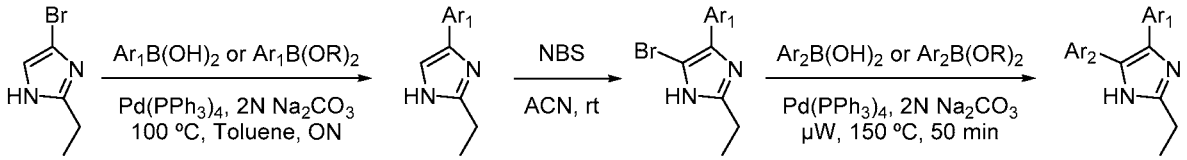


[0178] **Step 1:** A solution of 4-bromo-1,2-dimethyl-1*H*-imidazole (1.0 g, 5.7 mmol), (4-fluoro-3-methylphenyl)boronic acid (0.92 g, 6.0 mmol), tetrakis(triphenylphosphine)-palladium(0) (0.33 g, 0.3 mmol) and aqueous Na_2CO_3 (2 M, 10 mL, 20 mmol) in toluene (10 ml) was evacuated and then refilled with nitrogen (three cycles). Resulting reaction mixture was then allowed to stir at 100 °C overnight, cooled down to room temperature, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black residue. Column chromatography on silica gel, eluting with MeOH/DCM provided 4-(4-fluoro-3-methylphenyl)-1,2-dimethyl-1*H*-imidazole (0.88 g, 75%). MS *m/e*: 205 $(M+H)^+$.

[0179] **Step 2:** To a solution of 4-(4-fluoro-3-methylphenyl)-1,2-dimethyl-1*H*-imidazole (0.88 g, 4.3 mmol) in acetonitrile (10 mL), *N*-bromosuccinimide (0.81 g, 4.5 mmol) was added. The resulting reaction mixture was allowed to stir at room temperature for 1h, and then transferred dropwise into a stirred solution of ice-water (50 mL). The resulting white precipitate was filtered, washed with water and dried under vacuum overnight to give 5-bromo-4-(4-fluoro-3-methylphenyl)-1,2-dimethyl-1*H*-imidazole (0.94 g, 77%). MS *m/e*: 283 $(M+H)^+$.

[0180] **Step 3:** A degassed solution of 5-bromo-4-(4-fluoro-3-methylphenyl)-1,2-dimethyl-1*H*-imidazole (50 mg, 0.2 mmol), indazole-5-boronic acid pinacol ester (60 mg, 0.25 mmol), tetrakis(triphenylphosphine)palladium(0) (25 mg, 0.02 mmol) and aqueous Na_2CO_3 (2 M, 0.3 mL) in a mixture of DME/EtOH/H_2O (7:3:2, 1.0 mL) was irradiated in the microwave at 150 °C for 50 min. The reaction mixture was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black residue, which was purified by HPLC to provide 5-(4-(4-fluoro-3-methylphenyl)-1,2-dimethyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 321 $(M+H)^+$.

Scheme 5: General Synthesis of 2-Ethyl-4,5-diarylimidazoles

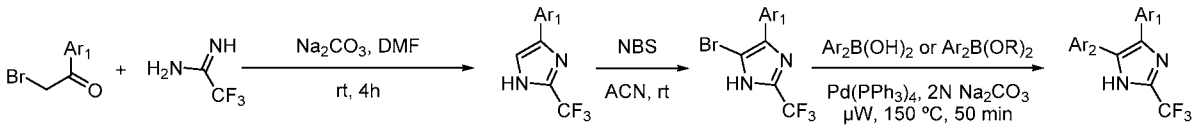


[0181] **Step 1:** A solution of 4-bromo-2-ethyl-1*H*-imidazole (1.0 g, 5.7 mmol), (4-fluoro-3-methylphenyl)boronic acid (0.97 g, 6.3 mmol), tetrakis(triphenylphosphine)palladium(0) (0.33 g, 0.3 mmol) and aqueous Na_2CO_3 (2 M, 10 mL, 20 mmol) in toluene (10 ml) was evacuated and then refilled with nitrogen (three cycles). Resulting reaction mixture was then allowed to stir at 100 °C overnight, cooled down to room temperature, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black residue. Column chromatography on silica gel, eluting with MeOH/DCM provided 2-ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazole as a colorless oil (0.95 g, 81%). MS *m/e*: 205 $(M+H)^+$.

[0182] **Step 2:** To a solution of 4-(4-fluoro-3-methylphenyl)-2-ethyl-1*H*-imidazole (0.95 g, 4.7 mmol) in acetonitrile (10 mL), *N*-bromosuccinimide (0.87 g, 4.9 mmol) was added. The resulting reaction mixture was allowed to stir at room temperature for 1h, concentrated and added water (30 mL) and dichloromethane (30 mL). The organic layer was then separated and the aqueous layer was extracted with dichloromethane (3x20 mL), dried ($MgSO_4$) and chromatographed on silica gel, eluting with MeOH/DCM, to give 5-bromo-2-ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazole (0.34 g, 26%). MS *m/e*: 283 $(M+H)^+$.

[0183] **Step 3:** A degassed solution of 5-bromo-4-(4-fluoro-3-methylphenyl)-2-ethyl-1*H*-imidazole (50 mg, 0.2 mmol), indazole-5-boronic acid pinacol ester (60 mg, 0.25 mmol), tetrakis(triphenylphosphine)palladium(0) (25 mg, 0.02 mmol) and aqueous Na_2CO_3 (2 M, 0.3 mL) in a mixture of DME/EtOH/H_2O (7:3:2, 1.0 mL) was irradiated in the microwave at 150 °C for 50 min. The reaction mixture was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black residue, which was purified by HPLC to provide 5-(2-ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 321 $(M+H)^+$.

Scheme 6: General Synthesis of 4,5-Diaryl-2-trifluoromethylimidazoles



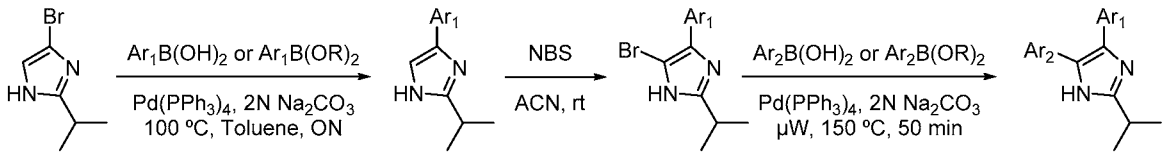
[0184] **Step 1:** To a solution of 2-bromo-3'-fluoroacetophenone (1.0 g, 4.3 mmol) in 10 mL of *N*,*N*-dimethylformamide was added the free base of 2,2,2-trifluoroacetimidamide (3 g, 26.8 mmol). The resulting solution was allowed to stir at room temperature for 4h, after

which time ethyl acetate (30 mL) was added. The resulting organic layer was then washed with saturated sodium bicarbonate solution and dried over sodium sulfate. The crude product was purified by silica gel chromatography to give 4-(3-chlorophenyl)-2-(trifluoromethyl)-1*H*-imidazole (0.38 g, 36%). MS *m/e*: 247 $(M+H)^+$.

[0185] **Step 2:** To a solution of 4-(3-chlorophenyl)-2-(trifluoromethyl)-1*H*-imidazole (0.38 g, 1.5 mmol) in acetonitrile (10 mL), *N*-bromosuccinimide (0.33 g, 1.9 mmol) was added. The resulting reaction mixture was allowed to stir at room temperature for 1h, concentrated and added water (30 mL) and dichloromethane (30 mL). The organic layer was then separated and the aqueous layer was extracted with dichloromethane (3x20 mL), dried ($MgSO_4$) and chromatographed on silica gel, eluting with MeOH/DCM, to give 5-bromo-4-(3-chlorophenyl)-2-(trifluoromethyl)-1*H*-imidazole (0.25 g, 50%). MS *m/e*: 325 $(M+H)^+$.

[0186] **Step 3:** A degassed solution of 5-bromo-4-(3-chlorophenyl)-2-(trifluoromethyl)-1*H*-imidazole (35 mg, 0.1 mmol), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo-[1,5-*a*]pyridine (32 mg, 0.13 mmol), tetrakis(triphenylphosphine)palladium(0) (25 mg, 0.02 mmol) and aqueous Na_2CO_3 (2 M, 0.3 mL) in a mixture of DME/EtOH/H_2O (7:3:2, 1.0 mL) was irradiated in the microwave at 100 °C for 30 min. The reaction mixture was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black residue, which was purified by HPLC to provide 6-(4-(3-chlorophenyl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. MS *m/e*: 364 $(M+H)^+$.

Scheme 7: General Synthesis of 4,5-Diaryl-2-isopropylimidazoles



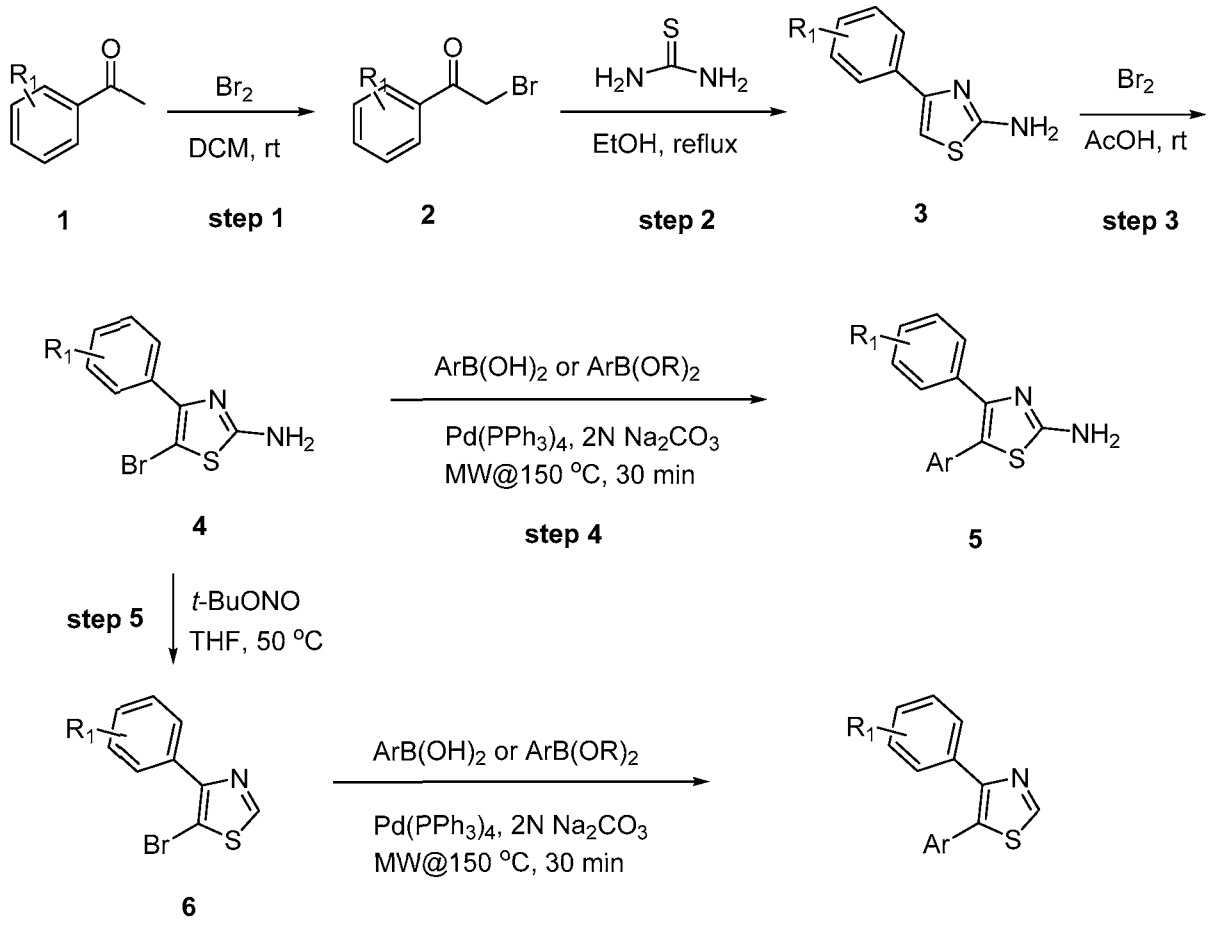
[0187] **Step 1:** A solution of 4-bromo-2-isopropyl-1*H*-imidazole (1.0 g, 5.3 mmol), *m*-tolylboronic acid (1.2 g, 8.8 mmol), tetrakis(triphenylphosphine)palladium(0) (0.33 g, 0.3 mmol) and aqueous Na_2CO_3 (4 M, 10 mL, 40 mmol) in toluene (20 ml) was evacuated and then refilled with nitrogen (three cycles). Resulting reaction mixture was then allowed to stir at 100 °C overnight, cooled down to room temperature, dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black residue. Column chromatography on silica gel, eluting with MeOH/DCM provided 2-isopropyl-4-(*m*-tolyl)-1*H*-imidazole as a yellow oil (0.43 g, 41%). MS *m/e*: 201 $(M+H)^+$.

[0188] **Step 2:** To a solution of 2-isopropyl-4-(*m*-tolyl)-1*H*-imidazole (0.43 g, 2.1 mmol) in acetonitrile (10 mL), *N*-bromosuccinimide (0.42 g, 2.4 mmol) was added. The resulting

reaction mixture was allowed to stir at room temperature for 1h, concentrated and added water (30 mL) and dichloromethane (30 mL). The organic layer was then separated and the aqueous layer was extracted with dichloromethane (3x20 mL), dried ($MgSO_4$) and chromatographed on silica gel, eluting with MeOH/DCM, to give 5-bromo-2-isopropyl-4-(*m*-tolyl)-1*H*-imidazole (0.45 g, 75%). MS *m/e*: 279 $(M+H)^+$.

[0189] **Step 3:** A degassed solution of 5-bromo-2-isopropyl-4-(*m*-tolyl)-1*H*-imidazole (50 mg, 0.18 mmol), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-[1,2,4]triazolo[1,5-a]pyridine (55 mg, 0.22 mmol), tetrakis(triphenylphosphine)palladium(0) (25 mg, 0.02 mmol) and aqueous Na_2CO_3 (2 M, 0.3 mL) in a mixture of DME/EtOH/H_2O (7:3:2, 1.0 mL) was irradiated in the microwave at 150 °C for 50 min. The reaction mixture was then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a black residue, which was purified by HPLC to provide 6-(2-isopropyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. MS *m/e*: 318 $(M+H)^+$.

Scheme 8: General Synthesis of Thiazoles



[0190] **Step 1:** To a solution of 2′,4’,5′-triifluoroacetophenone (2.4 g, 14 mmol) in dichloromethane (16 mL) at room temperature was added a solution of bromine (2.2 g, 13.9 mmol) in dichloromethane (7 mL) drop wise. Once the addition was complete, the resulting solution was stirred at room temperature for 1 h. Ice water was then added into reaction flask and the mixture was stirred for 15 min. The organic layer was separated, washed with water, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give 2-bromo-1-(2,4,5-trifluorophenyl)ethan-1-one as a pale yellow oil (3.0 g, 85%).

[0191] **Step 2:** To a mixture of 2-bromo-1-(3-chlorophenyl)ethan-1-one (0.5 g, 2.1 mmol) and thiourea (0.2 g, 2.3 mmol) in anhydrous EtOH (5 mL) was heated at reflux for 1h. After that, the solvent was removed in vacuo, and saturated aqueous $NaHCO_3$ was added. The mixture was then extracted with ethyl acetate. The combined organic phases were washed with brine, dried over sodium sulfate, filtered, and concentrated under reduced pressure to give 4-(3-chlorophenyl)thiazol-2-amine as a solid (0.4 g, 93%).

[0192] **Step 3:** To a solution of 4-(3-chlorophenyl)thiazol-2-amine (0.4 g, 2.0 mmol) in acetic acid (2 mL) was added bromine (0.1 g, 2.2 mmol) at room temperature. The mixture was stirred at room temperature for 2 min and solidified. The mixture was carefully basified with saturated aqueous $NaHCO_3$, and then extracted with dichloromethane. The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue, which was purified by chromatography eluting with ethyl acetate/hexanes (1/4) to provide 5-bromo-4-(3-chlorophenyl)thiazol-2-amine as a white solid (0.5 g, 92%).

[0193] **Step 4:** A mixture of 5-bromo-4-(3-chlorophenyl)thiazol-2-amine (0.04 g, 0.14 mmol), 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[*d*]thiazole (0.05 g, 0.18 mmol), tetrakis(triphenylphosphine)palladium(0) (0.02 g, 0.02 mmol), and 2.0 M of aqueous Na_2CO_3 (0.2 mL) in 1,2-dimethoxyethane (1.4 mL), EtOH (0.6 mL) and water (0.4 mL) was irradiated under microwave at 150 °C for 0.5 h. The mixture was then concentrated under reduced pressure to give a residue, which was purified by chromatography eluting with ethyl acetate to provide 5-(benzo[*d*]thiazol-6-yl)-4-(3-chlorophenyl)thiazol-2-amine as a pale white solid (0.03 g, 55%).

[0194] **Step 5:** A solution of 5-bromo-4-(*m*-tolyl)thiazol-2-amine (0.4 g, 1.6 mmol) and *tert*-butylnitrite (0.3 g, 2.4 mmol) in THF (15 mL) was heated at 50 °C for 4 h. The reaction mixture was diluted with ethyl acetate and washed with water. The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure to give a residue,

which was purified by chromatography eluting with ethyl acetate/hexanes (1/9) to give 5-bromo-4-(*m*-tolyl)thiazole (0.13 g, 33%).

[0195] Compound 1: 5-(4-Phenyl-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.01 (d, *J* = 1.0 Hz, 1H), 7.88 (s, 1H), 7.85 (dd, *J* = 1.6, 0.9 Hz, 1H), 7.51 (dt, *J* = 8.7, 1.0 Hz, 1H), 7.47 – 7.40 (m, 3H), 7.34 – 7.26 (m, 3H). MS *m/e*: 261 $(M+H)^+$.

[0196] Compound 2: 6-(4-Phenyl-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.02 (d, *J* = 1.0 Hz, 1H), 7.83 (s, 1H), 7.71 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.62 (q, *J* = 1.1 Hz, 1H), 7.49 – 7.41 (m, 2H), 7.37 – 7.27 (m, 3H), 7.23 (dd, *J* = 8.4, 1.4 Hz, 1H). MS *m/e*: 261 $(M+H)^+$.

[0197] Compound 3: 5-(4-(4-Fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.03 (d, *J* = 1.0 Hz, 1H), 7.84 (dd, *J* = 1.5, 0.9 Hz, 1H), 7.83 (s, 1H), 7.52 (dt, *J* = 8.7, 1.0 Hz, 1H), 7.42 (dd, *J* = 8.7, 1.5 Hz, 1H), 7.33 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.24 – 7.18 (m, 1H), 6.96 (dd, *J* = 9.7, 8.5 Hz, 1H), 2.20 (d, *J* = 1.9 Hz, 3H). MS *m/e*: 293 $(M+H)^+$.

[0198] Compound 4: 6-(4-(4-Fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.02 (d, *J* = 1.0 Hz, 1H), 7.80 (s, 1H), 7.72 (dd, *J* = 8.5, 0.9 Hz, 1H), 7.60 (q, *J* = 1.1 Hz, 1H), 7.34 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.28 – 7.18 (m, 2H), 6.99 (dd, *J* = 9.7, 8.5 Hz, 1H), 2.21 (d, *J* = 1.9 Hz, 3H). MS *m/e*: 293 $(M+H)^+$.

[0199] Compound 5: 6-(4-(4-Fluoro-3-methylphenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.10 (d, *J* = 1.0 Hz, 1H), 7.79 (dd, *J* = 1.5, 0.9 Hz, 1H), 7.76 (s, 1H), 7.65 (dt, *J* = 8.6, 1.0 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.12 – 7.07 (m, 1H), 6.79 (dd, *J* = 9.7, 8.6 Hz, 1H), 3.55 (s, 3H), 2.10 (d, *J* = 1.9 Hz, 3H). MS *m/e*: 307 $(M+H)^+$.

[0200] Compound 6 : 5-(4-(4-Chlorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.04 (d, *J* = 1.0 Hz, 1H), 7.84 (dd, *J* = 1.6, 0.9 Hz, 1H), 7.80 (s, 1H), 7.54 (dt, *J* = 8.7, 1.0 Hz, 1H), 7.44 – 7.40 (m, 3H), 7.29 (dt,, *J* = 8.8, 2.4, 2.1 Hz, 2H). MS *m/e*: 295 $(M+H)^+$.

[0201] Compound 7: 6-(4-(4-Fluoro-3-methylphenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.50 (s, 1H), 8.16 (d, *J* = 1.0 Hz, 1H), 7.94 (dd, *J* = 8.3, 0.9 Hz, 1H), 7.61 (q, *J* = 1.1 Hz, 1H), 7.29 (dd, *J* = 7.3, 1.5 Hz, 1H), 7.15 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.15 – 7.09 (m, 1H), 6.91 (t, *J* = 9.1 Hz, 1H), 3.69 (s, 3H), 2.14 (d, *J* = 1.9 Hz, 3H). MS *m/e*: 295 $(M+H)^+$.

[0202] Compound 8: 6-(4-(4-Fluoro-3-methylphenyl)-1-methyl-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.23 (s, 1H), 7.89 (s, 1H), 7.78 (dd, *J* = 8.3, 0.7 Hz, 1H), 7.60 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.30 (dd, *J* = 7.3, 2.1 Hz, 1H),

7.26 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.13 – 7.03 (m, 1H), 6.80 (t, *J* = 9.1 Hz, 1H), 3.89 (s, 3H), 3.57 (s, 3H), 2.11 (d, *J* = 1.9 Hz, 3H). MS *m/e*: 321 $(M+H)^+$.

[0203] Compound 9: 6-(4-(4-Fluoro-3-methylphenyl)-1-methyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 9.33 (s, 1H), 8.17 (dd, *J* = 8.5, 0.6 Hz, 1H), 8.11 (dd, *J* = 1.7, 0.6 Hz, 1H), 7.82 (s, 1H), 7.52 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.28 (dd, *J* = 7.6, 2.3 Hz, 1H), 7.10 – 7.05 (m, 1H), 6.82 (dd, *J* = 9.7, 8.6 Hz, 1H), 3.59 (s, 3H), 2.12 (d, *J* = 2.1 Hz, 3H). MS *m/e*: 324 $(M+H)^+$.

[0204] Compound 10: 5-(4-(4-Fluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.03 (d, *J* = 1.0 Hz, 1H), 7.93 (s, 1H), 7.84 (dd, *J* = 1.6, 0.9 Hz, 1H), 7.52 (dt, *J* = 8.7, 1.0 Hz, 1H), 7.49 – 7.36 (m, 3H), 7.10 – 6.98 (m, 2H). MS *m/e*: 279 $(M+H)^+$.

[0205] Compound 11: 6-(4-(4-Fluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.02 (d, *J* = 1.0 Hz, 1H), 7.88 (s, 1H), 7.72 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.60 (q, *J* = 1.1 Hz, 1H), 7.50 – 7.40 (m, 2H), 7.20 (dd, *J* = 8.4, 1.4 Hz, 1H), 7.13 – 7.00 (m, 2H). MS *m/e*: 279 $(M+H)^+$.

[0206] Compound 12: 6-(4-(4-Fluorophenyl)-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.12 (s, 1H), 7.81 (s, 1H), 7.62 (d, *J* = 2.6 Hz, 1H), 7.60 (d, *J* = 3.5 Hz, 1H), 7.53-7.37 (m, 2H), 7.32 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.16 – 6.91 (m, 2H), 3.83 (s, 3H). MS *m/e*: 293 $(M+H)^+$.

[0207] Compound 13: 6-(4-(4-Fluorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 9.22 (s, 1H), 8.12 (d, *J* = 1.2 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.85 (s, 1H), 7.58 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.51 – 7.37 (m, 2H), 7.13 – 7.04 (m, 2H). MS *m/e*: 296 $(M+H)^+$.

[0208] Compound 14: 6-(4-(4-Fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.52 (dd, *J* = 1.7, 1.0 Hz, 1H), 7.85 (s, 1H), 7.83 (d, *J* = 0.9 Hz, 1H), 7.58 (d, *J* = 1.4 Hz, 1H), 7.54 – 7.41 (m, 3H), 7.29 (dd, *J* = 9.4, 1.7 Hz, 1H), 7.18 – 7.07 (m, 2H). MS *m/e*: 279 $(M+H)^+$.

[0209] Compound 15: 5-(4-(*m*-Tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.02 (d, *J* = 1.0 Hz, 1H), 7.93 (s, 1H), 7.86 (dd, *J* = 1.6, 0.9 Hz, 1H), 7.51 (dt, *J* = 8.7, 0.9 Hz, 1H), 7.44 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.23 – 7.15 (m, 2H), 7.13 – 7.09 (m, 1H), 2.27 (s, 3H). MS *m/e*: 275 $(M+H)^+$.

[0210] Compound 16: 6-(4-(*m*-Tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.02 (d, *J* = 1.0 Hz, 1H), 7.83 (s, 1H), 7.70 (dd, *J* = 8.4, 0.9 Hz, 1H),

7.63 (q, *J* = 1.1 Hz, 1H), 7.32 – 7.28 (m, 1H), 7.26 – 7.19 (m, 3H), 7.16 – 7.08 (m, 1H), 2.29 (s, 3H). MS *m/e*: 275 $(M+H)^+$.

[0211] Compound 17: 1-Methyl-6-(4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-benzo[*d*]imidazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.11 (s, 1H), 7.85 (s, 1H), 7.63 (d, *J* = 1.2 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.34 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.30 (br s, 1H), 7.21 – 7.17 (m, 2H), 7.13 – 7.07 (m, 1H), 3.81 (s, 3H), 2.27 (s, 3H). MS *m/e*: 289 $(M+H)^+$.

[0212] Compound 18: 6-(4-(*m*-Tolyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 292 $(M+H)^+$.

[0213] Compound 19: 6-(4-(*m*-Tolyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.50 (dd, *J* = 1.7, 1.0 Hz, 1H), 7.83 (s, 1H), 7.80 (d, *J* = 0.6 Hz, 1H), 7.56 (d, *J* = 1.4 Hz, 1H), 7.46 (d, *J* = 9.4 Hz, 1H), 7.33 – 7.26 (m, 2H), 7.24 – 7.19 (m, 2H), 7.16 – 7.12 (m, 1H), 2.29 (s, 3H). MS *m/e*: 275 $(M+H)^+$.

[0214] Compound 20: 6-(4-(*m*-Tolyl)-1*H*-imidazol-5-yl)quinoxaline. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.82 (s, 2H), 8.19 (dd, *J* = 1.8, 0.7 Hz, 1H), 8.00 (dd, *J* = 8.8, 0.7 Hz, 1H), 7.95 (dd, *J* = 8.9, 1.8 Hz, 1H), 7.87 (s, 1H), 7.36 – 7.15 (m, 4H), 2.32 (s, 3H). MS *m/e*: 287 $(M+H)^+$.

[0215] Compound 21: 6-(4-(4-Fluoro-3-methylphenyl)-1-methyl-1*H*-imidazol-5-yl)quinoxaline. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.93 (q, *J* = 1.9 Hz, 2H), 8.17 (d, *J* = 8.8 Hz, 1H), 8.12 (d, *J* = 1.8 Hz, 1H), 7.86 (s, 1H), 7.78 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.30 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.09 (ddd, *J* = 7.6, 4.9, 2.3 Hz, 1H), 6.84 (dd, *J* = 9.5, 8.6 Hz, 1H), 3.68 (s, 3H), 2.13 (d, *J* = 2.1 Hz, 3H). MS *m/e*: 319 $(M+H)^+$.

[0216] Compound 22: 5-(4-(3-Chlorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.04 (d, *J* = 1.0 Hz, 1H), 7.85 (dd, *J* = 1.6, 0.9 Hz, 1H), 7.82 (s, 1H), 7.55 (dt, *J* = 8.8, 1.0 Hz, 1H), 7.49 – 7.47 (m, 1H), 7.41 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.36 – 7.31 (m, 1H), 7.26 – 7.21 (m, 2H). MS *m/e*: 295 $(M+H)^+$.

[0217] Compound 23: 6-(4-(3-Chlorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.05 (d, *J* = 1.0 Hz, 1H), 7.83 (s, 1H), 7.77 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.61 (q, *J* = 1.1 Hz, 1H), 7.51 – 7.47 (m, 1H), 7.38 – 7.33 (m, 1H), 7.29 – 7.26 (m, 2H), 7.21 (dd, *J* = 8.4, 1.4 Hz, 1H). MS *m/e*: 295 $(M+H)^+$.

[0218] Compound 24: 6-(4-(3-Chlorophenyl)-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.15 (s, 1H), 7.84 (s, 1H), 7.65 (d, *J* = 7.6 Hz, 1H), 7.63 (s, 1H), 7.51 – 7.48 (m, 1H), 7.37 – 7.30 (m, 2H), 7.28 – 7.24 (m, 2H), 3.85 (s, 3H). MS *m/e*: 309 $(M+H)^+$.

[0219] Compound 25: 6-(4-(3-Chlorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 9.23 (s, 1H), 8.13 (d, *J* = 1.5 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.85 (s, 1H), 7.58 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.50 – 7.44 (m, 1H), 7.36 – 7.25 (m, 3H). MS *m/e*: 312 $(M+H)^+$.

[0220] Compound 26: 6-(4-(3-Chlorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.55 (br s, 1H), 7.87 (s, 1H), 7.86 (s, 1H), 7.60 (d, *J* = 0.9 Hz, 1H), 7.55 (d, *J* = 9.4 Hz, 1H), 7.51 (t, *J* = 1.5 Hz, 1H), 7.38 – 7.27 (m, 4H). MS *m/e*: 295 $(M+H)^+$.

[0221] Compound 27: 5-(4-(3-Fluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 279 $(M+H)^+$.

[0222] Compound 28: 6-(4-(3-Fluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 279 $(M+H)^+$.

[0223] Compound 29: 6-(4-(3-Fluorophenyl)-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.13 (s, 1H), 7.81 (s, 1H), 7.65 – 7.63 (m, 2H), 7.35 – 7.13 (m, 4H), 7.02 – 6.91 (m, 1H), 3.83 (s, 3H). MS *m/e*: 293 $(M+H)^+$.

[0224] Compound 30: 6-(4-(3-Fluorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 9.28 (s, 1H), 8.17 (dd, *J* = 1.7, 0.6 Hz, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.88 (s, 1H), 7.63 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.32 (dd, *J* = 8.1, 6.0 Hz, 1H), 7.26 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.24 – 7.19 (m, 1H), 7.09 – 7.02 (m, 1H). MS *m/e*: 296 $(M+H)^+$.

[0225] Compound 31: 5-(4-(3,4-Difluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.06 (d, *J* = 1.0 Hz, 1H), 7.85 (dd, *J* = 1.6, 0.9 Hz, 1H), 7.81 (s, 1H), 7.56 (dt, *J* = 8.7, 1.0 Hz, 1H), 7.41 (dd, *J* = 8.7, 1.6 Hz, 1H), 7.37 – 7.27 (m, 1H), 7.24 – 7.10 (m, 2H). MS *m/e*: 297 $(M+H)^+$.

[0226] Compound 32: 6-(4-(3,4-Difluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.05 (d, *J* = 1.0 Hz, 1H), 7.84 (s, 1H), 7.77 (dd, *J* = 8.5, 0.6 Hz, 1H), 7.60 (q, *J* = 1.1 Hz, 1H), 7.39 – 7.30 (m, 1H), 7.24 – 7.16 (m, 3H). MS *m/e*: 297 $(M+H)^+$.

[0227] Compound 33: 6-(4-(3,4-Difluorophenyl)-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.15 (s, 1H), 7.82 (s, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.63 (dd, *J* = 1.7, 0.7 Hz, 1H), 7.38 – 7.29 (m, 2H), 7.25 – 7.10 (m, 2H), 3.86 (s, 3H). MS *m/e*: 311 $(M+H)^+$.

[0228] Compound 34: 6-(4-(3,4-Difluorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 9.25 (s, 1H), 8.13 (dd, *J* = 1.7, 0.6 Hz, 1H), 8.05 (dd, *J* = 8.6, 0.6

Hz, 1H), 7.84 (s, 1H), 7.58 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.39 – 7.28 (m, 1H), 7.25 – 7.16 (m, 2H). MS *m/e*: 314 $(M+H)^+$.

[0229] Compound 35: 6-(4-(3,4-Difluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.55 (dd, *J* = 1.8, 1.0 Hz, 1H), 7.89 – 7.83 (m, 2H), 7.59 (d, *J* = 1.4 Hz, 1H), 7.55 (dt, *J* = 9.4, 0.9 Hz, 1H), 7.42 – 7.34 (m, 1H), 7.29 (dd, *J* = 9.4, 1.6 Hz, 1H), 7.26 – 7.21 (m, 2H). MS *m/e*: 297 $(M+H)^+$.

[0230] Compound 36: 6-(4-(3,4-Difluorophenyl)-1*H*-imidazol-5-yl)quinoline. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.84 (dd, *J* = 4.4, 1.7 Hz, 1H), 8.31 (dd, *J* = 8.5, 0.9 Hz, 1H), 8.02 (s, 1H), 8.01 (d, *J* = 12.0 Hz, 1H), 7.88 (s, 1H), 7.79 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.54 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.41 – 7.32 (m, 1H), 7.26 – 7.19 (m, 2H). MS *m/e*: 308 $(M+H)^+$.

[0231] Compound 37: 6-(4-(4-Fluoro-3-methylphenyl)-1-methyl-1*H*-imidazol-5-yl)quinoline. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.91 (dd, *J* = 4.4, 1.7 Hz, 1H), 8.38 (dd, *J* = 8.5, 0.9 Hz, 1H), 8.11 (d, *J* = 8.8 Hz, 1H), 7.98 (d, *J* = 1.9 Hz, 1H), 7.82 (s, 1H), 7.69 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.59 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.29 (ddd, *J* = 7.6, 2.3, 0.9 Hz, 1H), 7.10 – 7.05 (m, 1H), 6.81 (dd, *J* = 9.7, 8.6 Hz, 1H), 3.62 (s, 3H), 2.10 (d, *J* = 1.9 Hz, 3H). MS *m/e*: 318 $(M+H)^+$.

[0232] Compound 38: 6-(4-(4-Fluorophenyl)-1*H*-imidazol-5-yl)quinoline. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.80 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.25 (dd, *J* = 8.5, 0.9 Hz, 1H), 8.00 (d, *J* = 1.9 Hz, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.86 (s, 1H), 7.78 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.50 (dd, *J* = 8.4, 4.4 Hz, 1H), 7.48 – 7.42 (m, 2H), 7.14 – 7.04 (m, 2H). MS *m/e*: 290 $(M+H)^+$.

[0233] Compound 39: 6-(4-(3-Chlorophenyl)-1*H*-imidazol-5-yl)quinoline. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.82 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.28 (d, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 2.0 Hz, 1H), 7.98 (d, *J* = 9.1 Hz, 1H), 7.88 (s, 1H), 7.78 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.56 – 7.46 (m, 3H), 7.34 – 7.28 (m, 2H). MS *m/e*: 306 $(M+H)^+$.

[0234] Compound 40: 6-(4-(3-Fluorophenyl)-1*H*-imidazol-5-yl)quinoline. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.82 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 8.03 (d, *J* = 2.0 Hz, 1H), 7.98 (d, *J* = 8.8 Hz, 1H), 7.88 (s, 1H), 7.79 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.53 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.36 – 7.28 (m, 1H), 7.28 – 7.16 (m, 2H), 7.08 – 7.01 (m, 1H). MS *m/e*: 290 $(M+H)^+$.

[0235] Compound 41: 5-(1-Methyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.08 (d, *J* = 1.0 Hz, 1H), 7.80 – 7.73 (m, 2H), 7.63 (dt, *J* = 8.6, 1.0 Hz, 1H), 7.30 (dd, *J* = 8.6, 1.5 Hz, 1H), 7.27 – 7.24 (m, 1H), 7.12 – 7.05 (m, 1H), 7.04 (dd, *J* = 8.7, 7.6 Hz, 1H), 6.96 – 6.91 (m, 1H), 3.54 (s, 3H), 2.16 (s, 3H). MS *m/e*: 289 $(M+H)^+$.

[0236] Compound 42: 6-(1-Methyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.15 (d, *J* = 1.0 Hz, 1H), 7.91 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.82 (s, 1H), 7.54 (q, *J* = 1.1 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.14 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.12 – 7.09 (m, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 7.00 – 6.95 (m, 1H), 3.61 (s, 3H), 2.21 (s, 3H). MS *m/e*: 289 $(M+H)^+$.

[0237] Compound 43: 1-Methyl-6-(1-methyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-benzo[*d*]imidazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.23 (s, 1H), 7.81 – 7.78 (m, 2H), 7.59 (dd, *J* = 1.6, 0.7 Hz, 1H), 7.32 – 7.29 (m, 1H), 7.27 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.12 – 7.07 (m, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.98 – 6.42 (m, 1H), 3.89 (s, 3H), 3.57 (s, 3H), 2.20 (s, 3H). MS *m/e*: 303 $(M+H)^+$.

[0238] Compound 44: 6-(1-Methyl-4-(m-tolyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole. ^{1}H NMR (CD_3OD, 300 MHz) δ 9.33 (s, 1H), 8.17 (dd, *J* = 8.4, 0.6 Hz, 1H), 8.08 (dd, *J* = 1.7, 0.6 Hz, 1H), 7.82 (s, 1H), 7.52 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.29 – 7.26 (m, 1H), 7.10 – 6.97 (m, 3H), 3.60 (s, 3H), 2.20 (s, 3H). MS *m/e*: 306 $(M+H)^+$.

[0239] Compound 45: 6-(1-Methyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. MS *m/e*: 289 $(M+H)^+$.

[0240] Compound 46: 6-(1-Methyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)quinoline. MS *m/e*: 300 $(M+H)^+$.

[0241] Compound 47: 6-(1-Methyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)quinoxaline. MS *m/e*: 301 $(M+H)^+$.

[0242] Compound 48: -(4-(4-Fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 293 $(M+H)^+$.

[0243] Compound 49: 6-(4-(4-Fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 293 $(M+H)^+$.

[0244] Compound 50: 6-(4-(4-Fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole. MS *m/e*: 307 $(M+H)^+$.

[0245] Compound 51: 6-(4-(4-Fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 310 $(M+H)^+$.

[0246] Compound 52: 5-(4-(4-Fluoro-3-methylphenyl)-1,2-dimethyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 321 $(M+H)^+$.

[0247] Compound 53: 6-(4-(4-Fluoro-3-methylphenyl)-1,2-dimethyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 321 $(M+H)^+$.

[0248] Compound 54: 6-(4-(4-Fluoro-3-methylphenyl)-1,2-dimethyl-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole. MS *m/e*: 335 $(M+H)^+$.

[0249] Compound 55: 6-(4-(4-Fluoro-3-methylphenyl)-1,2-dimethyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 338 $(M+H)^+$.

[0250] Compound 56: 5-(1,2-Dimethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 303 $(M+H)^+$.

[0251] Compound 57: 6-(1,2-Dimethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 303 $(M+H)^+$.

[0252] Compound 58: 6-(1,2-Dimethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole. MS *m/e*: 317 $(M+H)^+$.

[0253] Compound 59: 6-(1,2-Dimethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 320 $(M+H)^+$.

[0254] Compound 60: 5-(4-(3-Chlorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 309 $(M+H)^+$.

[0255] Compound 61: 6-(4-(3-Chlorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 309 $(M+H)^+$.

[0256] Compound 62: 6-(4-(3-Chlorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole. MS *m/e*: 323 $(M+H)^+$.

[0257] Compound 63: 6-(4-(3-Chlorophenyl)-1-methyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 326 $(M+H)^+$.

[0258] Compound 64: 5-(4-(3,4-Difluorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 311 $(M+H)^+$.

[0259] Compound 65: 6-(4-(3,4-Difluorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 311 $(M+H)^+$.

[0260] Compound 66: 6-(4-(3,4-Difluorophenyl)-1-methyl-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole. MS *m/e*: 325 $(M+H)^+$.

[0261] Compound 67: 6-(4-(3,4-Difluorophenyl)-1-methyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 328 $(M+H)^+$.

[0262] Compound 68: 6-(4-(3,4-Difluorophenyl)-1-methyl-1*H*-imidazol-5-yl)quinoxaline. MS *m/e*: 323 $(M+H)^+$.

[0263] Compound 69: 5-(4-(4-Methoxyphenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 305 $(M+H)^+$.

[0264] Compound 70: 6-(4-(4-Methoxyphenyl)-1-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 305 $(M+H)^+$.

[0265] Compound 71: 5-(4-(4-Fluoro-3-methylphenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 307 $(M+H)^+$.

[0266] Compound 72: 6-(4-(4-Fluoro-3-methylphenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 307 $(M+H)^+$.

[0267] Compound 73: 6-(4-(4-Fluoro-3-methylphenyl)-2-methyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 324 $(M+H)^+$.

[0268] Compound 74: 6-(4-(4-Fluoro-3-methylphenyl)-2-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. MS *m/e*: 307 $(M+H)^+$.

[0269] Compound 75: 6-(4-(4-Fluoro-3-methylphenyl)-2-methyl-1*H*-imidazol-5-yl)quinoline. ^1H NMR (CD_3OD, 300 MHz) δ 8.82 (dd, *J* = 4.4, 1.7 Hz, 1H), 8.28 (d, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 1.9 Hz, 1H), 7.95 (d, *J* = 8.8 Hz, 1H), 7.80 (dd, *J* = 8.9, 2.0 Hz, 1H), 7.54 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.35 (dd, *J* = 7.5, 2.1 Hz, 1H), 7.27 – 7.22 (m, 1H), 7.03 (dd, *J* = 9.7, 8.5 Hz, 1H), 2.50 (s, 3H), 2.25 (d, *J* = 1.5 Hz, 3H). MS *m/e*: 318 $(M+H)^+$.

[0270] Compound 76: 6-(4-(4-Fluoro-3-methylphenyl)-2-methyl-1*H*-imidazol-5-yl)quinoxaline. MS *m/e*: 319 $(M+H)^+$.

[0271] Compound 77: 5-(4-(4-Fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 293 $(M+H)^+$.

[0272] Compound 78: 6-(4-(4-Fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 293 $(M+H)^+$.

[0273] Compound 79: 6-(4-(4-Fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole. MS *m/e*: 307 $(M+H)^+$.

[0274] Compound 80: 6-(4-(4-Fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 310 $(M+H)^+$.

[0275] Compound 81: 6-(4-(4-Fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. MS *m/e*: 293 $(M+H)^+$.

[0276] Compound 82: 6-(4-(4-Fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)quinoxaline. MS *m/e*: 305 $(M+H)^+$.

[0277] Compound 83: 5-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 311 $(M+H)^+$.

[0278] Compound 84: 6-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 311 $(M+H)^+$.

[0279] Compound 85: 6-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1-methyl-1*H*-benzo[*d*]imidazole. MS *m/e*: 325 $(M+H)^+$.

[0280] Compound 86: 6-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 328 $(M+H)^+$.

[0281] Compound 87: 6-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. MS *m/e*: 311 $(M+H)^+$.

[0282] Compound 88: 6-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)quinoline. MS *m/e*: 322 $(M+H)^+$.

[0283] Compound 89: 6-(4-(3,4-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)quinoxaline. MS *m/e*: 323 $(M+H)^+$.

[0284] Compound 90: 5-(2-Methyl-4-(3,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 329 $(M+H)^+$.

[0285] Compound 91: 6-(2-Methyl-4-(3,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 329 $(M+H)^+$.

[0286] Compound 92: 6-(2-Methyl-4-(3,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. MS *m/e*: 330 $(M+H)^+$.

[0287] Compound 93: 6-(2-Methyl-4-(3,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 346 $(M+H)^+$.

[0288] Compound 94: 6-(2-Methyl-4-(3,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. MS *m/e*: 329 $(M+H)^+$.

[0289] Compound 95: 6-(2-Methyl-4-(3,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)quinoline. MS *m/e*: 340 $(M+H)^+$.

[0290] Compound 96: 6-(2-Methyl-4-(3,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)quinoxaline. MS *m/e*: 341 $(M+H)^+$.

[0291] Compound 97: 5-(2-Methyl-4-(2,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 329 $(M+H)^+$.

[0292] Compound 98: 6-(2-Methyl-4-(2,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. MS *m/e*: 330 $(M+H)^+$.

[0293] Compound 99: 6-(2-Methyl-4-(2,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 346 $(M+H)^+$.

[0294] Compound 100: 6-(2-Methyl-4-(2,4,5-trifluorophenyl)-1*H*-imidazol-5-yl)quinoline. MS *m/e*: 340 $(M+H)^+$.

[0295] Compound 101: 5-(4-(3-Chlorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 309 $(M+H)^+$.

[0296] Compound 102: 6-(4-(3-Chlorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 309 $(M+H)^+$.

[0297] Compound 103: 6-(4-(3-Chlorophenyl)-2-methyl-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. MS *m/e*: 310 $(M+H)^+$.

[0298] Compound 104: 6-(4-(3-Chlorophenyl)-2-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. MS *m/e*: 309 $(M+H)^+$.

[0299] Compound 105: 6-(4-(3-Chlorophenyl)-2-methyl-1*H*-imidazol-5-yl)quinoline. MS *m/e*: 320 $(M+H)^+$.

[0300] Compound 106: 5-(2-Ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 321 $(M+H)^+$.

[0301] Compound 107: 6-(2-Ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 321 $(M+H)^+$.

[0302] Compound 108: 6-(2-Ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. MS *m/e*: 322 $(M+H)^+$.

[0303] Compound 109: 6-(2-Ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 338 $(M+H)^+$.

[0304] Compound 110: 6-(2-Ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. MS *m/e*: 321 $(M+H)^+$.

[0305] Compound 111: 6-(2-Ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)quinoline. MS *m/e*: 332 $(M+H)^+$.

[0306] Compound 112: 6-(2-Ethyl-4-(4-fluoro-3-methylphenyl)-1*H*-imidazol-5-yl)quinoxaline. MS *m/e*: 333 $(M+H)^+$.

[0307] Compound 113: 5-(2-Ethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 303 $(M+H)^+$.

[0308] Compound 114: 6-(2-Ethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 303 $(M+H)^+$.

[0309] Compound 115: 6-(2-Ethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. ^{1}H NMR (CD_3OD, 300 MHz) δ 8.82 (dd, *J* = 1.5, 1.1 Hz, 1H), 8.40 (s, 1H), 7.77 – 7.67 (m, 2H), 7.33 – 7.31 (m, 1H), 7.29 (d, *J* = 7.0 Hz, 1H), 7.25 – 7.19 (m, 2H), 2.85 (q, *J* = 7.7 Hz, 2H), 2.35 (s, 3H), 1.41 (t, *J* = 7.7 Hz, 3H). MS *m/e*: 304 $(M+H)^+$.

[0310] Compound 116: 6-(2-Ethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 320 $(M+H)^+$.

[0311] Compound 117: 6-(2-Ethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. MS *m/e*: 303 $(M+H)^+$.

[0312] Compound 118: 6-(2-Ethyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)quinoxaline. MS *m/e*: 315 $(M+H)^+$.

[0313] Compound 119: 5-(2-Ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 307 $(M+H)^+$.

[0314] Compound 120: 6-(2-Ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 307 $(M+H)^+$.

[0315] Compound 121: 6-(2-Ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. MS *m/e*: 308 $(M+H)^+$.

[0316] Compound 122: 6-(2-Ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 324 $(M+H)^+$.

[0317] Compound 123: 6-(2-Ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. MS *m/e*: 307 $(M+H)^+$.

[0318] Compound 124: 5-(4-(3-Chlorophenyl)-2-ethyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 323 $(M+H)^+$.

[0319] Compound 125: 6-(4-(3-Chlorophenyl)-2-ethyl-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. MS *m/e*: 324 $(M+H)^+$.

[0320] Compound 126: 6-(4-(3-Chlorophenyl)-2-ethyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 340 $(M+H)^+$.

[0321] Compound 127: 6-(4-(3-Chlorophenyl)-2-ethyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. MS *m/e*: 323 $(M+H)^+$.

[0322] Compound 128: 6-(4-(3-Chlorophenyl)-2-ethyl-1*H*-imidazol-5-yl)quinoline. MS *m/e*: 334 $(M+H)^+$.

[0323] Compound 129: 6-(4-(3-Chlorophenyl)-2-ethyl-1*H*-imidazol-5-yl)quinoxaline. MS *m/e*: 335 $(M+H)^+$.

[0324] Compound 130: 5-(4-(3,4-Difluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 325 $(M+H)^+$.

[0325] Compound 131: 6-(4-(3,4-Difluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 325 $(M+H)^+$.

[0326] Compound 132: 6-(4-(3,4-Difluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. MS *m/e*: 326 $(M+H)^+$.

[0327] Compound 133: 6-(4-(3,4-Difluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 342 $(M+H)^+$.

[0328] Compound 134: 6-(4-(3,4-Difluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. MS *m/e*: 325 $(M+H)^+$.

[0329] Compound 135: 6-(4-(3,4-Difluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)quinoxaline. MS *m/e*: 337 $(M+H)^+$.

[0330] Compound 136: 6-(2-Ethyl-4-(3-fluorophenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. MS *m/e*: 308 $(M+H)^+$.

[0331] Compound 137: 6-(2-Ethyl-4-(3-fluorophenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 324 $(M+H)^+$.

[0332] Compound 138: 6-(2-Ethyl-4-(3-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. MS *m/e*: 307 $(M+H)^+$.

[0333] Compound 139: 5-(4-(3-Chloro-5-fluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 341 $(M+H)^+$.

[0334] Compound 140: 6-(4-(3-Chloro-5-fluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 358 $(M+H)^+$.

[0335] Compound 141: 6-(4-(3-Chloro-5-fluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)quinoxaline. MS *m/e*: 353 $(M+H)^+$.

[0336] Compound 142: 5-(2-Ethyl-4-(3-fluoro-5-methylphenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 321 $(M+H)^+$.

[0337] Compound 143: 6-(2-Ethyl-4-(3-fluoro-5-methylphenyl)-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 321 $(M+H)^+$.

[0338] Compound 144: 6-(2-Ethyl-4-(3-fluoro-5-methylphenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. MS *m/e*: 322 $(M+H)^+$.

[0339] Compound 145: 6-(2-Ethyl-4-(3-fluoro-5-methylphenyl)-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 338 $(M+H)^+$.

[0340] Compound 146: 6-(2-Ethyl-4-(3-fluoro-5-methylphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine. MS *m/e*: 321 $(M+H)^+$.

[0341] Compound 147: 6-(2-Ethyl-4-(3-fluoro-5-methylphenyl)-1*H*-imidazol-5-yl)quinoxaline. MS *m/e*: 333 $(M+H)^+$.

[0342] Compound 148: 5-(4-(3,5-Difluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole. MS *m/e*: 311 $(M+H)^+$.

[0343] Compound 149: 6-(4-(3,5-Difluorophenyl)-2-ethyl-1*H*-imidazol-5-yl)benzo[*d*]thiazole. MS *m/e*: 342 $(M+H)^+$.

[0344] Compound 150: 6-(4-(3-Chlorophenyl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. MS *m/e*: 364 $(M+H)^+$.

[0345] Compound 151: 6-(4-(4-Fluorophenyl)-2-(trifluoromethyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. MS *m/e*: 348 $(M+H)^+$.

[0346] Compound 152: 6-(2-Isopropyl-4-(*m*-tolyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine. MS *m/e*: 318 $(M+H)^+$.

[0347] Compound 153: 5-(1H-indazol-6-yl)-4-(*m*-tolyl)thiazole ^{1}H NMR (CD3OD, 300 MHz) 9.04 (m, 1H), 8.05 (m, 1H), 7.73 (m, 1H), 7.51 (m, 1H), 7.32 (m, 1H), 7.12 (m, 4H), 2.24 (s, 3H) ppm; MS *m/e*: 292 $(M+H)^+$

[0348] Compound 154: 5-(1H-indazol-5-yl)-4-(*m*-tolyl)thiazole. ^{1}H NMR (CD3OD, 300 MHz) 8.98 (m, 1H), 8.03 (m, 1H), 7.79 (m, 1H), 7.50 (m, 1H), 7.29 (m, 2H), 7.15 (m, 3H), 2.23 (s, 3H) ppm; MS *m/e*: 292 $(M+H)^+$

[0349] Compound 155: 4-(4-fluoro-3-methylphenyl)-5-(imidazo[1,2-a]pyridin-6-yl)thiazol-2-amine. ^{1}H NMR (DMSO-d_6, 300 MHz)) 8.54 (m, 1H), 7.89 (m, 1H), 7.55 (m, 1H), 7.42 (m, 2H), 7.18 (bs, 2H), 7.13 (m, 1H), 6.96 (m, 2H), 2.14 (s, 3H) ppm; MS *m/e*: 325 $(M+H)^+$

[0350] Compound 156: 4-(4-fluoro-3-methylphenyl)-5-(1H-indazol-5-yl)thiazole. ^{1}H NMR (DMSO-d_6, 300 MHz) 9.14 (m, 1H), 8.08 (m, 1H), 7.81 (m, 1H), 7.53 (m, 1H), 7.47(m, 1H), 7.23 (m, 1H), 7.15 (m, 1H), 7.00 (m, 1H), 2.13 (s, 3H) ppm; MS *m/e*: 310 $(M+H)^+$

[0351] Compound 157: 5-(1H-indazol-5-yl)-4-(4-methoxyphenyl)thiazol-2-amine

[0352] MS *m/e*: 323 $(M+H)^+$

[0353] Compound 158: 4-(4-fluoro-3-methylphenyl)-5-(quinoxalin-6-yl)thiazol-2-amine. ^{1}H NMR (CD3OD, 300 MHz) 8.81 (m, 2H), 7.90 (m, 2H), 7.60 (m, 1H), 7.35 (m, 1H), 7.19 (m, 1H), 6.95 (m, 1H), 2.20 (s, 3H) ppm; MS *m/e*: 337 $(M+H)^+$

[0354] Compound 159: 4-(4-fluoro-3-methylphenyl)-5-(1H-indazol-6-yl)thiazole. ^{1}H NMR (CD3OD, 300 MHz) 9.26 (m, 1H), 9.06 (m, 1H), 8.06 (m, 1H), 8.01 (m, 1H), 7.47 (m, 1H), 7.37 (m, 1H), 7.20 (m, 1H), 6.93 (m, 1H), 2.17 (s, 3H) ppm; MS *m/e*: 310 $(M+H)^+$

[0355] Compound 160: 4-(4-fluoro-3-methylphenyl)-5-(1H-indazol-5-yl)thiazol-2-amine

[0356] ^{1}H NMR (CD3OD, 300 MHz) 7.98 (m, 1H), 7.66 (m, 1H), 7.42 (m, 1H), 7.28 (m, 1H), 7.19 (m, 1H), 7.13 (m, 1H), 6.86 (m, 1H), 2.14 (s, 3H) ppm; MS *m/e*: 325 $(M+H)^+$

[0357] Compound 161: 6-(4-(*m*-tolyl)thiazol-5-yl)benzo[d]thiazole. ^{1}H NMR (CD3OD, 300 MHz) 9.03 (s, 1H), 8.05 (m, 1H), 7.74 (m, 1H), 7.51 (m, 1H), 7.37 (m, 1H), 7.22 (m, 1H), 7.08 (m, 1H), 6.93 (m, 1H), 2.16 (s, 3H) ppm; MS *m/e*: 309 $(M+H)^+$

[0358] Compound 162: 5-(benzo[d]thiazol-6-yl)-4-(4-fluoro-3-methylphenyl)thiazol-2-amine. ^{1}H NMR (DMSO-d_6, 300 MHz) 9.35 (m, 1H), 8.05 (m, 1H), 7.95 (m, 1H), 7.37 (m, 1H), 7.30 (m, 1H), 7.18 (bs, 2H), 7.08 (m, 1H), 6.96 (m, 1H), 2.13 (s, 3H) ppm; MS *m/e*: 342 $(M+H)^+$

[0359] Compound 163: 5-(imidazo[1,2-a]pyridin-6-yl)-4-(4-methoxyphenyl)thiazol-2-amine. MS *m/e*: 323 $(M+H^+)$

[0360] Compound 164: 4-(3-chlorophenyl)-5-(imidazo[1,2-a]pyridin-6-yl)thiazol-2-amine. MS *m/e*: 327 $(M+H)^+$

[0361] Compound 165: 6-(4-(4-fluoro-3-methylphenyl)thiazol-5-yl)benzo[*d*]thiazole. ^1H NMR (CD3OD, 300 MHz) 9.27 (m, 1H), 9.06 (m, 1H), 8.08 (m, 1H), 8.02 (m, 1H), 7.47 (m, 1H), 7.32 (m, 1H), 7.16 (m, 2H), 2.24 (s, 3H) ppm; MS *m/e*: 327 $(M+H)^+$

[0362] Compound 166: 5-(benzo[*d*]thiazol-6-yl)-4-(3-chlorophenyl)thiazol-2-amine. ^1H NMR (CD3OD, 300 MHz) 9.28 (m, 1H), 8.03 (m, 2H), 7.35 (m, 5H) ppm; MS *m/e*: 344 $(M+H)^+$

[0363] Compound 167: 4-(4-fluoro-3-methylphenyl)-5-(imidazo[1,2-a]pyridin-6-yl)thiazole. MS *m/e*: 310 $(M+H)^+$

[0364] Compound 168: 4-(3-chlorophenyl)-5-(1H-indazol-5-yl)thiazol-2-amine. ^1H NMR (CD3OD, 300 MHz) 8.00 (m, 1H), 7.69 (m, 1H), 7.45 (m, 2H), 7.21 (m, 4H) ppm; MS *m/e*: 327 $(M+H)^+$

[0365] Compound 169: 4-(3-chlorophenyl)-5-(quinoxalin-6-yl)thiazol-2-amine. ^1H NMR (CD3OD, 300 MHz) 8.82 (m, 2H), 7.93 (m, 2H), 7.61 (m, 1H), 7.48 (m, 1H), 7.30 (m, 3H) ppm; MS *m/e*: 339 $(M+H)^+$

[0366] Compound 170: 4-(4-fluorophenyl)-5-(quinoxalin-6-yl)thiazol-2-amine. ^1H NMR (CD3OD, 300 MHz) 8.81 (m, 2H), 7.91 (m, 1H), 7.60 (m, 2H), 7.45 (m, 2H), 7.05 (m, 2H) ppm; MS *m/e*: 323 $(M+H)^+$

[0367] Compound 171: 5-(imidazo[1,2-a]pyridin-6-yl)-4-(3-(trifluoromethyl)phenyl)thiazol-2-amine. ^1H NMR (DMSO-d_6, 300 MHz) 8.61 (m, 1H), 7.90 (m, 1H), 7.82 (m, 1H), 7.57 (m, 3H), 7.47 (m, 2H), 7.31 (bs, 2H), 6.97 (m, 1H) ppm; MS *m/e*: 361 $(M+H)^+$

[0368] Compound 172: 4-(3-chlorophenyl)-5-(1H-indazol-6-yl)thiazol-2-amine. ^1H NMR (CD3OD, 300 MHz) 8.05 (m, 1H), 7.75 (m, 1H), 7.48 (m, 2H), 7.40 (m, 1H), 7.32 (m, 2H), 7.02 (m, 1H) ppm; MS *m/e*: 327 $(M+H)^+$

[0369] Compound 173: 5-(1H-indazol-6-yl)-4-(4-methoxyphenyl)thiazol-2-amine. MS *m/e*: 323 $(M+H)^+$

[0370] Compound 174: 4-(4-fluoro-3-methylphenyl)-5-(1H-indazol-6-yl)thiazol-2-amine. ^1H NMR (CD3OD, 300 MHz) 7.99 (m, 1H), 7.71 (m, 2H), 7.56 (m, 1H), 7.48 (m, 2H), 7.36 (m, 1H), 7.22 (m, 1H) ppm; MS *m/e*: 325 $(M+H)^+$

[0371] Compound 175: 5-(1H-indazol-5-yl)-4-(3-(trifluoromethyl)phenyl)thiazol-2-amine. ^1H NMR (CD3OD, 300 MHz) 8.00 (m, 1H), 7.66 (m, 1H), 7.42 (m, 1H), 7.28 (m, 1H), 7.19 (m, 1H), 7.13 (m, 1H), 6.86 (m, 1H), 2.14 (s, 3H) ppm; MS *m/e*: 361 $(M+H)^+$

[0372] Compound 176: 5-(benzo[d]thiazol-6-yl)-4-(3-(trifluoromethyl)phenyl)thiazol-2-amine. ^{1}H NMR (CD3OD, 300 MHz) 9.23 (m, 1H), 7.97 (m, 2H), 7.72 (m, 1H), 7.56 (m, 2H), 7.41 (m, 2H) ppm; MS *m/e*: 378 $(M+H)^+$

[0373] Compound 177: 5-(1H-indazol-5-yl)-4-(3-methoxyphenyl)thiazol-2-amine. ^{1}H NMR (DMSO-d_6, 300 MHz) 13.1 (s, 1H), 8.02 (s, 1H), 7.66 (m, 1H), 7.45 (m, 1H), 7.15 (m, 1H), 7.08 (m, 3H), 6.93 (m, 2H), 6.74 (m, 1H) ppm; MS *m/e*: 323 $(M+H)^+$

[0374] Compound 178: 5-(benzo[d]thiazol-6-yl)-4-(3-fluorophenyl)thiazol-2-amine

[0375] ^{1}H NMR (CD3OD, 300 MHz) 9.22 (m, 1H), 7.96 (m, 2H), 7.39 (m, 1H), 7.20 (m, 3H), 6.99 (m, 1H) ppm; MS *m/e*: 328 $(M+H)^+$

[0376] Compound 179: 4-(3-fluorophenyl)-5-(1H-indazol-5-yl)thiazol-2-amine. ^{1}H NMR (CD3OD, 300 MHz) 8.05 (m, 1H), 7.79 (m, 1H), 7.52 (m, 1H), 7.36 (m, 1H), 7.23 (m, 1H), 7.17 (m, 3H) ppm; MS *m/e*: 311 $(M+H)^+$

[0377] Compound 180: 5-(quinoxalin-6-yl)-4-(3-(trifluoromethyl)phenyl)thiazol-2-amine. ^{1}H NMR (DMSO-d_6, 300 MHz) 8.89 (m, 2H), 7.97 (m, 1H), 7.90 (m, 1H), 7.79 (m, 1H), 7.62 (m, 3H), 7.48 (m, 1H) ppm; MS *m/e*: 373 $(M+H)^+$

[0378] Compound 181: 6-(4-(4-fluorophenyl)thiazol-5-yl)benzo[d]thiazole. MS *m/e*: 313 $(M+H)^+$

[0379] Compound 182: 4-(4-methoxyphenyl)-5-(quinoxalin-6-yl)thiazol-2-amine. ^{1}H NMR (CD3OD, 300 MHz) 8.87 (s, 1H), 8.01 (m, 2H), 7.62 (m, 1H), 7.38 (m, 2H), 6.97 (m, 2H), 3.82 (s, 3H) ppm; MS *m/e*: 335 $(M+H)^+$

[0380] Compound 183: 4-(3-fluorophenyl)-5-(quinoxalin-6-yl)thiazol-2-amine. ^{1}H NMR (DMSO-d_6, 300 MHz) 8.88 (m, 2H), 7.97 (m, 1H), 7.87 (m, 1H), 7.58 (m, 1H), 7.30 (m, 1H), 7.19 (m, 3H) ppm; MS *m/e*: 323 $(M+H)^+$

[0381] Compound 184: 5-(imidazo[1,2-a]pyridin-6-yl)-4-(3-methoxyphenyl)thiazol-2-amine. MS *m/e*: 323 $(M+H)^+$

[0382] Compound 185: 5-(1H-indazol-6-yl)-4-(3-(trifluoromethyl)phenyl)thiazol-2-amine. ^{1}H NMR (CD3OD, 300 MHz) 8.06 (m, 1H), 7.75 (m, 2H), 7.68 (m, 1H), 7.61 (m, 1H), 7.52 (m, 2H), 7.01 (m,1H) ppm; MS *m/e*: 361$(M+H)^+$

[0383] Compound 186: 5-(benzo[d]thiazol-6-yl)-4-(3-methoxyphenyl)thiazol-2-amine. MS *m/e*: 340 $(M+H)^+$

[0384] Compound 187: 4-(3-fluorophenyl)-5-(imidazo[1,2-a]pyridin-6-yl)thiazol-2-amine. MS *m/e*: 311 $(M+H)^+$

[0385] Compound 188: 4-(4-fluorophenyl)-5-(imidazo[1,2-a]pyridin-6-yl)-N-methylthiazol-2-amine. MS *m/e*: 325 $(M+H)^+$

Example 2: AlphaScreen® *SureFire*® SMAD3 (p-Ser423/425) Assay

[0386] The p-SMAD-3 (Ser423/425) *SureFire*® assay has been designed to measure the phosphorylation of endogenous cellular p-SMAD-3 (Ser423/425) in cell lysates and is a system for the screening of both modulators of receptor activation (*e.g.* agonists and antagonists) as well as agents acting intracellularly, such as small molecule inhibitors of upstream events. The assay will measure p-SMAD-3 (Ser423/425) activation by either cloned or endogenous receptors, and can be applied to primary cells.

P-SMAD-3 (Ser423/425) *SureFire*® Assay Protocols

Step A: Preparation of buffers

[0387] 1X Lysis buffer: 1ml of 5X Lysis buffer was diluted with 4ml of sterile water. After dilution, excess 1X Lysis buffer can be frozen and thawed up to 5 times without loss in activity.

[0388] Activation buffer: The buffer was warmed slowly to 37°C and gently mixed to re-suspend. Activation buffer can be stored at room temperature with no loss in activity.

[0389] Reaction buffer: The buffer was kept at 4 °C while in use.

[0390] AlphaScreen® Protein A IgG Kit: The kit was stored at 4 °C in the dark.

[0391] Reaction buffer + Activation buffer + AlphaScreen® Acceptor beads: Reaction buffer (40 parts), Activation Buffer (10 parts) and Acceptor beads (1 part) were mixed and the mixture was stored at room temperature and used the same day. Mixture was added to 384-well plates; excess mixturewas discarded.

[0392] Dilution buffer + AlphaScreen® Donor beads: Dilution buffer (20 parts) and Donor beads (1 part) were mixed and the mixture was stored at room temperature and used the same day. Excess mixture was discarded.

[0393] Assay control samples: After reconstitution in 250 µl of water, lysates were at -20 °C in single use aliquots.

Step B: Preparation of samples and cells

[0394] 96-well Assay Protocol for 293FT and RMS13 adherent cells can be carried out manually or in high throughput with liquid handling robots.

[0395] The cells (80 µL of cells for 96 well plates) were plated in collagen coated tissue culture plates in RPMI or FreeStyle medium (Invitrogen)and incubated overnight. For manual analysis, 6 plates for GDF8, 6 plates for TGF-β, and optionally 6 plates for Alk5ca(ALK5 constitutively active) were used.

[0396] The compound dilution plates were prepared as follows: 12 µL of DMSO was transferred into first column of 96-well plate, and 16 µL of DMSO was transferred into columns 2-12 of the 96-well plate. 12 µL of compound solution was transferred into first column of the DMSO-containing 96-well plate. Three-fold dilution was performed up to column 10 of the DMSO-containing 96-well plate.

Step C: Treatment and analysis

[0397] The plate containing cells were treated with compounds for about 10minutes, and then ligand was added. GDF8 or TGFb was added to plates to stimulate. 293FL cells were stimulatedfor 90 minutes at 37 °C; and RMS13 cells were stimulated for 60 minutes at 37 °C. The medium was then removed from the cells, and 1X Lysis Buffer (about 25 µL) was added and the plate was gently agitated on plate shaker for 5-10 minutes.

[0398] The lysate (5µL) was then placed into 384-well shallow plates avoiding the generation of bubbles. To this, the Reaction Buffer + Activation Buffer + AlphaScreen® Acceptor beadsmixture(5 µL) was added. The plate was sealed with adhesive cover and shielded from light (*e.g.*, with metal foil), and agitated gently on plate shaker for 2 hours at room temperature.

[0399] Dilution buffer + AlphaScreen® Donor beads (2 µL) was then added, and the plate was intubated on the plate shaker for an additional 1½ hours. After completion, the plate was read on Synergy-4 or Enspire plate reader, using AlphaScreen® pSMAD3® settings.

[0400] Representative results for inhibition of GDF8 (data = GDF pSMAD (MPC11) (µM)) and TGF-β **(**data = TGF-β pSMAD (MPC-11) (µM)) signaling are shown in the following table:

No.	GDF8	TGF-β
1	0.07	0.23
2	0.06	0.2
3	0.01	0.01
4	0.01	0.02
5	0.01	0.02
6	0.16	0.62
7	0.04	0.15
8	0.09	0.21
9	0.06	0.33

No.	GDF8	TGF-β
10	0.01	0.06
11	0.04	0.13
12	0.13	0.27
13	0.12	0.38
14	0.61	1.82
15	0.01	0.06
16	0.02	0.1
17	0.05	0.14
18	0.04	0.15

No.	GDF8	TGF-β
19	0.15	0.73
20	0.18	0.16
21	0.38	0.74
22	0.02	0.03
23	0.01	0.03
24	0.01	0.01
25	0.04	0.06
26	0.22	0.26
27	0.09	0.12

No.	GDF8	TGF-β
28	0.05	0.06
29	0.29	-
30	0.27	0.32
31	0.02	0.09
32	0.05	0.14
33	0.06	0.07
34	0.07	0.14
35	0.3	0.64
36	0.5	1.48
37	0.26	0.92
38	0.93	2.55
39	0.19	0.39
40	0.46	1.22
41	0.02	0.06
42	0.03	0.15
43	0.19	0.53
44	0.18	0.72
45	0.44	1.78
46	0.26	1.68
47	0.18	0.66
48	0.06	0.25
49	0.57	1.21
50	1.02	1.87
51	0.78	2.71
52	0.21	0.91
53	0.78	3.34
54	0.41	3.1
55	0.84	7.76
56	0.73	5.3
57	0.71	9.21

No.	GDF8	TGF-β
58	0.99	9.64
59	0.69	6.75
60	0.02	0.06
61	0.03	0.15
62	0.05	0.22
63	0.06	0.23
64	0.09	0.27
65	0.22	1.06
66	0.52	0.98
67	0.58	1.68
68	1.05	2.87
69	0.14	1.77
70	0.7	5.22
71	0.09	0.8
72	0.1	0.97
73	0.1	0.95
74	0.2	1.41
75	0.51	4.39
76	0.19	1.21
77	0.22	1.43
78	0.29	2.47
79	0.11	0.85
80	0.22	1.63
81	0.39	2.62
82	0.48	3.27
83	0.13	1.33
84	0.32	2.9
85	0.18	0.67
86	0.22	1.28
87	0.33	3.46

No.	GDF8	TGF-β
88	1.02	11.48
89	0.43	4.19
90	0.63	3.56
91	0.39	2.23
92	0.47	2.27
93	0.3	2.34
94	0.58	2.91
95	0.3	1.88
96	0.44	2.43
97	0.1	0.54
98	0.05	0.19
99	0.04	0.24
100	0.17	1.37
101	0.14	0.5
102	0.06	0.44
103	0.13	0.69
104	0.08	0.51
105	0.27	2.04
106	0.15	0.92
107	0.34	1.85
108	0.08	0.4
109	0.15	0.87
110	0.25	1.05
111	0.79	4.48
112	0.28	1.37
113	0.46	3.11
114	0.18	1.13
115	0.16	0.75
116	0.28	1.52
117	0.33	2.18

No.	GDF8	TGF-β
118	0.23	1.39
119	0.41	4.74
120	0.47	8.16
121	0.46	2.07
122	0.58	4.53
123	0.74	9.37
124	0.54	1.34
125	0.05	0.12
126	0.09	0.34
127	0.19	0.57
128	0.46	1.48
129	0.29	1.34
130	0.65	2.32
131	0.92	3.91
132	0.55	1.39
133	0.36	2.21
134	0.87	2.54
135	0.77	3.42
136	0.75	2.3
137	0.57	2.54
138	0.73	3.26
139	0.65	2.03
140	0.62	2.22
141	0.66	2.91

No.	GDF8	TGF-β
142	0.67	4.39
143	0.45	3.14
144	0.31	1.53
145	0.53	2.95
146	1	5.96
147	0.55	2.21
148	0.73	2.84
149	0.72	3.22
150	0.35	0.85
151	0.59	1.4
152	0.19	0.38
153	0.0113	0.2073
154	0.0145	0.1161
155	0.0229	0.0724
156	0.0253	0.1335
157	0.0256	0.1595
158	0.036	0.2278
159	0.0367	0.1709
160	0.0385	0.0998
161	0.0468	0.4273
162	0.0523	0.1274
163	0.054	0.1685
164	0.0663	0.2183
165	0.0696	0.2621

No.	GDF8	TGF-β
166	0.0702	0.2204
167	0.078	0.215
168	0.08	0.3379
169	0.0951	0.2358
170	0.0986	0.6559
171	0.1088	0.4229
172	0.121	0.9089
173	0.1237	0.8982
174	0.1444	0.4309
175	0.1545	0.9379
176	0.1582	0.5998
177	0.2345	1.035
178	0.2516	1.1
179	0.2681	1.277
180	0.3011	0.6209
181	0.3363	4.552
182	0.3516	1.122
183	0.3646	1.485
184	0.4024	1.165
185	0.4252	2.357
186	0.4775	1.11
187	0.481	3.098
188	0.7845	0.3647

[0401] Analytical LC-MS/HPLC retention time reported for each example and intermediate uses one of the following general analytical LC-MS/HPLC conditions:

[0402] **Method A**: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7 μm particles; Mobile Phase A: 5:95 acetonitrile:water with 0.1 % TFA; Mobile Phase B: 95:5 acetonitrile:water with 0.1 % TFA; Temperature: 50 °C; Gradient: 0-100 % B over 3 minutes, then a 0.75 minute hold at 100 % B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

[0403] **Method B**: Column Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7 μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM NH_4OAc; Mobile Phase B: 95:5 acetonitrile:water with 10 mM NH_4OAc; Temperature: 50 °C; Gradient: 0-100 % B over 3 minutes, then a 0.75 minute hold at 100 % B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

[0404] **Method C**: Column: Waters Acquity UPLC BEH C18, 2.1 x 50 mm, 1.7μm particles; Mobile Phase A: acetonitrile with 0.05 % TFA; Mobile Phase B: water with 0.05 % TFA; Temperature: 50 °C; Gradient: 2-98 % B over 1.5 minutes, then a 0.1-minute hold at 100 % B; Flow: 0.8 mL/min; Detection: UV at 220 nm.

[0405] **Method D**: Column: Phenomenex LUNA C18, 30 x 2, 3 μm particles; Mobile Phase A: 5:95 acetonitrile:water with 10 mM NH_4OAc; Mobile Phase B: 95:5 acetonitrile:water with 10 mM NH_4OAc; Temperature: 50 °C; Gradient: 0-100 % B over 3 minutes, then a 0.75 minute hold at 100 % B; Flow: 1.0 mL/min; Detection: UV at 220 nm.

[0406] **Method E**: Phenomenex Luna 2.0 X 50 mm 3 μm column; Mobile Phase A: 10:90 methanol:water with 0.1% TFA; Mobile Phase B: 90:10 methanol:water with 0.1% TFA; Temperature: 50 °C; Gradient: 0-100 % B over 4 minutes, then a 1.0 minute hold at 100 % B; flow rate 0.8 mL/min; Detection: UV at 220 nm.

[0407] **Method F**: Column: Waters Acquity UPLC BEH C18 (2.1 x 50 mm), 1.7 μ; Mobile phase A: 0.1 % TFA in water; Mobile phase B: 0.1 % TFA in acetonitrile; Gradient = 20-90 % B over 1.1 minute, then a 0.6 minute hold at 90 % B; Temperature: 50 °C; Flow rate: 0.7 mL/min; Detection: UV at 220 nm.

[0408] **Method G**: Column: Waters Acquity UPLC BEH C18 (2.1 x 50 mm) 1.7 μ, Mobile phase A: 10 mM NH_4OAc in water:acetonitrile (95:5); Mobile phase B: 10 mM NH_4OAc in water:acetonitrile (5:95), Gradient = 20-90 % B over 1.1 minute, then a 0.6 minute hold at 90% B; Temperature: 50 °C; Flow rate: 0.7 mL/min; Detection: UV at 220 nm

[0409] **Method H**: Column: Ascentis Express C18 (2.1 x 50 mm), 2.7 μ; Mobile phase A: 10 mM NH_4OAc in water:acetonitrile (95:5), Mobile phase B: 10 mM NH_4OAc in water:acetonitrile (5:95), Gradient = 0-100 % B over 3 minutes; Temperature: 50 °C; Flow rate: 1.1 mL/min; Detection: UV at 220 nm.

[0410] **Method I**: Column: Ascentis Express C18 (50 x 2.1) mm, 2.7 μ; Mobile phase A: 0.1 % TFA in water:acetonitrile (95:5), Mobile phase B: 0.1 % TFA in water:acetonitrile (5:95), Gradient = 0-100 % B over 3 minutes; Temperature: 50 °C; Flow rate: 1.1 mL/min; Detection: UV at 220 nm.

[0411] **Method J**: Column: Kinetex XB-C18 (75 x 3 mm) 2.6 μ; Mobile phase A: 10 mM HCO_2NH_4 in water:acetonitrile (98:2), Mobile phase B: 10 mM HCO_2NH_4 in water:acetonitrile (2:98), Gradient = 20-100 % B over 4 minutes, then a 0.6 minute hold at 100 % B; Temperature: 27 °C; Flow rate: 1.0 mL/min; Detection: UV at 220 nm.

[0412] **Method K**: Column: ZORBAX- SBC18 (50 x 4.6 mm) 5 μ; Mobile phase A: 10 mM HCO_2NH_4 in water: acetonitrile (98:2), Mobile phase B: 10 mM HCO_2NH_4 in water:acetonitrile (2:98), Gradient = 20-100 % B over 4 minutes, then a 0.6 minute hold at 100 % B; Temperature: 27 °C; Flow rate: 1.5 mL/min; Detection: UV at 220 nm

[0413] **Method L**: Column: Waters X-Bridge C18, 19 x 150 mm, 5 μ; Mobile Phase A: 0.1% TFA in water; Mobile Phase B: acetonitrile; Gradient: 10-100 % B over 25 minutes, then a 5 minute hold at 100 % B; Flow: 15 mL/min.

[0414] **Method M**: Column: Inertsil ODS, 250 x 20 mm ID, 5μ; Mobile Phase A: 10 mM NH_4OAc in water; Mobile Phase B: methanol; Gradient: 10-100 % B over 25 minutes, then a 5 minute hold at 100 % B; Flow: 17 mL/min.

[0415] **Method N**: Column: Inertsil ODS, 150 x 4.6 mm, 5μ; Mobile Phase A: 10 mM NH_4OAc in water; Mobile Phase B: acetonitrile; Gradient: 0-100 % B over 18 minutes, then a 5 minute hold at 100% B; Flow: 17 mL/min.

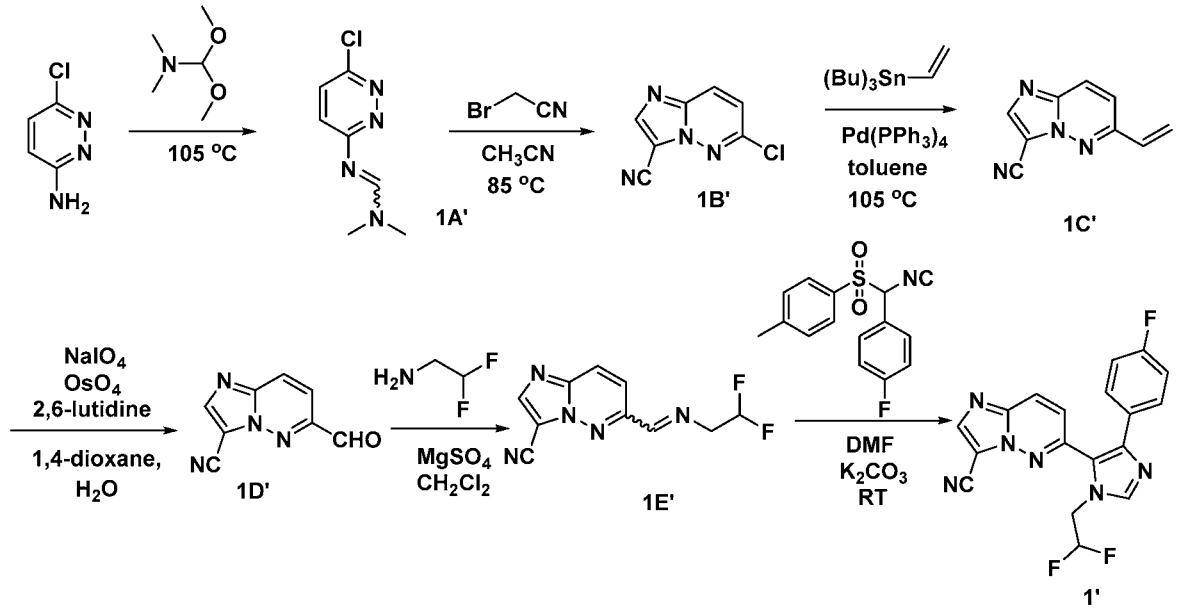
[0416] **Method O**: Column: Sunfire C18, 150 x 19 mm ID, 5 μ; Mobile Phase A: 10 mM NH_4OAc in water; Mobile Phase B: acetonitrile; Gradient: 0-100 % B over 18 minutes, then a 5 minute hold at 100 % B; Flow: 17 mL/min.

[0417] **Method P**: Column: Waters X-Bridge C18, 19 x 150 mm, 5μ; Mobile Phase A: 10 mM NH_4OAc in water; Mobile Phase B: acetonitrile; Gradient: 0-100 % B over 18 minutes, then a 5 minute hold at 100 % B; Flow: 17 mL/min.

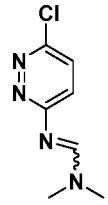
[0418] **Method Q**: Column: Inertsil ODS, 250 x 20 mm ID, 5 μ; Mobile Phase A: 0.1% TFA in water; Mobile Phase B: acetonitrile; Gradient: 10-100 % B over 25 minutes, then a 5 minute hold at 100 % B; Flow: 17 mL/min.

[0419] **Method R**: Column: Symmetry C8, 300 x 19 mm ID, 7 μ; Mobile Phase A: 10 mM NH_4OAc in water; Mobile Phase B: acetonitrile; Gradient: 0-100 % B over 18 minutes, then a 5 minute hold at 100 % B; Flow: 17 mL/min.

Scheme 1

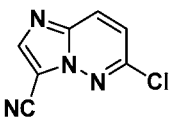


Intermediate 1A′: *N*'-(6-chloropyridazin-3-yl)-*N*,*N*-dimethylformimidamide



[0420] A suspension of 6-chloropyridazin-3-amine (7.3 g, 56 mmol) in 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (7.9 g, 62 mmol) was heated at 105 °C for 2 h. The reaction mixture was cooled to RT and concentrated to give **1A′** (10.3 g, 100 %) as a tan solid. MS (ES): *m/z* = 185/187 $[M+H]^+$; HPLC Ret. Time 0.38 min. (HPLC Method C).

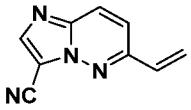
Intermediate 1B′: 6-chloroimidazo[1,2-*b*]pyridazine-3-carbonitrile



[0421] To a suspension of **1A′** (10.3 g, 56 mmol) in acetonitrile (75 mL) was added bromoacetonitrile (10.2 g, 80.5 mmol). The reaction mixture was heated at 85 °C for 6 h. The suspension became a solution and then suspension again (HBr salt). The reaction mixture was cooled to RT and concentrated *in vacuo*. The residue was diluted with DCM, treated with Hunig's base (19.64 mL, 112 mmol) and the resulting solution wasstirred at RT for 1 h and concentrated. The residue was purified by silica gel chromatography (220 g RediSep® column, eluting with a gradient from 0-55 % EtOAc in hexanes). Fractions containing the

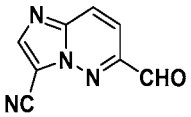
product were combined and evaporated to afford intermediate **1B′** (10.2 g, 50.8 % yield) as a tan powder. MS (ES): *m/z* = 179/181 $[M+H]^+$; HPLC Ret. Time 0.63 min. (HPLC Method C).

Intermediate 1C′: 6-vinylimidazo[1,2-*b*]pyridazine-3-carbonitrile



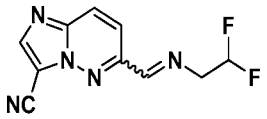
[0422] To a pressure bottle were added tributyl(vinyl)stannane (11.63 g, 36.7 mmol), **1B′** (2.2 g, 12.22 mmol) and toluene (15 mL). The solution was purged with nitrogen for 2 min. and $Pd(Ph_3P)_4$ (1.41 g, 1.222 mmol) was added. The reaction mixture was heated at 105 °C overnight, cooled to RT and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (80 g RediSep® column, eluting with a gradient from 0-85 % EtOAc in hexanes). Fractions containing the product were combined and evaporated to afford intermediate **1C′** (1.34 g, 64.4 % yield) as a tan powder. MS (ES): *m/z* = 171 $[M+H]^+$; HPLC Ret. Time 0.66 min. (HPLC Method C); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.23 (s, 1H), 8.05 (d, *J* = 9.5 Hz, 1H), 7.54 (d, *J* = 9.5 Hz, 1H), 6.95 (dd, *J* = 17.8, 11.0 Hz, 1H), 6.28 (d, *J* = 17.8 Hz, 1H), 5.85 (d, *J* = 11.0 Hz, 1H).

Intermediate 1D′: 6-formylimidazo[1,2-*b*]pyridazine-3-carbonitrile



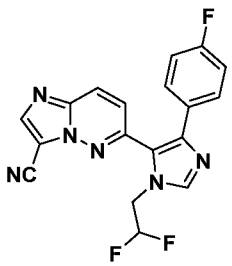
[0423] To a solution of intermediate **1C′** (290 mg, 1.704 mmol) in 1,4-dioxane (12 mL) and water (4 mL) were added 2,6-lutidine (0.397 mL, 3.41 mmol), sodium periodate (1458 mg, 6.82 mmol), and 4 % aq. solution of osmium tetroxide (0.401 mL, 0.051 mmol). The reaction mixture was stirred at RT for 4 h and diluted with water and DCM. The layers were separated. The aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated and the residue was purified by silica gel chromatography (80 g RediSep® column, eluting with a gradient from 15-65 % EtOAc in hexanes). Fractions containing the product were combined and evaporated to afford intermediate **1D′** (210 mg, 71.6 % yield). MS (ES): *m/z* = 357.2; HPLC Ret. Time 2.711 (HPLC method E); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.18 (d, *J* = 1.0 Hz, 1H), 8.44 (s, 1H), 8.27 (dd, *J* = 9.4, 0.9 Hz, 1H), 7.92 (d, *J* = 9.3 Hz, 1H).

Intermediate 1E′: 6-(((2,2-difluoroethyl)imino)methyl)imidazo[1,2-*b*]pyridazine-3-carbonitrile



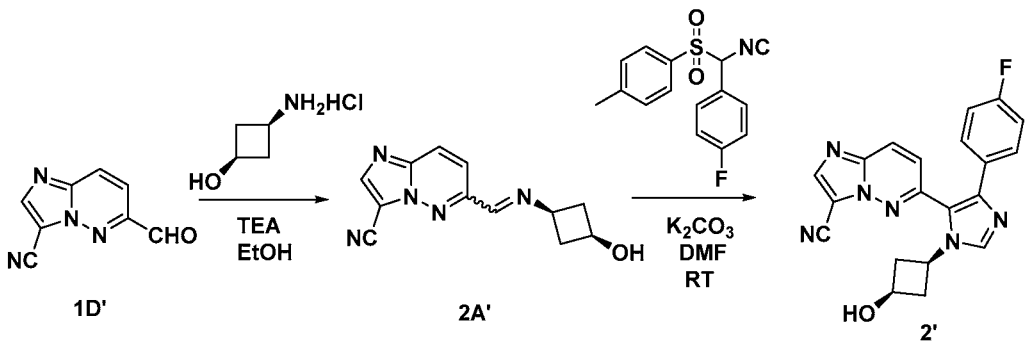
[0424] To a solution of intermediate **1D′** (210 mg, 1.22 mmol) in DCM (10 mL) were added anhydrous magnesium sulfate (1175 mg, 9.76 mmol) and 2,2-difluoroethanamine (109 mg, 1.342 mmol). The reaction mixture was stirred at RT for 4 h and filtered. The filtrate was concentrated and the crude product was used in the next step without purification. MS (ES): *m/z* = 236 $[M+H]^+$; HPLC Ret. Time 1.43 min. (HPLC Method D); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.55 (s, 1H), 8.31 (s, 1H), 8.18 - 8.02 (m, 2H), 6.19 (t, *J* = 4.3 Hz, 1H), 4.13 (ddd, *J* = 14.9, 4.3, 1.5 Hz, 2H).

Example 1′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

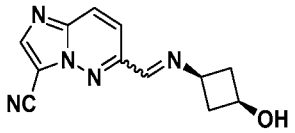


[0425] To a solution of intermediate **1E′** (26 mg, 0.111 mmol) in DMF (1 mL) were added 1-fluoro-4-(isocyano(tosyl)methyl)benzene (32 mg, 0.111 mmol) and potassium carbonate (20 mg, 1.44 mmol). The reaction mixture was stirred at RT overnight, and diluted with EtOAc and water, The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated. The crude product was dissolved in a mixture of DMF and methanol and purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **1′** (18.1 mg, 44 % yield). MS (ES): *m/z* = 369 $[M+H]^+$; HPLC Ret. Time 1.322 and 1.532 min. (HPLC Methods A and B, respectively); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.29 (s, 1H), 7.93 (d, *J* = 9.5 Hz, 1H), 7.83 (s, 1H), 7.56 - 7.47 (m, 2H), 7.18 - 7.04 (m, 3H), 6.38 (t, *J* = 3.8 Hz, 1H), 4.71 (dd, *J* = 13.9, 3.6 Hz, 2H).

Scheme 2

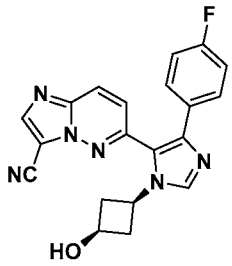


Intermediate 2A′: 6-(((*cis*-3-hydroxycyclobutyl)imino)methyl)imidazo[1,2-*b*]pyridazine-3-carbonitrile



[0426] To a solution of intermediate **1D′** (280 mg, 1.627 mmol) in ethanol (10 mL) were added *cis*-3-aminocyclobutanol hydrochloride (220 mg, 1.780 mmol) and TEA (340 μL, 2.440 mmol). The reaction mixture was stirred at RT for 6 h. It became a suspension after 2 h. The reaction mixture was concentrated to afford a residue that was used in the next step without further purification. MS (ES): *m/z* = 242 $[M+H]^+$; HPLC Ret. Time 1.20 min. (HPLC Method D); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.38 (d, *J* = 1.3 Hz, 1H), 8.28 (s, 1H), 8.16 - 8.02 (m, 2H), 4.29 (t, *J* = 7.3 Hz, 1H), 4.00 - 3.84 (m, 1H), 2.96 - 2.78 (m, 2H), 2.28 - 2.14 (m, 2H).

Example 2′: 6-(4-(4-fluorophenyl)-1-*cis*-3-hydroxycyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

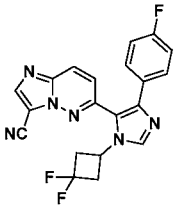
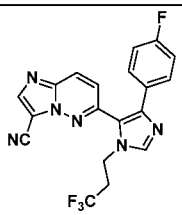
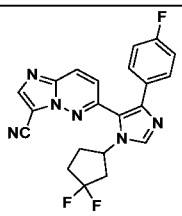
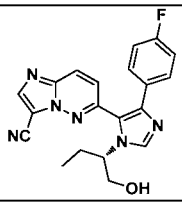
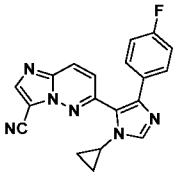


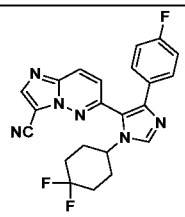
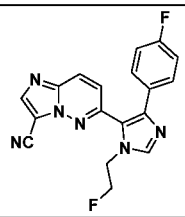
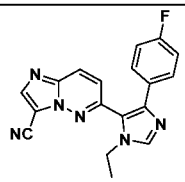
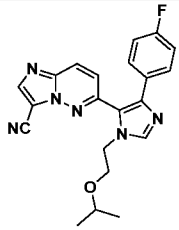
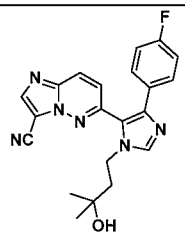
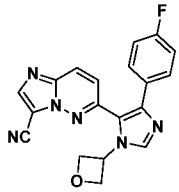
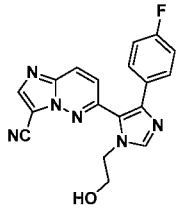
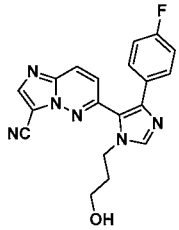
[0427] To a solution of intermediate **2A′** (200 mg, 0.829 mmol) in DMF (2 mL) were added 1-fluoro-4-(isocyano(tosyl)methyl)benzene (240 mg, 0.829 mmol) and potassium carbonate (115 mg, 0.829 mmol). The reaction mixture was stirred at RT overnight, and diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and

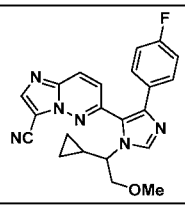
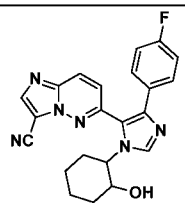
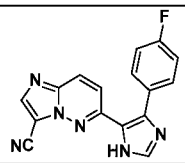
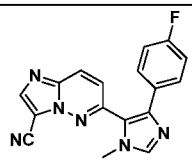
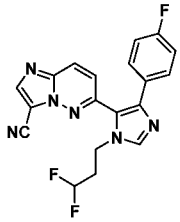
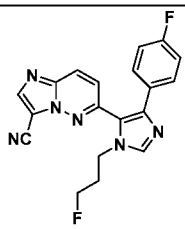
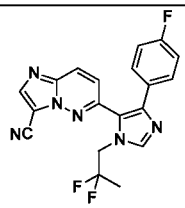
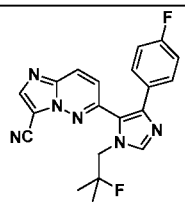
filtered. The filtrate was concentrated and the crude product was purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **2′** (152 mg, 49 % yield). MS (ES): *m/z* = 375.1 $[M+H]^+$; HPLC Ret. Time 0.997 and 1.218 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.64 (s, 1H), 8.32 (d, *J* = 9.2 Hz, 1H), 8.25 (s, 1H), 7.52 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.30 (d, *J* = 9.2 Hz, 1H), 7.14 (t, *J* = 8.8 Hz, 2H), 4.30 (t, *J* = 7.7 Hz, 1H), 3.90 (d, *J* = 5.9 Hz, 1H), 2.85 - 2.73 (m, 2H), 2.38 - 2.18 (m, 3H).

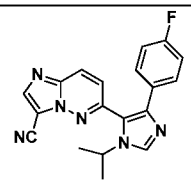
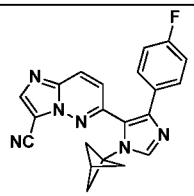
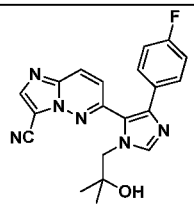
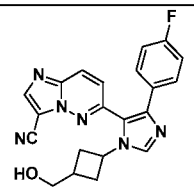
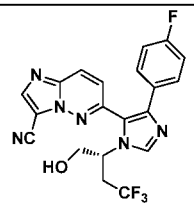
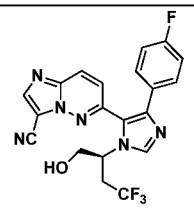
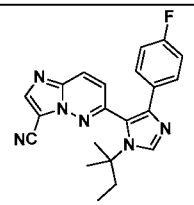
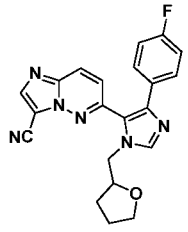
[0428] Compounds shown in **Table 1** have been prepared in a manner similar to Example **1′**, if the amine is a free base, or a manner similar to Example **2′**, if the amine is an HCl salt, using intermediate **1D′** and 1-fluoro-4-(isocyano(tosyl)methyl)benzene.

Table 1

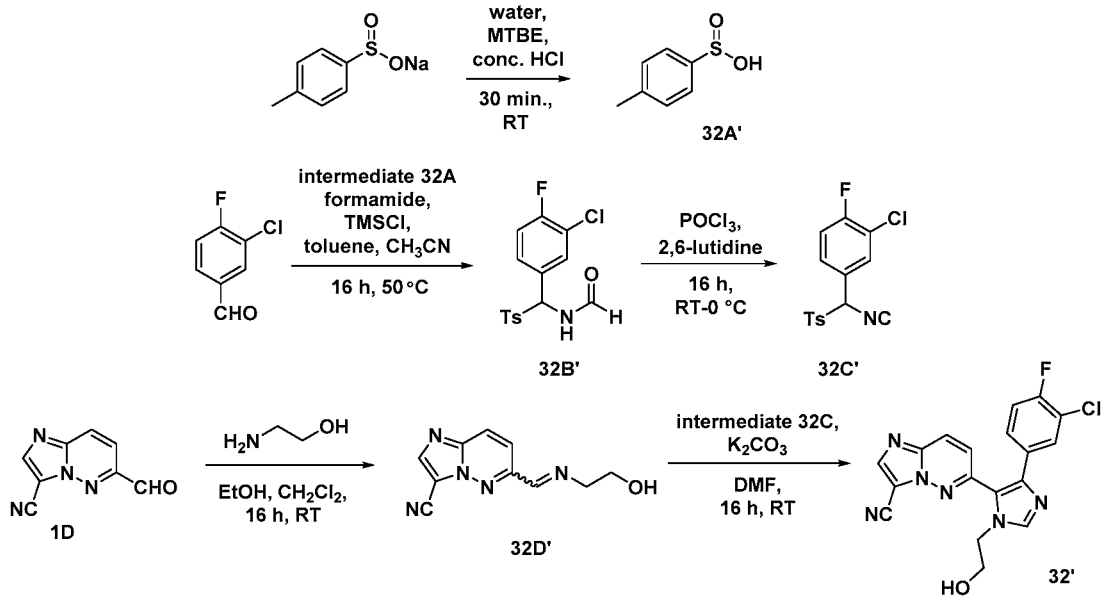
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
3′		6-(1-(3,3-difluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	395.0	1.307 1.619	A B
4′		6-(4-(4-fluorophenyl)-1-(3,3,3-trifluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	400.9	1.389 1.668	A B
5′		6-(1-(3,3-difluorocyclopentyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	409.0	1.363 1.679	A B
6′		(*S*)-6-(4-(4-fluorophenyl)-1-(1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	377.1	1.222 1.423	A B
7′		6-(1-cyclopropyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	345.0	1.175 1.606	A B

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
8′		6-(1-(4,4-difluorocyclohexyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	423.0	1.355 1.731	A B
9′		6-(1-(2-fluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	351.0	1.287 1.423	A B
10′		6-(1-ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	333.1	1.195 1.571	A B
11′		6-(4-(4-fluorophenyl)-1-(2-*iso*propoxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	391.1	1.412 1.651	A B
12′		6-(4-(4-fluorophenyl)-1-(3-hydroxy-3-methylbutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	391.1	1.150 1.540	A B
13′		6-(4-(4-fluorophenyl)-1-(oxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	361.0	1.056 1.263	A B
14′		6-(4-(4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	349.1	1.135 1.212	A B
15′		6-(4-(4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	363.1	1.054 1.274	A B

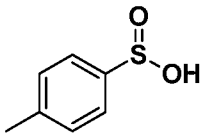
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
16′		6-(1-(1-cyclopropyl-2-methoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	403.1	1.274 1.727	A B
17′		6-(4-(4-fluorophenyl)-1-(2-hydroxycyclohexyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	403.4	1.274 1.670	A B
18′		6-(4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	305.1	1.151 1.323	A B
19′		6-(4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	319.2	0.87 1.21	A B
20′		6-(1-(3,3-difluoropropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	383.3	1.22 1.54	A B
*21′		6-(4-(4-fluorophenyl)-1-(3-fluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	365.3	1.165 1.50	A B
22′		6-(1-(2,2-difluoropropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	383.3	1.35 1.56	A B
23′		6-(1-(2-fluoro-2-methylpropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	379.3	1.289 1.627	A B

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
24′		6-(4-(4-fluorophenyl)-1-isopropyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	347.2	2.129	J
25′		6-(1-(bicyclo[1.1.1]pentan-1-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	371.2	1.182 1.60	A B
26′		6-(4-(4-fluorophenyl)-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	377.3	1.123 1.36	A B
27′		6-(4-(4-fluorophenyl)-1-(3-(hydroxymethyl)cyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	389.3	1.09 1.352	A B
28′		(*R*)-6-(4-(4-fluorophenyl)-1-(4,4,4-trifluoro-1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	431.3	1.274 1.46	A B
29′		(*S*)-6-(4-(4-fluorophenyl)-1-(4,4,4-trifluoro-1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	431.3	1.274 1.46	A B
30′		6-(4-(4-fluorophenyl)-1-(*tert*-pentyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	375.0	1.30	I
31′		6-(4-(4-fluorophenyl)-1-((tetrahydrofuran-2-yl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	389.0	1.633 1.265	H I

Scheme 3

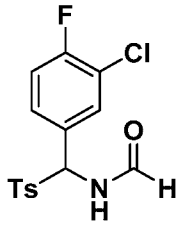


Intermediate 32A′: 4-methylbenzenesulfinic acid



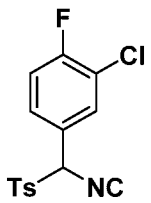
[0429] Sodium 4-methylbenzenesulfinate (25 g, 140 mmol) was dissolved in water (175 mL) and stirred for 20 min. The solution was diluted with MTBE (15 mL) and treated with conc. HCl (11.69 mL, 140 mmol). The resultant mixture was stirred for 20 min. and the two layers were separated. Toluene (~150 mL) was added to the organic layer and the organic layer was concentrated until most of the solvent was removed (water bath temperature < 35 °C). Heptane (~100 mL) was then added to the residue to precipitate out a white solid. The solid was filtered off and the filter-cake was washed with some more heptane and dried under high vacuum to afford intermediate **32A′** (12.9 g, 58.9 % yield) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 12.38 (br. s, 1H), 7.63 - 7.51 (m, 2H), 7.45 - 7.32 (m, J = 7.8 Hz, 2H), 2.38 (s, 3H).

Intermediate 32B′: *N*-((3-chloro-4-fluorophenyl)(tosyl)methyl)formamide



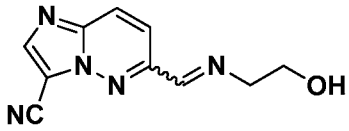
[0430] To a solution of 3-chloro-4-fluorobenzaldehyde (7.0 mL, 59.6 mmol) in toluene (27.4 mL) and acetonitrile (27.4 mL) were added formamide (5.93 mL, 149 mmol), TMS-Cl (8.38 mL, 65.6 mmol) and intermediate **32A′** (12.66 g, 81 mmol). The reaction mixture was heated in an oil-bath at 50 °C for 16 h, cooled to RT and quenched by adding water (~20 mL) to generate a precipitate. To the mixture was then added MTBE (~15 mL) and the mixture was stirred for a few min. before being filtered off. The filter-cake was washed with water and then air-dried. It was purified by silica gel chromatography (220 g RediSep® column, eluting with a gradient of 5-90 % EtOAc in hexanes). Fractions containing the product were combined and evaporated to afford intermediate **32B′** (12.9 g, 63.3 % yield) as a white solid. MS (ES): *m/z* = 341.9 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.75 (d, *J* = 10.8 Hz, 1H), 7.98 (d, *J* = 1.0 Hz, 1H), 7.91 - 7.81 (m, 1H), 7.79 - 7.69 (m, 2H), 7.67 - 7.58 (m, 1H), 7.53 - 7.41 (m, 3H), 6.55 (d, *J* = 10.5 Hz, 1H), 2.46 - 2.39 (m, 3H).

Intermediate 32C′: 2-chloro-1-fluoro-4-(isocyano(tosyl)methyl)benzene



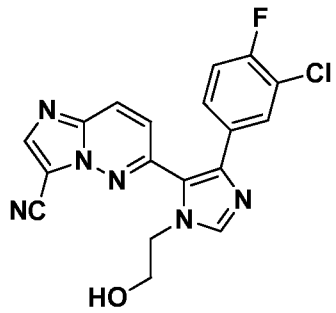
[0431] To a solution of intermediate **32B′** (12.58 g, 36.8 mmol) in THF (184 mL) was added $POCl_3$ (8.58 mL, 92 mmol) at RT. The reaction mixture was stirred for 30 min, cooled to 0 °C, and treated with 2,6-lutidine (27.9 mL, 239 mmol). The resultant mixture was stirred for 1 h at 0 °C and then at RT for 16 h. The reaction was poured into ice-cold aq. $NaHCO_3$ solution and extracted with EtOAc (3 x 125 mL). The combined organic layers were washed with 1N aq. HCl, followed by satd. aq. $NaHCO_3$, water and brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give a solid, which was purified bysilica gel chromatography (120 g RediSep® column, eluting with a gradient of 0-25 % EtOAc in hexanes). Fractions containing the product were combined and evaporated to afford intermediate **32C′** (8.5 g, 71.3 % yield) as a pale yellow solid. MS (ES): *m/z* = 322.2 $[M-H]^+$; HPLC Ret. Time 2.67 min. (HPLC Method D); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.71 (d, *J* = 8.3 Hz, 3H), 7.66 - 7.55 (m, 3H), 7.51 (dd, *J* = 6.9, 2.1 Hz, 1H), 7.40 (dt, *J* = 4.3, 2.0 Hz, 1H), 2.48 (s, 3H).

Intermediate 32D′: 6-(((2-hydroxyethyl)imino)methyl)imidazo[1,2-*b*]pyridazine-3-carbonitrile



[0432] To a solution of 2-aminoethanol (0.257 mL, 4.25 mmol) in ethanol (19.3 mL) and DCM (19.3 mL) was added intermediate **1D′** (0.665 g, 3.86 mmol). The reaction mixture was stirred at RT for 16 h and concentrated to dryness under reduced pressure (water-bath temp. <25 °C) to afford intermediate **32D′** (0.84 g, crude). MS (ES): *m/z* = 216.04 $[M+H]^+$; HPLC Ret. Time 1.46 min. (HPLC Method D). The intermediate was sufficiently pure to use directly in the next step without purification.

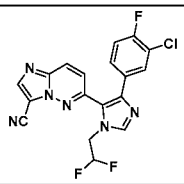
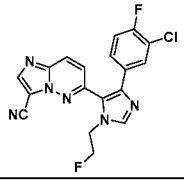
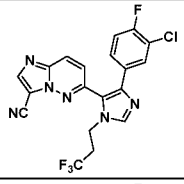
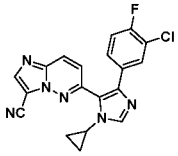
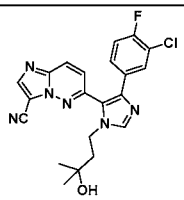
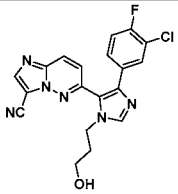
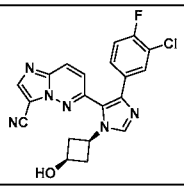
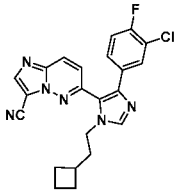
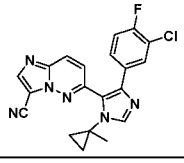
Example 32′: 6-(4-(3-chloro-4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

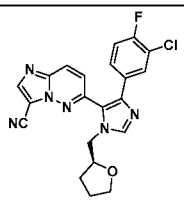
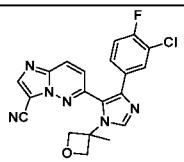
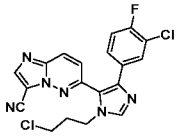
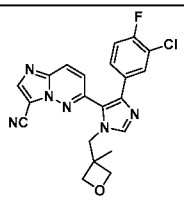
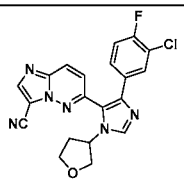
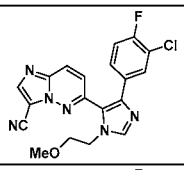
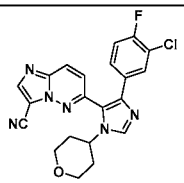
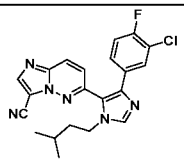
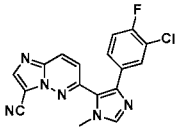
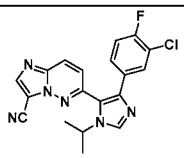


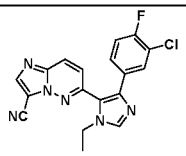
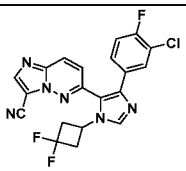
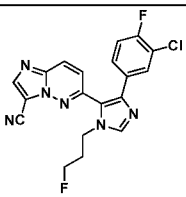
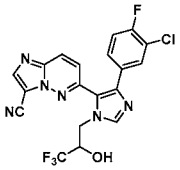
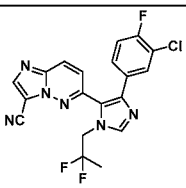
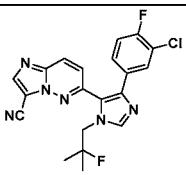
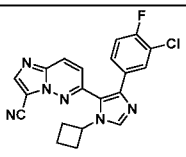
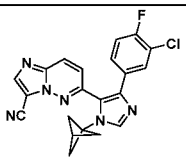
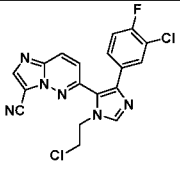
[0433] To intermediate **32D′** (0.84 g, crude) was added potassium carbonate (0.694 g, 5.02 mmol) and a solution of intermediate **32C′** (1.25 g, 3.86 mmol) in DMF (~10 mL). The resultant mixture was stirred at RT for 16 h. The resulting precipitate was then filtered off and filter-cake rinsed with DCM. The combined filtrates were concentrated under reduced pressure to afford a crude syrup, which was purified by silica gel chromatography (120 g RediSep® column, eluting with a gradient of 1-5 % MeOH in EtOAc). Fractions containing the desired product were evaporated to afford Example **32′** (1.4 g, 94 % yield) as a pale yellow solid. MS (ES): *m/z* = 383.2 $[M+H]^+$; HPLC Ret. Time 1.27 min. and 1.36 min. (HPLC Methods A and B, respectively); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.65 (s, 1H), 8.33 (d, *J* = 9.3 Hz, 1H), 8.00 (s, 1H), 7.75 (dd, *J* = 7.3, 2.3 Hz, 1H), 7.46 - 7.28 (m, 3H), 4.84 (t, *J* = 5.4 Hz, 1H), 4.40 - 4.15 (m, 3H), 3.45 (dd, *J* = 7.0, 5.3 Hz, 1H).

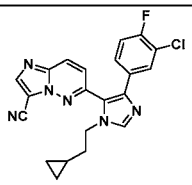
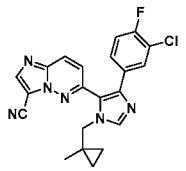
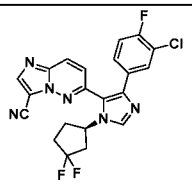
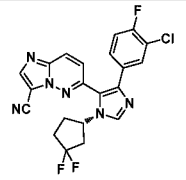
[0434] Compounds shown in **Table 2** have been prepared in a manner similar to Example **1′**, if the amine is a free base or a manner similar to Example **2′**, if the amine is an HCl salt, using intermediates **1D′** and **32C′**.

Table 2

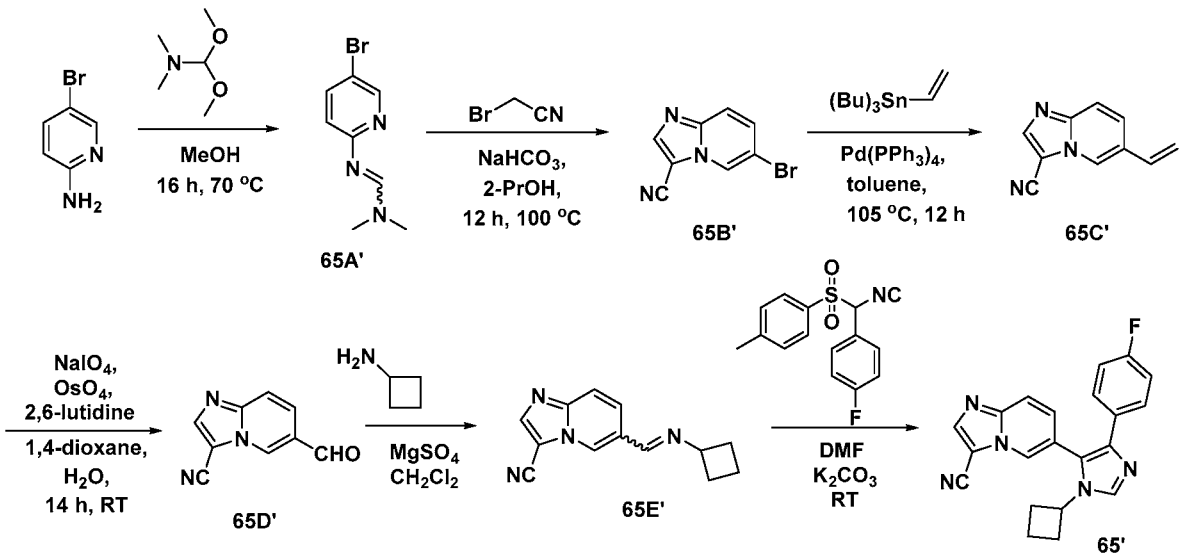
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
33′		6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	403.0	1.544 1.658	A B
34′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-fluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	385.0	1.511 1.603	A B
35′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3,3-trifluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	435.2	1.501 1.676	A B
36′		6-(4-(3-chloro-4-fluorophenyl)-1-cyclopropyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	379.0	1.308 1.612	A B
37′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-hydroxy-3-methylbutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	425.1	1.383 1.623	A B
38′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	397.1	1.166 1.530	A B
39′		6-(4-(3-chloro-4-fluorophenyl)-1-((*cis*)-3-hydroxycyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	427.0	1.031 1.252	A B
40′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-cyclobutylethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	421.3	1.612 1.916	A B
41′		6-(4-(3-chloro-4-fluorophenyl)-1-(1-methylcyclopropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	393	1.453 1.776	A B

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
42′		(*S*)-6-(4-(3-chloro-4-fluorophenyl)-1-((tetrahydrofuran-2-yl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	423.1	1.41 1.687	A B
43′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-methyloxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	409.0	1.389 1.448	A B
44′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-chloropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	415.0	1.48 1.787	A B
45′		6-(4-(3-chloro-4-fluorophenyl)-1-((3-methyloxetan-3-yl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	423.1	1.379 1.568	A B
46′		6-(4-(3-chloro-4-fluorophenyl)-1-(tetrahydrofuran-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	409.0	1.307 1.449	A B
47′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-methoxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	397.0	1.344 1.620	A B
48′		6-(4-(3-chloro-4-fluorophenyl)-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	423.0	1.62 2.194	A B
49′		6-(4-(3-chloro-4-fluorophenyl)-1-*iso*pentyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	409.1	1.603 1.994	A B
50′		6-(4-(3-chloro-4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	353.1	1.55 1.49	A B
51′		6-(4-(3-chloro-4-fluorophenyl)-1-isopropyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	381.3	1.36 1.74	A B

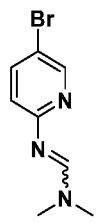
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
52′		6-(4-(3-chloro-4-fluorophenyl)-1-ethyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	367.2	1.15 1.51	A B
53′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	429.05	1. 68 1. 75	A B
54′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-fluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	399.2	1.50 1.63	A B
55′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3,3-trifluoro-2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	451.2	1.47 1.64	A B
56′		6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	417.2	1.62 1.77	A B
57′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-fluoro-2-methylpropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	413.3	1.56 1.81	A B
58′		6-(4-(3-chloro-4-fluorophenyl)-1-cyclobutyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	393.3	1.38 1.66	A B
59′		6-(1-(bicyclo[1.1.1]pentan-1-yl)-4-(3-chloro-4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	405.2	1.55 1.85	A B
60′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-chloroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	401.1	1.49 1.73	A B

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
61′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-cyclopropylethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	407.3	1.53 1.89	A B
62′		6-(4-(3-chloro-4-fluorophenyl)-1-((1-methylcyclopropyl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	407.3	1.40 1.75	A B
63′		(*R*)-6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclopentyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	443.0	1.580 1.848	A B
64′		(*S*)-6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclopentyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	443.0	1.576 1.847	A B

Scheme 4

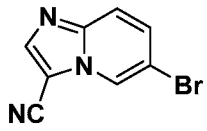


Intermediate 65A′: *N*′-(5-bromopyridin-2-yl)-*N*,*N*-dimethylformimidamide



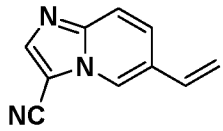
[0435] A solution of 5-bromopyridin-2-amine (12 g, 69.4 mmol) and 1,1-dimethoxy-*N*,*N*-dimethylmethanamine (12.84 mL, 90 mmol) in MeOH (72.2 mL) was heated in an oil-bath at 70 °C for 16 h. The reaction mixture was concentrated under reduced pressure to near dryness to give an oil. The oil was dissolved in hexanes the solution evaporated to dryness to afford intermediate **65A′** (15.66 g, >99 % yield) as a solid. MS (ES): *m/z* = 228/230.0 $[M+H]^+$. The solid was used directly in cyclization step without further purification.

Intermediate 65B′: 6-bromoimidazo[1,2-*a*]pyridine-3-carbonitrile



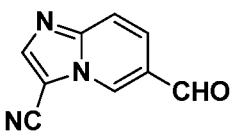
[0436] To a suspension of intermediate **65A′** (12.0 g, 52.6 mmol) and sodium bicarbonate (13.26 g, 158 mmol) in 2-propanol (133 mL) was added 2-bromoacetonitrile (9.46 mL, 132 mmol). The reaction mixture was heated in an oil-bath at 100 °C for 12 h. The reaction was then poured into water (~250 mL) and the mixture was stirred at RT for 1 h. The solid was filtered off and the filter-cake was washed with water until the filtrate was light yellow in color. The solid was dried under high vacuum to afford intermediate **65B′** (8.0 g, 68.5 % yield) as a dark solid. MS (ES): *m/z* = 222/224.0 $[M+H]^+$.

Intermediate 65C′: 6-vinylimidazo[1,2-*a*]pyridine-3-carbonitrile



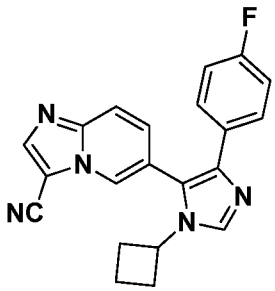
[0437] Intermediate **65C′** was synthesized analogous to intermediate **1C′** by coupling intermediate **65B′** and tributyl(vinyl)stannane. The crude product was purified by silica gel chromatography (120 g RediSep® column, eluting with a gradient of 10-60 % EtOAc in hexanes). Fractions containing the desired product were combined and evaporated to afford intermediate **65C′** (1.625 g, 82 % yield). MS (ES): *m/z* = 170.1 $[M+H]^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.74 (s, 1H), 8.44 (s, 1H), 7.93 (dd, *J* = 9.4, 1.6 Hz, 1H), 7.84 (d, *J* = 9.5 Hz, 1H), 6.92 (dd, *J* = 17.8, 11.0 Hz, 1H), 6.05 (d, *J* = 17.6 Hz, 1H), 5.45 (d, *J* = 11.0 Hz, 1H).

Intermediate 65D′: 6-formylimidazo[1,2-*a*]pyridine-3-carbonitrile



[0438] Intermediate **65D′** was synthesized analogous to intermediate **1D′** by treating intermediate **65C′** with $OsO_4/NaIO_4$. The crude product was purified by silica gel chromatography (40 g RediSep® column, eluting with a gradient of 40-60 % EtOAc in hexanes). Fractions containing the desired product were combined and evaporated to afford intermediate **65D′** (0.24 g, 95 % yield). MS (ES): *m/z* = 172.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.14 (d, *J* = 0.8 Hz, 1H), 9.52 (dd, *J* = 1.6, 0.9 Hz, 1H), 8.63 (s, 1H), 8.01 - 7.92 (m, 1H), 7.91 - 7.82 (m, 1H).

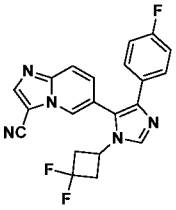
Example 65′: 6-(1-cyclobutyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile

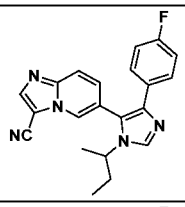
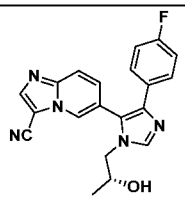
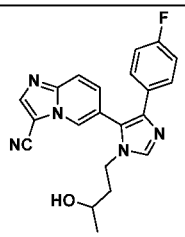
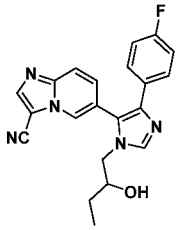
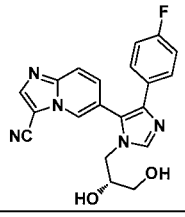
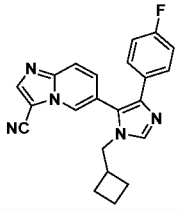
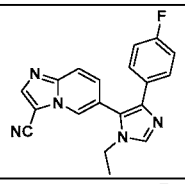
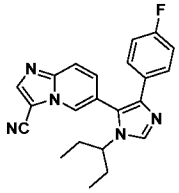


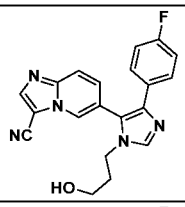
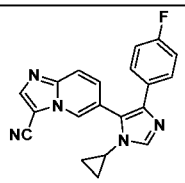
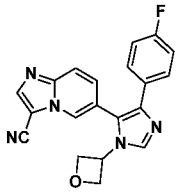
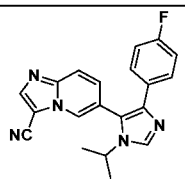
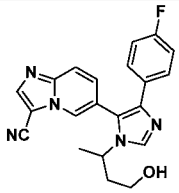
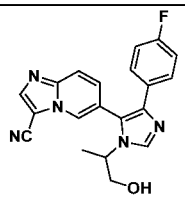
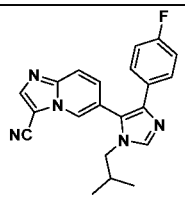
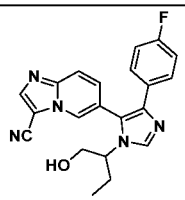
[0439] Example **65′** was synthesized analogous to Example **1′** (Scheme **1**) by treating intermediate **65D′** with cyclobutanamine to first form the imine intermediate **65E′**, followed by reacting intermediate **65E′** with 1-fluoro-4-(isocyano(tosyl)methyl)benzene. The crude product was purified via preparative HPLC. Fractions containing the product were combined and evaporated to afford Example **65′** (56.2 mg, 63.15 % yield). MS (ES): *m/z* = 358.1 $[M+H]^+$; HPLC Ret. Time 1.099 min. and 1.666 min. (HPLC Methods A and B, respectively); ^1H NMR (500 MHz, DMSO-d_6) δ ppm 9.18 (s, 1H), 8.88 (s, 1H), 8.57 (s, 1H), 7.98 (d, *J* = 9.5 Hz, 1H), 7.57 - 7.41 (m, 3H), 7.31 - 7.12 (m, 2H), 4.69 (t, *J* = 8.3 Hz, 1H), 2.46 (d, *J* = 9.9 Hz, 2H), 2.26 - 2.12 (m, 2H), 1.82 - 1.65 (m, 2H).C

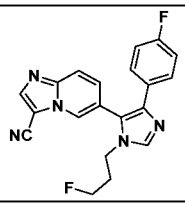
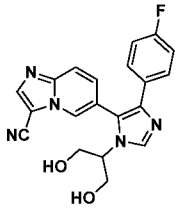
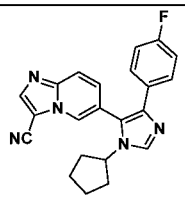
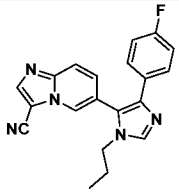
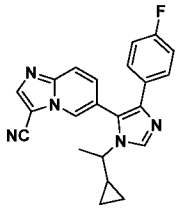
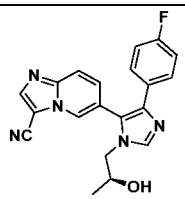
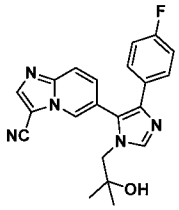
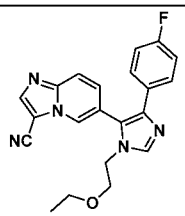
[0440] Compounds shown in **Table 3** have been prepared in a manner similar to Example **1′**, if the amine is a free base, or in a manner similar to Example **2′**, if the amine is an HCl salt, using aldehyde intermediate **65D′** and 1-fluoro-4-(isocyano(tosyl)methyl)benzene.

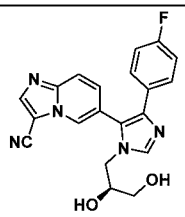
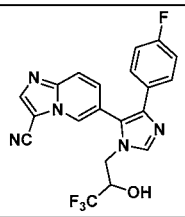
Table 3

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
66′		6-(1-(3,3-difluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	394.0	1.186 1.464	A B

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
67′		6-(1-(sec-butyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	360.1	1.128 1.664	A B
68′		(*R*)-6-(4-(4-fluorophenyl)-1-(2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	362.0	1.086 1.225	A B
69′		6-(4-(4-fluorophenyl)-1-(3-hydroxybutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	376.1	1.065 1.247	A B
70′		6-(4-(4-fluorophenyl)-1-(2-hydroxybutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	376.0	1.137 1.288	A B
71′		(*R*)-6-(1-(2,3-dihydroxypropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	378.1	0.962 1.175	A B
72′		6-(1-(cyclobutylmethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	372.1	1.198 1.680	A B
73′		6-(1-ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	332.1	1.019 1.487	A B
74′		6-(4-(4-fluorophenyl)-1-(pentan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	374.1	1.210 1.711	A B

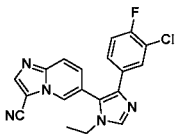
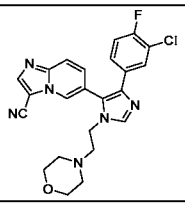
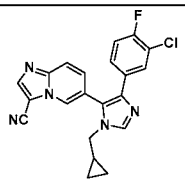
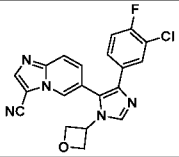
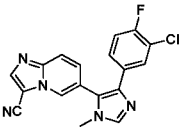
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
75′		6-(4-(4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	362.1	0.963 1.33	A B
76′		6-(4-(4-fluorophenyl)-1-(3-methylbutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	374.1	1.364 1.72	A B
77′		6-(1-cyclopropyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	344.1	1.043 1.556	A B
78′		6-(4-(4-fluorophenyl)-1-(oxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	360.1	1.004 1.323	A B
79′		6-(4-(4-fluorophenyl)-1-isopropyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	346.2	1.078 1.578	A B
80′		6-(4-(4-fluorophenyl)-1-(4-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	376.1	0.96 1.303	A B
81′		6-(4-(4-fluorophenyl)-1-(1-hydroxypropan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	362.1	0.879 1.355	A B
82′		6-(4-(4-fluorophenyl)-1-isobutyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	360.1	1.152 1.683	A B
83′		6-(4-(4-fluorophenyl)-1-(1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	376.0	1.119 1.293	A B

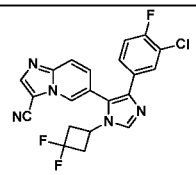
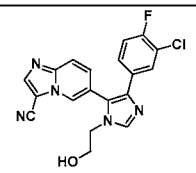
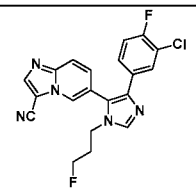
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
84′		6-(4-(4-fluorophenyl)-1-(3-fluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	364.2	1.129 1.357	A B
85′		6-(1-(1,3-dihydroxypropan-2-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	378.1	1.031 1.095	A B
86′		6-(1-cyclopentyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	372.1	1.156 1.748	A B
87′		6-(4-(4-fluorophenyl)-1-propyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	346.1	1.086 1.586	A B
88′		6-(1-(1-cyclopropylethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	372.1	1.164 1.695	A B
89′		(*S*)-6-(4-(4-fluorophenyl)-1-(2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	362.0	1.095 1.224	A B
90′		6-(4-(4-fluorophenyl)-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	376.1	1.245 1.304	A B
91′		6-(1-(2-ethoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	376.0	1.209 1.432	A B

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
92′		(*S*)-6-(1-(2,3-dihydroxypropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	378.1	0.955 1.247	A B
93′		6-(4-(4-fluorophenyl)-1-(3,3,3-trifluoro-2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	416.0	1.157 1.369	A B

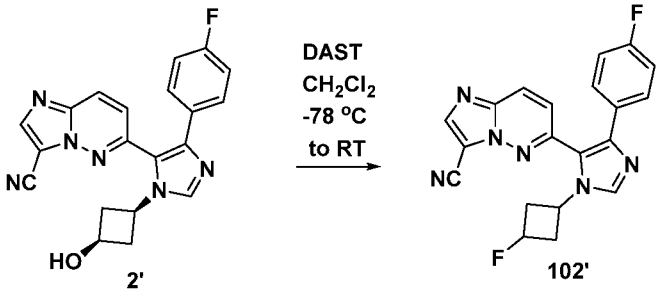
[0441] Compounds shown in **Table 4** have been prepared in a manner similar to Example **1′**, if the amine is a free base, or in a manner similar to Example **2′**, if the amine is an HCl salt, using intermediates aldehyde **65D′** and **32C′**.

Table 4

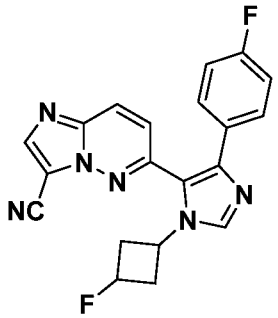
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
94′		6-(4-(3-chloro-4-fluorophenyl)-1-ethyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	366.0	1.211 1.561	A B
95′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-morpholinoethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	451.3	1.139 1.501	A B
96′		6-(4-(3-chloro-4-fluorophenyl)-1-(cyclopropylmethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	392.0	1.277 1.686	A B
97′		6-(4-(3-chloro-4-fluorophenyl)-1-(oxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	394.0	1.167 1.467	A B
98′		6-(4-(3-chloro-4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	352.08	1.232 1.567	A B

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
99′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	428.12	1.400 1.803	A B
100′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	382.2	1.131 1.342	A B
101′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-fluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	398.2	1.279 1.532	A B

Scheme 5



Example 102′: 6-(1-(3-fluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

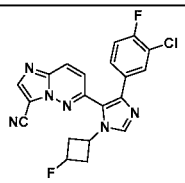


[0442] To a solution of Example **2′** (144 mg, 0.385 mmol) in DCM (10 mL) at -78 °C under nitrogen was added DAST (0.203 mL, 1.539 mmol). The reaction mixture was gradually warmed up to RT overnight and quenched slowly with sat'd aq. $NaHCO_3$ solution. The mixture was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated and the crude product was dissolved in a mixture of DMF and methanol and purified via preparative HPLC. Fractions

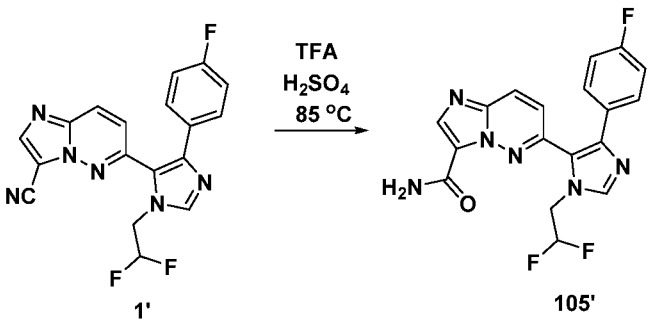
containing the desired product were combined and dried under vacuum to afford Example **102′** (31.5 mg, 21 % yield). MS (ES): *m/z* = 377.1 $[M+H]^+$; HPLC Ret. Time 1.186 min. and 1.524 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.64 (s, 1H), 8.40 - 8.22 (m, 2H), 7.53 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.26 (d, *J* = 9.2 Hz, 1H), 7.16 (t, *J* = 8.8 Hz, 2H), 5.52 - 5.29 (m, 1H), 5.16 (t, *J* = 7.7 Hz, 1H), 3.03 - 2.84 (m, 2H), 2.84 - 2.68 (m, 2H).

[0443] Compounds shown in **Table 5** have been prepared in a manner similar to Example **102′** using DAST. Example **103′** was synthesized from Example **6′** and Example **104′** was synthesized from Example **39′**.

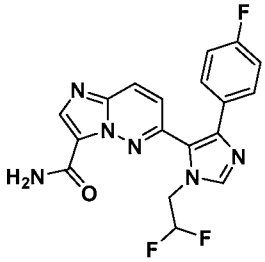
Table 5

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
103′		(*S*)-6-(1-(1-fluorobutan-2-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	379.1	1.236 1.676	A B
104′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-fluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	411.0	1.392 1.715	A B

Scheme 6



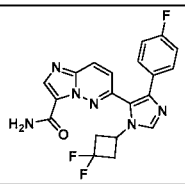
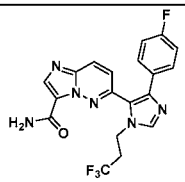
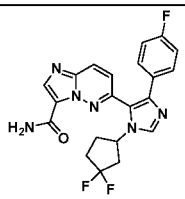
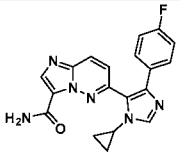
Example 105′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide

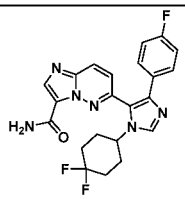
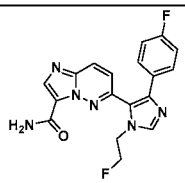
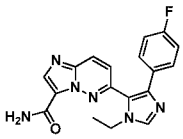


[0444] To a vial were added TFA (0.063 mL, 0.815 mmol) and conc. sulfuric acid (0.014 mL, 0.272 mmol). The resulting mixture was allowed to stir for 5 min. prior to the addition of a solution of Example **1′** (25 mg, 0.068 mmol) in TFA (0.5 mL). The reaction mixture was heated at 85 °C for 2 h. The reaction mixture was cooled to RT and concentrated. The residue was neutralized with sat'd aq. $NaHCO_3$ solution and diluted with DCM. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated. The crude product was dissolved in a mixture of DMF and methanol and purified by preparative HPLC. Fractions containing the desired product were combined and evaporated to Example **105′** (9 mg, 34 % yield). MS (ES): *m/z* = 387.0 $[M+H]^+$; HPLC Ret. Time 1.679 min. and 1.763 min. (HPLC Methods, A and B, respectively); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.58 (s, 1H), 8.06 (d, *J* = 9.5 Hz, 1H), 7.84 (s, 1H), 7.56 – 7.42 (m, 2H), 7.18 – 6.89 (m, 3H), 6.07 (t, *J* = 3.0 Hz, 1H), 5.93 (t, *J* = 3.0 Hz, 1H), 4.61 (dd, *J* = 14.8, 3.0 Hz, 2H).

[0445] Compounds shown in **Table 6** have been prepared in a manner similar to Example **105′** by heating the corresponding cyano compounds with TFA and sulfuric acid.

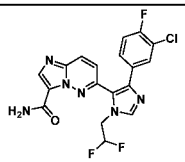
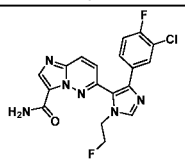
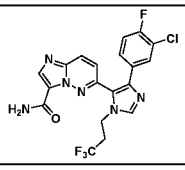
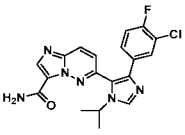
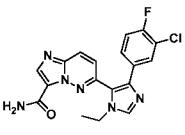
Table 6

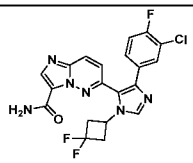
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
106′		6-(1-(3,3-difluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	412.9	1.019 1.280	A B
107′		6-(4-(4-fluorophenyl)-1-(3,3,3-trifluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	419.0	1.087 1.298	A B
108′		6-(1-(3,3-difluorocyclopentyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	427.0	1.036 1.335	A B
109′		6-(1-cyclopropyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	363.0	0.954 1.270	A B

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
110′		6-(1-(4,4-difluorocyclohexyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	441.1	1.087 1.487	A B
111′		6-(1-(2-fluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	369.0	1.047 1.118	A B
112′		6-(1-ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	351.1	0.85 1.191	A B

[0446] Compounds shown in **Table 7** have been prepared in a manner similar to Example **105′** by heating the corresponding cyano compounds with TFA and sulfuric acid.

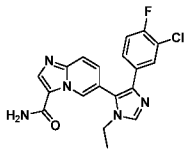
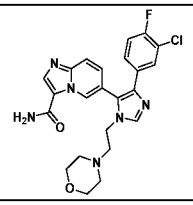
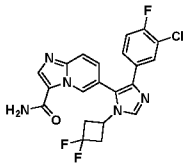
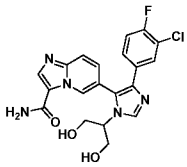
Table 7

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
113′		6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	421.0	1.207 1.346	A B
114′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-fluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	403.1	1.092 1.308	A B
115′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3,3-trifluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	452.9	1.308 1.612	A B
116′		6-(4-(3-chloro-4-fluorophenyl)-1-isopropyl-1H-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	399.1	1.156 1.484	A B
117′		6-(4-(3-chloro-4-fluorophenyl)-1-ethyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	385.0	1.098 1.271	A B

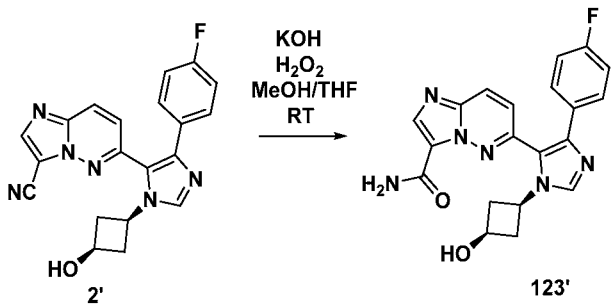
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
118′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	447.0	1.296 1.531	A B

[0447] Compounds shown in **Table 8** have been prepared in a manner similar to Example **105′** by heating the corresponding cyano compounds with TFA and sulfuric acid.

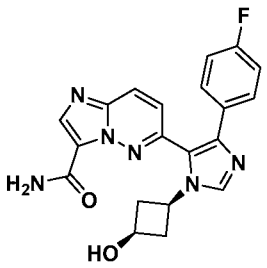
Table 8

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
119′		6-(4-(3-chloro-4-fluorophenyl)-1-ethyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	384.0	1.091 1.396	A B
120′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-morpholinoethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	469.0	1.111 1.359	A B
121′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	446.1	1.139 1.570	A B
122′		6-(4-(3-chloro-4-fluorophenyl)-1-(1,3-dihydroxypropan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	430.1	0.996 1.236	A B

Scheme 7



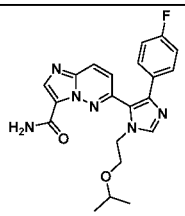
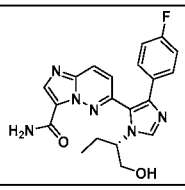
Example 123′: 6-(4-(4-fluorophenyl)-1-*cis*-3-hydroxycyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide

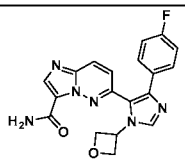
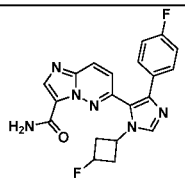
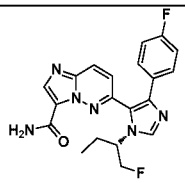
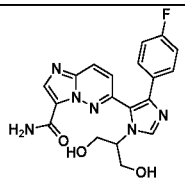
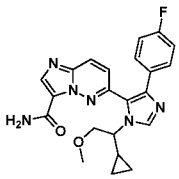
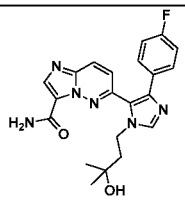
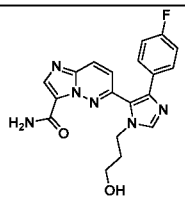
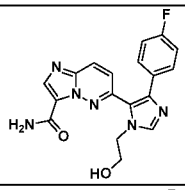
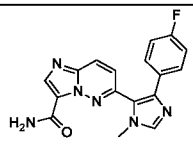


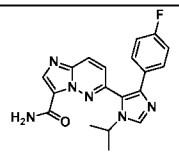
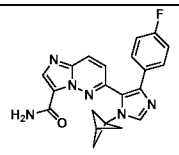
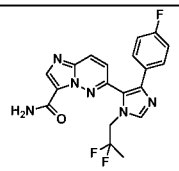
[0448] To a solution of Example **2′** (50 mg, 0.134 mmol) in MeOH (1 mL) and THF (1 mL) were added two drops of 4 M KOH solution and a 30 % aq. solution of H_2O_2 (0.041 mL, 1.336 mmol) dropwise. The reaction mixture was stirred at RT for 1 h, neutralized with 1N HCl solution and diluted with DCM. The layers was separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated. The crude product was dissolved in a mixture of DMF and methanol and purified via preparative HPLC. Fractions containing the desired product were combined and evaporated to afford Example **123′** (12.5 mg, 24 % yield). MS (ES): *m/z* = 393.1 $[M+H]^+$; HPLC Ret. Time 0.954 min. and 1.096 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.35 (s, 1H), 8.30 (d, *J* = 9.5 Hz, 1H), 8.02 (s, 1H), 7.85 (s, 2H), 7.49 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.25 (d, *J* = 9.5 Hz, 1H), 7.13 (t, *J* = 8.8 Hz, 2H), 4.30 - 4.19 (m, 2H), 1.72 - 1.52 (m, 2H), 0.96 (s, 6H).

[0449] Compounds shown in **Table 9** have been prepared in a manner similar to Example **123′** using potassium hydroxide, hydrogen peroxide, and the corresponding cyano compounds.

Table 9

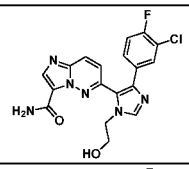
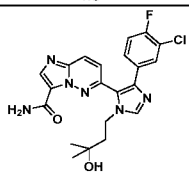
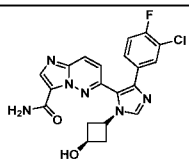
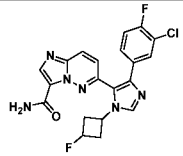
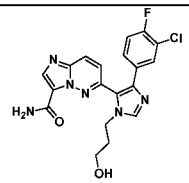
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
124′		6-(4-(4-fluorophenyl)-1-(2-*iso*propoxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	409.1	1.048 1.415	A B
125′		(*S*)-6-(4-(4-fluorophenyl)-1-(1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide	395.1	0.896 1.055	A B

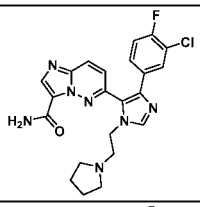
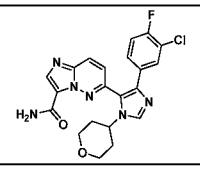
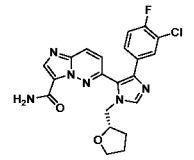
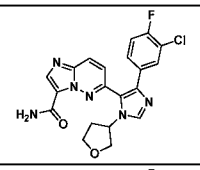
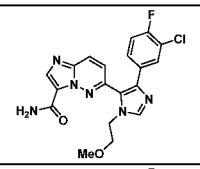
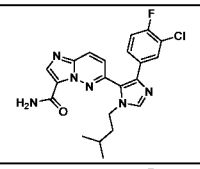
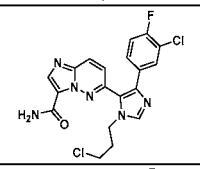
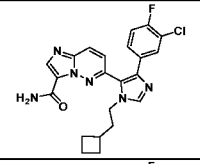
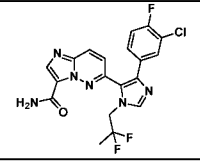
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
126′		6-(4-(4-fluorophenyl)-1-(oxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	379.1	0.884 1.071	A B
127′		6-(1-(3-fluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	395.1	1.038 1.218	A B
128′		(*S*)-6-(1-(1-fluorobutan-2-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	397.1	1.094 1.29	A B
129′		6-(1-(1,3-dihydroxypropan-2-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	397.1	0.824 1.076	A B
130′		6-(1-(1-cyclopropyl-2-methoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	421.1	1.0 1.416	A B
131′		6-(4-(4-fluorophenyl)-1-(3-hydroxy-3-methylbutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	409.1	0.906 1.215	A B
132′		6-(4-(4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	363.1	1.054 1.274	A B
133′		6-(4-(4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	349.1	1.135 1.212	A B
134′		6-(4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	337.0	0.903 1.075	A B

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
135′		6-(4-(4-fluorophenyl)-1-isopropyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	365.1	0.966 1.227	A B
136′		6-(1-(bicyclo[1.1.1]pentan-1-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	389.1	1.015 1.29	A B
137′		6-(1-(2,2-difluoropropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	401.0	1.082 1.275	A B

[0450] Compounds shown in **Table 10** have been prepared in a manner similar to Example **123′** using potassium hydroxide, hydrogen peroxide, and the corresponding cyano compounds.

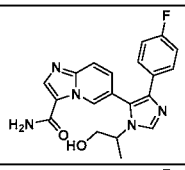
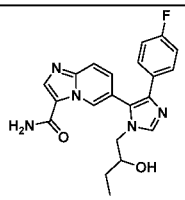
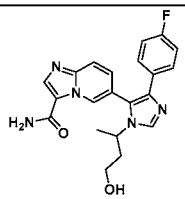
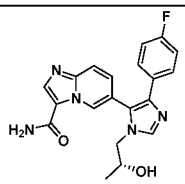
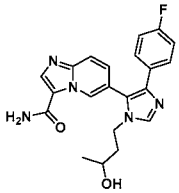
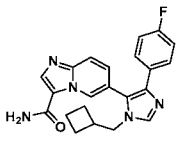
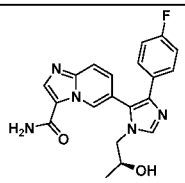
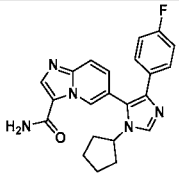
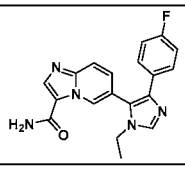
Table 10

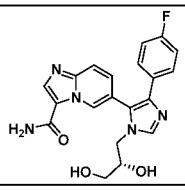
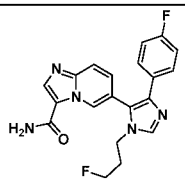
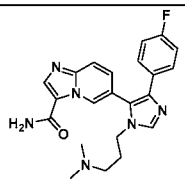
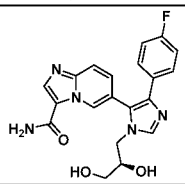
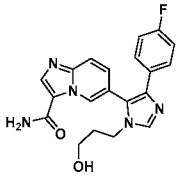
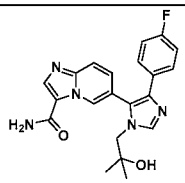
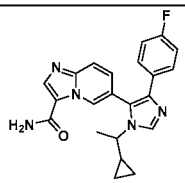
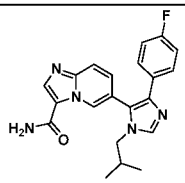
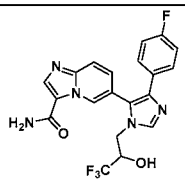
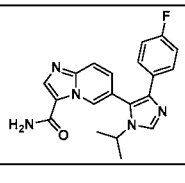
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
138′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	401.05	0.7 0.91	A B
139′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-hydroxy-3-methylbutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	443.4	1.000 1.310	A B
140′		6-(4-(3-chloro-4-fluorophenyl)-1-((*1s,3s*)-3-hydroxycyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	427.1	1.013 1.252	A B
141′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-fluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	429.0	1.088 1.358	A B
142′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	397.1	1.166 1.53	A B

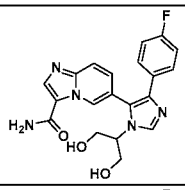
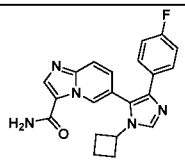
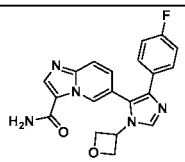
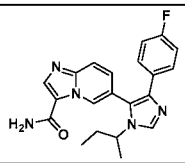
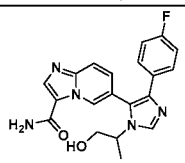
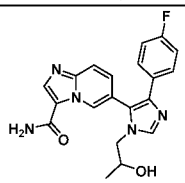
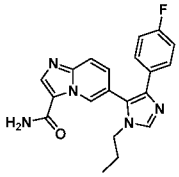
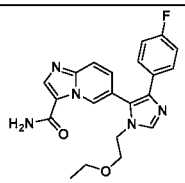
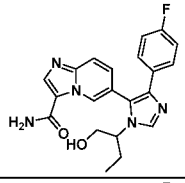
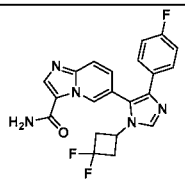
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
143′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	454.1	0.84 1.01	A B
144′		6-(4-(3-chloro-4-fluorophenyl)-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	441.2	0.85 1.18	A B
145′		(*S*)-6-(4-(3-chloro-4-fluorophenyl)-1-((tetrahydrofuran-2-yl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	441.1	0.89 1.22	A B
146′		6-(4-(3-chloro-4-fluorophenyl)-1-(tetrahydrofuran-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	427.1	0.83 1.14	A B
147′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-methoxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	415.1	0.86 1.16	A B
148′		6-(4-(3-chloro-4-fluorophenyl)-1-isopentyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	425.2	1.04 1.46	A B
149′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-chloropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	433.1	0.94 1.29	A B
150′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-cyclobutylethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	439.2	1.09 1.5	A B
151′		6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	435.1	1.368 1.526	A B

[0451] Compounds shown in **Table 11** have been prepared in a manner similar to Example **123′** using potassium hydroxide, hydrogen peroxide, and the corresponding cyano compounds.

Table 11

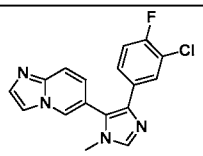
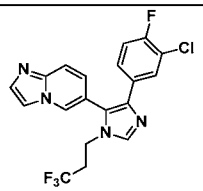
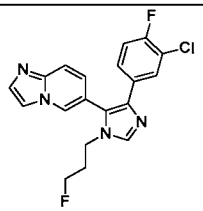
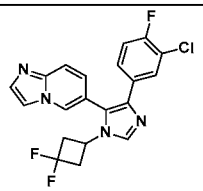
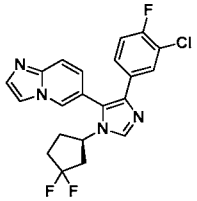
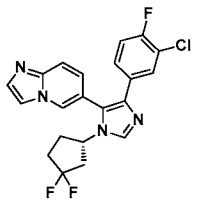
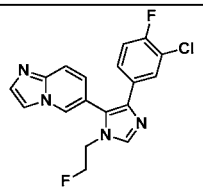
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
152′		6-(4-(4-fluorophenyl)-1-(1-hydroxypropan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	380.1	0.812 1.062	A B
153′		6-(4-(4-fluorophenyl)-1-(2-hydroxybutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	394.1	0.844 1.108	A B
154′		6-(4-(4-fluorophenyl)-1-(4-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	394.1	0.827 1.086	A B
155′		(*R*)-6-(4-(4-fluorophenyl)-1-(2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	380.1	0.784 1.067	A B
156′		6-(4-(4-fluorophenyl)-1-(3-hydroxybutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	394.1	0.846 1.098	A B
157′		6-(1-(cyclobutylmethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	390.0	1.065 1.284	A B
158′		(*S*)-6-(4-(4-fluorophenyl)-1-(2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	380.1	0.819 1.046	A B
159′		6-(1-cyclopentyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	390.1	0.928 1.352	A B
160′		6-(1-ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	350.1	0.831 1.144	A B

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
161′		(*S*)-6-(1-(2,3-dihydroxypropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	396.1	0.686 0.996	A B
162′		6-(4-(4-fluorophenyl)-1-(3-fluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	382.1	0.844 1.168	A B
163′		6-(1-(3-(dimethylamino)propyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	407.1	0.676 1.006	A B
164′		(*R*)-6-(1-(2,3-dihydroxypropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	396.1	0.782 0.982	A B
165′		6-(4-(4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	380.1	0.907 1.048	A B
166′		6-(4-(4-fluorophenyl)-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	394.1	0.84 1.074	A B
167′		6-(1-(1-cyclopropylethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	390.0	1.059 1.228	A B
168′		6-(4-(4-fluorophenyl)-1-*iso*butyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	378.1	0.912 1.316	A B
169′		6-(4-(4-fluorophenyl)-1-(3,3,3-trifluoro-2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	434.0	0.875 1.164	A B
170′		6-(4-(4-fluorophenyl)-1-*iso*propyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	364.1	0.859 1.214	A B

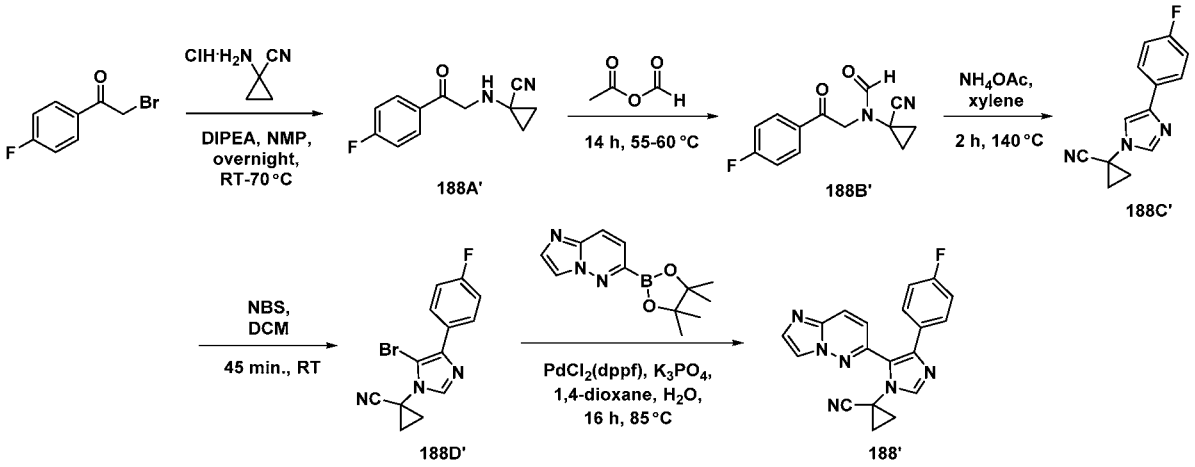
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
171′		6-(1-(1,3-dihydroxypropan-2-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	396.1	0.787 0.978	A B
172′		6-(1-cyclobutyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	376.1	0.878 1.278	A B
173′		6-(4-(4-fluorophenyl)-1-(oxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	378.1	0.82 1.079	A B
174′		6-(1-(sec-butyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	378.1	0.91 1.288	A B
175′		6-(4-(4-fluorophenyl)-1-(1-hydroxypropan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	380.1	0.816 1.063	A B
176′		6-(4-(4-fluorophenyl)-1-(2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	360.1	0.598 1.056	A B
177′		6-(4-(4-fluorophenyl)-1-propyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	364.1	0.874 1.231	A B
178′		6-(1-(2-ethoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	394.1	0.899 1.21	A B
179′		6-(4-(4-fluorophenyl)-1-(1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	394.1	0.855 1.126	A B
180′		6-(1-(3,3-difluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	412	1.047 1.199	A B

[0452] Compounds shown in **Table 12** have been prepared in a manner similar to Example **1′**, if the amine is a free base, or in a manner similar to Example **2′**, if the amine is an HCl salt, using imidazo[1,2-*a*]pyridine-6-carbaldehyde and intermediate **32C′**.

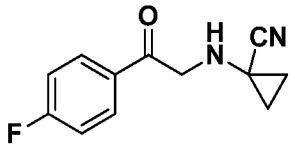
Table 12

Ex.	Structure	Name	$[M+H]^+$	Ret. Time (min.)	HPLC Method
181′		6-(4-(3-chloro-4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine	327.1	1.494 0.911	A B
182′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3,3-trifluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine	409.2	1.636 1.058	A B
183′		6-(4-(3-chloro-4-fluorophenyl)-1-(3-fluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine	373.2	1.603 0.955	A B
184′		6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine	403.2	1.634 1.039	A B
185′		(*R*)-6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclopentyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine	417.3	1.782 0.960	A B
186′		(*S*)-6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclopentyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine	417.0	1.784 1.066	A B
187′		6-(4-(3-chloro-4-fluorophenyl)-1-(2-fluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine	359.2	0.952 1.548	A B

Scheme 8

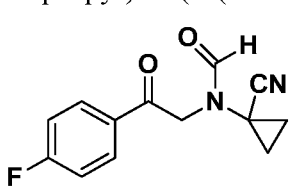


Intermediate 188A': 1-((2-(4-fluorophenyl)-2-oxoethyl)amino)cyclopropanecarbonitrile



[0453] To a solution of 2-bromo-1-(4-fluorophenyl)ethanone (3.0 g, 13.82 mmol) and DIPEA (7.24 mL, 41.5 mmol) in NMP (55.3 mL) was added 1-aminocyclopropanecarbonitrile, HCl (1.859 g, 15.20 mmol) and the reaction mixture was stirred overnight at RT. Since the starting material was not completely consumed, the mixture was heated in an oil-bath at 70 °C for 1 h, cooled to RT, diluted with water and extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, filtered. The filtrate was concentrated under reduced pressure (water-bath temp. ~25 °C) and the residue was purified by silica gel chromatography (40 g RediSep® column, eluting with 30 % EtOAc in hexanes). Fractions containing the product were combined and evaporated to afford intermediate **188A'** (1.66 g, 54.97 % yield) as an oil. MS (ES): *m/z* = 219.15 $[M+H]^+$; HPLC Ret. Time min. 2.903 (HPLC Method E).

Intermediate 188B': *N*-(1-cyanocyclopropyl)-*N*-(2-(4-fluorophenyl)-2-oxoethyl)formamide

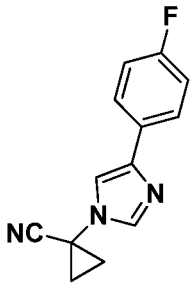


[0454] Acetic formic anhydride (reference: *Journal of Organic Chemistry*, **2007**, *72(16)*, 6135-6142): Acetic anhydride (37.0 mL) and formic acid (18.07 mL) were heated in an oil-

bath (bath temperature 55 °C) for 2 h to form acetic formic anhydride that was used in the reaction without any purification or analysis.

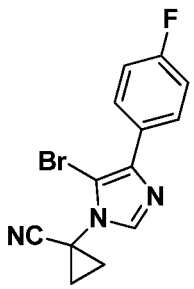
[0455] The above acetic formic anhydride was added to intermediate **188A'** (1.66 g, 7.61 mmol) and the resultant reaction mixture was continued heating at 55-60 °C for 14 h. The mixture was then cooled in an ice-bath, very carefully basified with satd. aq. $NaHCO_3$ solution to pH ~8 and extracted with EtOAc (3 x 50 mL). The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to afford intermediate **188B'** (1.787 g, 95 % yield, crude) as a semi-solid. MS (ES): *m/z* = 269.1 $[M+Na]^+$; HPLC Ret. Time min. 2.575 (HPLC Method E), which was used directly in the next step without purification.

Intermediate 188C': 1-(4-(4-fluorophenyl)-1*H*-imidazol-1-yl)cyclopropanecarbonitrile



[0456] A solution of intermediate **188B'** (1.787 g, 7.26 mmol) and NH_4OAc (5.65 g, 72.6 mmol) in xylene (72.6 mL) was heated in a sealed tube in an oil-bath at 140 °C for 2 h. The solvent was concentrated to 1/2 the volume and the concentrated reaction mixture was purified by silica gel chromatography (40 g RediSep® column, eluting with 40 % EtOAc in DCM). Fractions containing the desired product were combined and evaporated to afford intermediate **188C'** (0.97 g, 58.8 % yield) as a brown solid. MS (ES): *m/z* = 228.12 $[M+H]^+$; HPLC Ret. Time 2.503 min. (HPLC Method E).

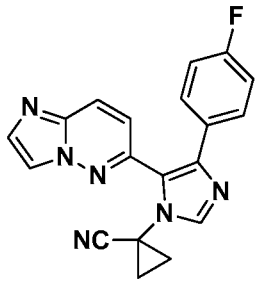
Intermediate 188D': 1-(5-bromo-4-(4-fluorophenyl)-1*H*-imidazol-1-yl)cyclopropanecarbonitrile



[0457] To a solution of intermediate **188C'** (0.125 g, 0.550 mmol) in DCM (5.50 mL) was added NBS (0.109 g, 0.605 mmol). The reaction mixture was stirred at RT for 45 min.

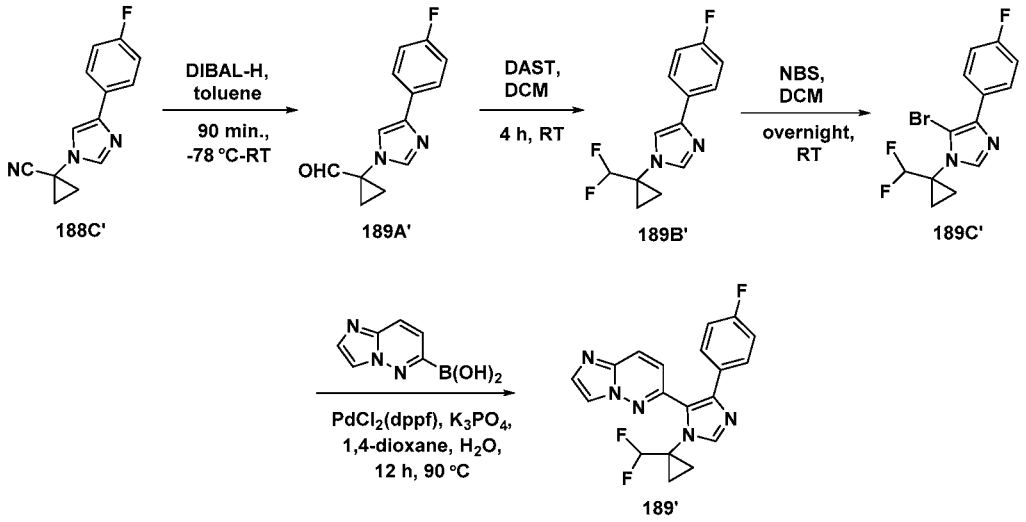
The solvent was evaporated and the residue was purified by silica gel chromatography (40 g RediSep® column, eluting with 20 % EtOAc in DCM) to afford intermediate **188D′** (0.146 g, 87 % yield) as a solid. MS (ES): *m/z* = 306/308 $[M+H]^+$; HPLC Ret. Time 3.445 min. (HPLC Method E).

Example 188′: 1-(4-(4-fluorophenyl)-5-(imidazo[1,2-*b*]pyridazin-6-yl)-1*H*-imidazol-1-yl)cyclopropanecarbonitrile

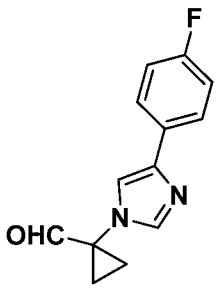


[0458] To a degassed suspension of intermediate **188D′** (0.03 g, 0.098 mmol) and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-ylimidazo[1,2-*b*]pyridazine (reference: US 2015/0038506 A1) (0.048 g, 0.196 mmol) in 2M aq. solution of K_3PO_4 (0.147 mL, 0.294 mmol) and 1,4-dioxane (1.0 mL) was added $PdCl_2$(dppf) (7.17 mg, 9.80 µmol). The mixture was degassed again for 2 min. and then heated in an oil-bath at 85 °C for 16 h. The reaction mixture was concentrated to dryness under reduced pressure and the residue was extracted with DCM (3 x 5 mL). The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the crude residue was purified via preparative HPLC. Fractions containing the desired product were combined and evaporated to afford Example **188′** (0.026 g, 64.4 % yield). MS (ES): *m/z* = 345.0 $[M+H]^+$; HPLC Ret. Time 1.01 min. and 1.374 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.40 (br. s., 1H), 8.29 (s, 1H), 8.20 (d, *J* = 7.3 Hz, 1H), 7.95 (br. s., 1H), 7.51 (dd, *J* = 8.6, 5.7 Hz, 2H), 7.18 (t, *J* = 9.0 Hz, 2H), 7.10 (d, *J* = 7.7 Hz, 1H), 1.85 - 1.70 (m, 4H).

Scheme 9

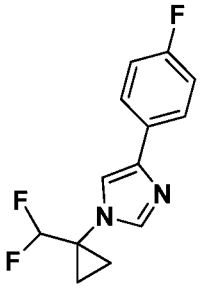


Intermediate 189A': 1-(4-(4-fluorophenyl)-1*H*-imidazol-1-yl)cyclopropanecarbaldehyde, 2 TFA



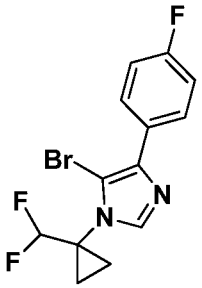
[0459] To a -78 °C solution of intermediate **188C'** (0.65 g, 2.86 mmol) in toluene (22.88 mL) was added dropwise, DIBAL-H (5.72 mL, 5.72 mmol, 1M solution in THF). The reaction mixture was stirred at that temperature for 30 min. and then at RT for 1 h. The reaction was quenched with MeOH and satd. aq.Na_2SO_4. The resultant mixture was stirred for 30 min. and the inorganics were filtered off. The filter-cake was washed with EtOAc. The combined filtrates were transferred to a separatory funnel and the two layers were separated. The aq. layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified via preparative HPLC. Fractions containing the desired product were combined and evaporated to afford intermediate **189A'** (0.368 g, 28.1 % yield) as the bis-TFA salt. MS (ES): *m/z* = 231.0 $[M+H]^+$; HPLC Ret. Time 3.053 min. (HPLC Method D).

Intermediate 189B′: 1-(1-(difluoromethyl)cyclopropyl)-4-(4-fluorophenyl)-1*H*-imidazole



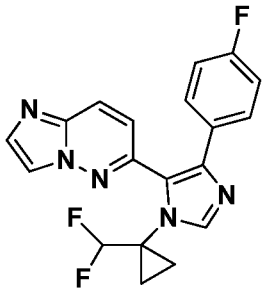
[0460] To a solution of intermediate **189A′** (0.343 g, 0.748 mmol) in DCM (7.5 mL) was added DAST (0.3 mL, 2.245 mmol) and the reaction mixture was stirred at RT for 4 h. The mixture was quenched with some ice-water. The two layers were separated and the aq. layer was extracted with DCM. The combined organic layers were washed with satd. aq. $NaHCO_3$ solution (2 x 10 mL) and brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (24 g RediSep® column, eluting with a gradient of 30-50 % EtOAc in DCM). Fractions containing the product were combined and evaporated to afford intermediate **189B′** (0.15 g, 79 % yield) as a colorless oil. MS (ES): *m/z* = 253.09 $[M+H]^+$; HPLC Ret. Time 2.548 min. (HPLC Method E).

Intermediate 189C′: 5-bromo-1-(1-(difluoromethyl)cyclopropyl)-4-(4-fluorophenyl)-1*H*-imidazole



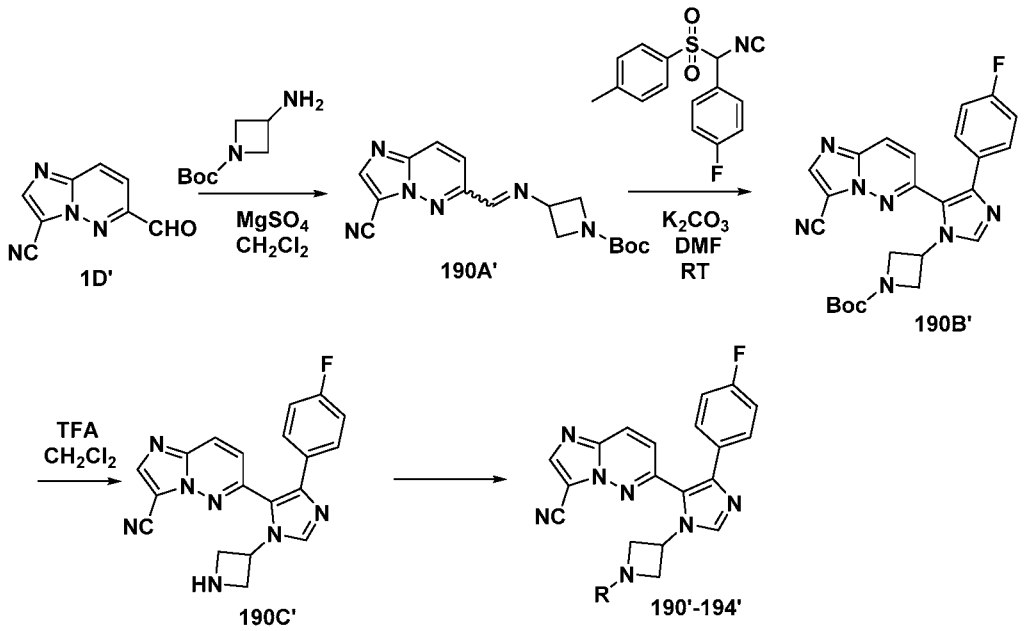
[0461] To a solution of intermediate **189B′** (0.15 g, 0.595 mmol) in DCM (5.95 mL) was added NBS (0.118 g, 0.654 mmol) and the reaction mixture was stirred overnight at RT. The reaction mixture was directly purified by silica gel chromatography (40 g RediSep® column, eluting with 25 % EtOAc in DCM). Fractions containing the product were combined and evaporated to afford intermediate **189C′** (0.158 g, 80 % yield) as a colorless oil. MS (ES): *m/z* = 331/333 $[M+H]^+$; HPLC Ret. Time 0.97 min. (HPLC Method C).

Example 189′: 6-(1-(1-(difluoromethyl)cyclopropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine

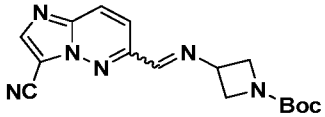


[0462] Example **189′** was synthesized analogous to Example **188′** via a Suzuki coupling between intermediate **189C′** and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-ylimidazo[1,2-*b*]pyridazine. The residue was purified via preparative HPLC. Fractions containing the desired product were combined and evaporated to afford Example **189′** (0.007 g, 16.91 % yield). MS (ES): *m/z* = 370.2 $[M+H]^+$; HPLC Ret. Time 1.116 min. and 1.551 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.41 (s, 1H), 8.15 (d, *J* = 9.5 Hz, 1H), 8.09 (s, 1H), 7.88 (d, *J* = 0.7 Hz, 1H), 7.45 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.15 (t, *J* = 8.8 Hz, 2H), 7.07 (d, *J* = 9.5 Hz, 1H), 6.28 (s, 1H), 1.39 (br. s., 2H), 1.30 - 1.21 (m, 2H).

Scheme 10

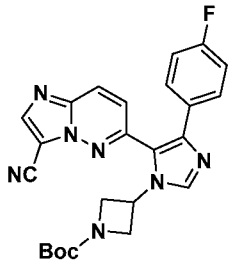


Intermediate 190A′: *tert*-butyl 3-(((3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)methylene)amino)azetidine-1-carboxylate



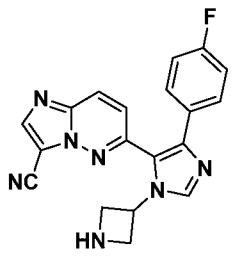
[0463] To a solution of intermediate **1D′** (0.81 g, 4.71 mmol) in DCM (30 mL) were added magnesium sulfate (5.66 g, 47.1 mmol) and *tert*-butyl 3-aminoazetidine-1-carboxylate (0.851 g, 4.94 mmol). The suspension was stirred at RT overnight, filtered and washed with DCM. The combined filtrates were concentrated and the crude product was used directly in the next step without purification. MS (ES): *m/z* = 325.2 $[M-H]^+$; HPLC Ret. Time 1.573 min. (HPLC Method D).

Intermediate 190B′: *tert*-butyl 3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-4-(4-fluorophenyl)-1*H*-imidazol-1-yl)azetidine-1-carboxylate



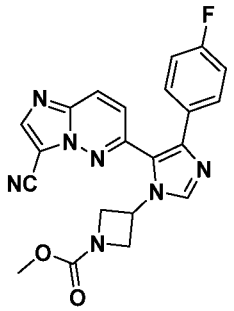
[0464] To a solution of intermediate **190A′** (1.52 g, 4.7 mmol) in DMF (10 mL) were added potassium carbonate (0.780 g, 5.65 mmol) and 1-fluoro-4-(isocyano(tosyl)methyl)benzene (1.361 g, 4.71 mmol). The reaction mixture was stirred at RT overnight, and diluted with EtOAc and water. The layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated and the crude product was purified by silica gel chromatography (80 g RediSep® column, eluting with a gradient from 10-100 % B in DCM, B: 10 % MeOH in DCM). Fractions containing the product were combined and evaporated to afford intermediate **190B′** (1.1 g, 51 % yield). MS (ES): *m/z* = 460.1 $[M+H]^+$; HPLC Ret. Time 0.78 min. (HPLC Method C); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.30 (s, 1H), 8.11 (s, 1H), 7.92 (d, *J* = 9.5 Hz, 1H), 7.53 - 7.43 (m, 2H), 7.20 - 7.03 (m, 3H), 5.40 (ddd, *J* = 7.8, 5.1, 2.6 Hz, 1H), 4.56 (t, *J* = 8.7 Hz, 2H), 4.25 (dd, *J* = 9.8, 5.0 Hz, 2H), 1.50 (s, 9H).

Intermediate 190C′: 6-(1-(azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile



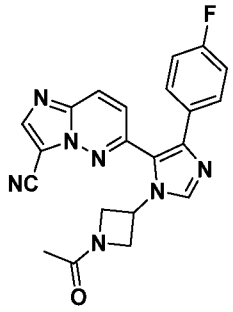
[0465] To a solution of intermediate **190B′** (500 mg, 1.008 mmol) in DCM was added TFA (2 mL). The reaction mixture was stirred at RT overnight and concentrated. The residue was diluted with DCM and sat'd aq. $NaHCO_3$ solution. The layers were separated and the aqueous layer was extracted with DCM twice. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated and the crude product was used in the next step. A small amount of the crude material was purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **190C′**. MS (ES): *m/z* = 360.1 $[M+H]^+$; HPLC Ret. Time 1.076 min. and 1.092 min. (HPLC Methods A and B, respectively).

Example 190′: methyl 3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-4-(4-fluorophenyl)-1*H*-imidazol-1-yl)azetidine-1-carboxylate



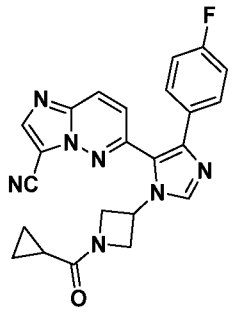
[0466] To a solution of Example **190C′** (45 mg, 0.114 mmol) and Hunig's base (0.060 mL, 0.341 mmol) in THF (4 mL) was added methyl carbonochloridate (12.89 mg, 0.136 mmol). The reaction mixture was stirred at RT overnight and concentrated. The residue was dissolved in a mixture of DMF and methanol and purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **190′** (15.8 mg, 33 % yield). MS (ES): *m/z* = 418.1 $[M+H]^+$; HPLC Ret. Time 1.26 min. and 1.404 min. (HPLC Methods A and B, respectively); ^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.64 (s, 1H), 8.53 (s, 1H), 8.32 (d, *J* = 9.5 Hz, 1H), 7.54 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.27 (d, *J* = 9.5 Hz, 1H), 7.16 (t, *J* = 8.8 Hz, 2H), 5.28 (t, *J* = 7.0 Hz, 1H), 4.36 (br. s., 4H), 3.59 (s, 3H).

Example 191′: 6-(1-(1-acetylazetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile



[0467] To a solution of intermediate **190C′** (45 mg, 0.064 mmol) in THF were added pyridine (31.1 μL, 0.385 mmol) and acetyl chloride (15.11 mg, 0.192 mmol). The reaction mixture was stirred at RT overnight and then concentrated. The residue was dissolved in a mixture of DMF and methanol and purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **191′** (10.5 mg, 39 % yield). MS (ES): *m/z* = 402.1 $[M+H]^+$; HPLC Ret. Time 1.066 min. and 1.244 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.65 (s, 1H), 8.52 (s, 1H), 8.32 (d, *J* = 9.2 Hz, 1H), 7.55 (dd, *J* = 8.6, 5.7 Hz, 2H), 7.27 (d, *J* = 9.5 Hz, 1H), 7.17 (t, *J* = 8.8 Hz, 2H), 5.27 (t, *J* = 5.9 Hz, 1H), 4.65 - 4.51 (m, 2H), 4.35 - 4.24 (m, 2H), 1.81 (s, 3H).

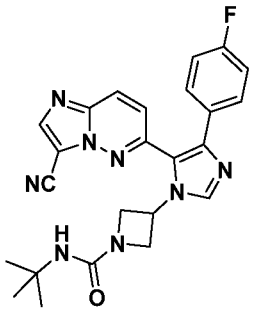
Example 192′: 6-(1-(1-(cyclopropanecarbonyl)azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile



[0468] To a solution of intermediate **190C′** (45 mg, 0.125 mmol) in THF (5 mL) were added pyridine (0.051 mL, 0.626 mmol) and cyclopropanecarbonyl chloride (13.09 mg, 0.125 mmol). The reaction mixture was stirred at RT overnight and then concentrated. The residue was dissolved in a mixture of DMF and methanol and purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **192′** (10.5 mg, 39 % yield). MS (ES): *m/z* = 428.1 $[M+H]^+$; HPLC Ret. Time 1.186 min. and 1.402 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6)

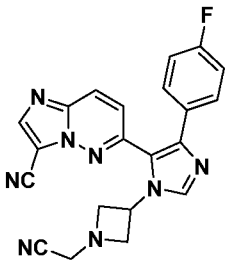
δ ppm 8.65 (s, 1H), 8.54 (s, 1H), 8.33 (d, *J* = 9.5 Hz, 1H), 7.55 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.29 (d, *J* = 9.5 Hz, 1H), 7.17 (t, *J* = 8.8 Hz, 2H), 5.34 (t, *J* = 7.5 Hz, 1H), 4.81 - 4.70 (m, 1H), 4.66 (br. s., 1H), 4.32 (br. s., 2H), 1.63 - 1.47 (m, 1H), 0.81 - 0.64 (m, 4H).

Example 193′: *N*-(*tert*-butyl)-3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-4-(4-fluorophenyl)-1*H*-imidazol-1-yl)azetidine-1-carboxamide



[0469] To a solution of intermediate **190C′** (40 mg, 0.101 mmol) in DMF (1 mL) were added Hunig's base (0.053 mL, 0.303 mmol) and 2-isocyanato-2-methylpropane (15.03 mg, 0.152 mmol). The reaction mixture was stirred at RT for 2 h. The residue was dissolved a mixture of DMF and methanol and purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **193′** (21.4 mg, 46 % yield). MS (ES): *m/z* = 459.1 $[M+H]^+$; HPLC Ret. Time 1.4 min. and 1.576 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.65 (s, 1H), 8.41 (s, 1H), 8.33 (d, *J* = 9.5 Hz, 1H), 7.55 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.28 (d, *J* = 9.5 Hz, 1H), 7.17 (t, *J* = 9.0 Hz, 2H), 5.19 (t, *J* = 5.5 Hz, 1H), 4.23 (t, *J* = 8.4 Hz, 2H), 4.10 (dd, *J* = 8.8, 5.5 Hz, 2H), 1.24 (s, 9H).

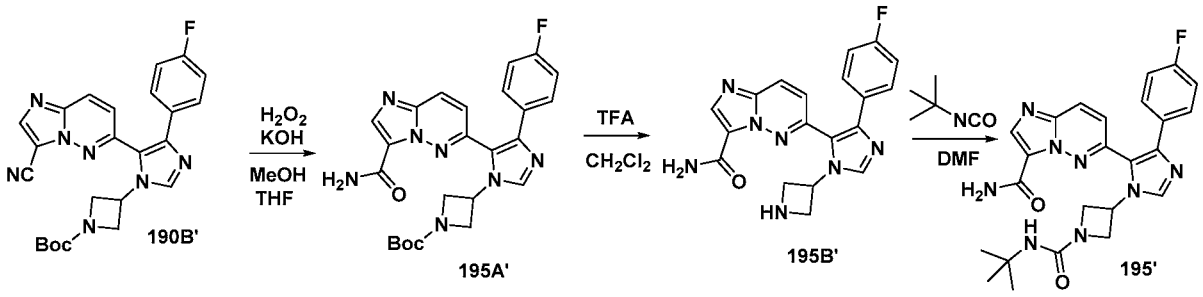
Example 194′: 6-(1-(1-(cyanomethyl)azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile



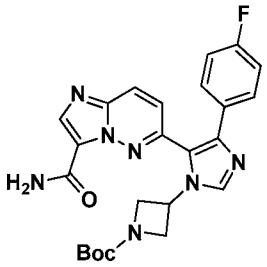
[0470] To a solution of intermediate **190C′** (45 mg, 0.125 mmol) in DMF were added 2-bromoacetonitrile (45.1 mg, 0.376 mmol) and potassium carbonate (34.6 mg, 0.250 mmol). The reaction mixture was stirred at RT overnight, filtered and washed with MeOH. The filtrate was concentrated and the residue was dissolved in a mixture of DMF and methanol, and purified via preparative HPLC. Fractions containing the desired product were combined

and dried under vacuum to afford Example **194'** (25.6 mg, 51 % yield). MS (ES): *m/z* = 399.1 $[M+H]^+$; HPLC Ret. Time 1.12 min. and 1.384 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.64 (s, 1H), 8.38 (s, 1H), 8.31 (d, *J* = 9.5 Hz, 1H), 7.54 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.27 (d, *J* = 9.2 Hz, 1H), 7.17 (t, *J* = 8.8 Hz, 2H), 5.03 (t, *J* = 6.6 Hz, 1H), 3.88 - 3.71 (m, 2H), 3.77 (s, 2H), 3.71 - 3.52 (m, 2H).

Scheme 11

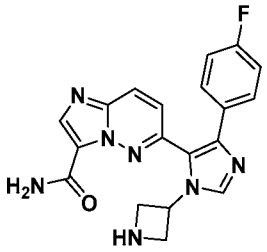


Intermediate 195A': *tert*-butyl 3-(5-(3-carbamoylimidazo[1,2-*b*]pyridazin-6-yl)-4-(4-fluorophenyl)-1*H*-imidazol-1-yl)azetidine-1-carboxylate



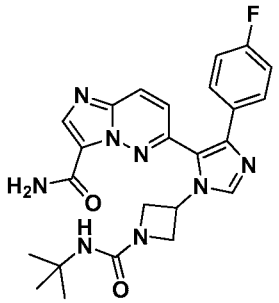
[0471] To a solution of intermediate **190B'** (300 mg, 0.653 mmol) in MeOH (10 mL) and THF (10 mL) were added 4 M solution of potassium hydroxide (0.326 mL, 1.306 mmol) and 30 % solution of H_2O_2 (0.667 mL, 6.53 mmol). The reaction mixture was stirred at RT overnight and concentrated. The residue was carefully neutralized with 1 N HCl to pH 7, diluted with DCM and sat'd aq. $NaHCO_3$. The layers were separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated and the residue was dissolved in a mixture of DMF and methanol and purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **195A'** (248 mg, 79 % yield). MS (ES): m/z = 478.1 $[M+H]^+$; HPLC Ret. Time 1.162 min. and 1.387 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.47 (s, 1H), 8.36 (s, 1H), 8.30 (d, *J* = 9.2 Hz, 1H), 7.83 (br. s., 2H), 7.50 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.22 (d, *J* = 9.2 Hz, 1H), 5.27 (t, *J* = 7.0 Hz, 1H), 4.22 (d, *J* = 8.1 Hz, 4H), 1.38 (s, 9H).

Intermediate 195B′: 6-(1-(azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide



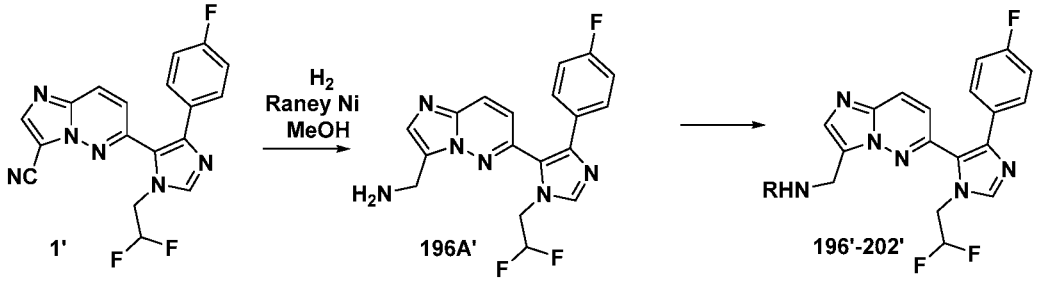
[0472] To a solution of intermediate **195A′** (248 mg, 0.52 mmol) in DCM (12 mL) was added TFA (1 mL). The reaction mixture was stirred at RT overnight and concentrated. The crude material was dissolved in a mixture of DMF and methanol and purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **195B′** (248 mg, 79 % yield). MS (ES): *m/z* = 378.1 $[M+H]^+$; HPLC Ret. Time 0.825 min. and 0.962 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.36 (s, 1H), 8.38 (s, 1H), 8.30 (d, *J* = 9.2 Hz, 1H), 7.88 (br. s., 2H, NH_2), 7.81 (br. s., 1H, NH), 7.54 - 7.45 (m, 2H), 7.21 (d, *J* = 9.5 Hz, 1H), 7.18 - 7.08 (m, 2H), 5.24 - 5.12 (m, 1H), 3.87 - 3.76 (m, 2H), 3.76 - 3.60 (m, 2H).

Example 195′: 6-(1-(1-(tert-butylcarbamoyl)azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide

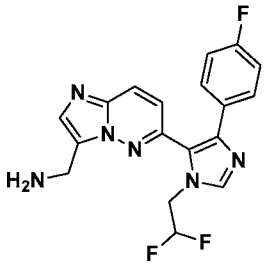


[0473] To a solution of Example **195B′** (30 mg, 0.042 mmol) in DMF (1 mL) were added TEA (5.81 µL, 0.042 mmol) and 2-isocyanato-2-methylpropane (4.13 mg, 0.042 mmol). The reaction mixture was stirred at RT for 2 h and purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **195′** (15.7 mg, 79 % yield). MS (ES): *m/z* = 477.1 $[M+H]^+$; HPLC Ret. Time 1.058 min. and 1.252 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.36 (d, *J* = 2.2 Hz, 2H), 8.30 (d, *J* = 9.2 Hz, 1H), 7.83 (s, 2H), 7.51 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.23 (d, *J* = 9.5 Hz, 1H), 7.15 (t, *J* = 8.8 Hz, 2H), 5.24 (s, 1H), 4.22 - 4.07 (m, 2H), 4.02 (dd, *J* = 8.8, 5.5 Hz, 2H), 1.28 - 1.13 (m, 9H).

Scheme 12

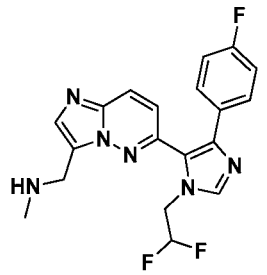


Intermediate 196A': (6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methanamine



[0474] To a suspension of Example **1'** (110 mg, 0.299 mmol) in MeOH (60 mL) (2 M NH_3 MeOH solution) was added Raney Nickel under nitrogen. The reaction mixture was exposed to 50 psi hydrogen at RT overnight. The reaction mixture was passed through a pad of Celite® and washed with MeOH. The filtrate was concentrated and the crude material was dissolved in MeOH and purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford intermediate **196A'**. MS (ES): m/z = 373.1 $[M+H]^+$; HPLC Ret. Time 0.926 min. and 1.103 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.13 - 7.97 (m, 2H), 7.75 (br. s., 1H), 7.50 (dd, J = 8.4, 5.5 Hz, 2H), 7.18 (t, J = 8.8 Hz, 2H), 6.93 (d, J = 8.4 Hz, 1H), 6.41 (t, J = 14.7 Hz, 1H), 4.77 (t, J = 14.7 Hz, 2H), 4.11 (br. s., 2H).

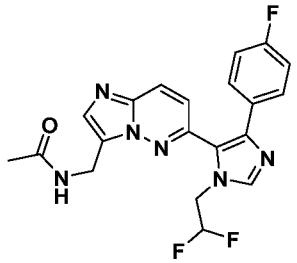
Example 196': (6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methanamine



[0475] A solution of intermediate **196A'** (35 mg, 0.072 mmol) in ethyl formate (267 mg, 3.60 mmol) was heated at 70 °C for 6 h, cooled to RT and concentrated. The residue was

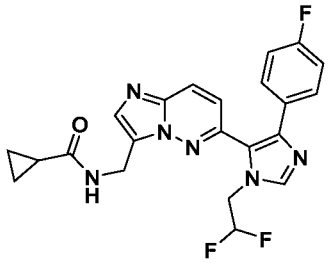
dissolved in THF (5 mL). BH_3-dimethyl sulfide (0.014 mL, 0.144 mmol) was added and the reaction mixture was heated at 70 °C for 2 h. The reaction mixture was cooled to RT and carefully quenched with MeOH. The reaction mixture was stirred at RT for 1 h and then concentrated. The crude material was dissolved in a mixture of DMF and methanol and purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **196′** (10.4 mg, 37 % yield). MS (ES): *m/z* = 387.2 $[M+H]^+$; HPLC Ret. Time 0.952 min. and 1.063 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.09 - 7.98 (m, 2H), 7.86 - 7.72 (m, 1H), 7.49 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.17 (t, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 9.5 Hz, 1H), 6.41 (m, 1H), 4.85 - 4.67 (m, 2H), 4.07 (s, 1H), 3.1 (s, 3H).

Example 197′: *N*-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)acetamide



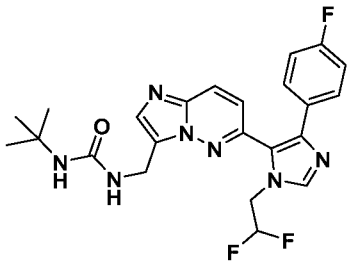
[0476] To a solution of intermediate **196A′** (30 mg, 0.081 mmol) in THF (5 mL) were added pyridine (0.014 mL, 0.177 mmol) and acetic anhydride (9.87 mg, 0.097 mmol). The reaction mixture was stirred at RT overnight, quenched with MeOH and concentrated. The residue was dissolved in a mixture of DMF and methanol and purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **197′** (19.8 mg, 59 % yield). MS (ES): *m/z* = 415.1 $[M+H]^+$; HPLC Ret. Time 0.982 min. and 1.247 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.09 (d, *J* = 9.5 Hz, 1H), 8.04 (s, 1H), 7.77 (s, 1H), 7.56 - 7.45 (m, 2H), 7.18 (t, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 9.5 Hz, 1H), 6.39 (m, 1H), 4.90 - 4.74 (m, 2H), 4.66 (d, *J* = 5.1 Hz, 2H), 1.86 (s, 3H).

Example 198′: *N*-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)cyclopropanecarboxamide



[0477] To a solution of **196A′** (30 mg, 0.081 mmol) in THF (5 mL) were added pyridine (0.014 mL, 0.177 mmol) and cyclopropanecarbonyl chloride (10.11 mg, 0.097 mmol). The reaction mixture was stirred at RT for 2 h, quenched with MeOH and concentrated. The residue was dissolved in a mixture of DMF and methanol and purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **198′** (25 mg, 70 % yield). MS (ES): *m/z* = 441.1 $[M+H]^+$; HPLC Ret. Time 1.066 min. and 1.378 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.09 (d, *J* = 9.5 Hz, 1H), 8.04 (s, 1H), 7.77 (s, 1H), 7.50 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.18 (t, *J* = 8.8 Hz, 2H), 6.96 (d, *J* = 9.5 Hz, 1H), 6.35 (m, 1H), 4.88 - 4.74 (m, 2H), 4.70 (d, *J* = 5.5 Hz, 2H), 1.65 - 1.51 (m, 1H), 0.73 - 0.63 (m, 4H).

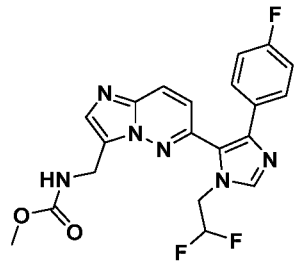
Example 199′: 1-(*tert*-butyl)-3-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)urea



[0478] To a solution of intermediate **196A′** (25 mg, 0.067 mmol) in THF (3 mL) was added 2-isocyanato-2-methylpropane (6.66 mg, 0.067 mmol). The reaction mixture was stirred at RT for 30 min, quenched with MeOH and concentrated. The residue was dissolved in a mixture of DMF and methanol and purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **199′** (14.4 mg, 45 % yield). MS (ES): *m/z* = 472.1 $[M+H]^+$; HPLC Ret. Time 1.203 min. and 1.515 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.13 - 7.96 (m, 2H), 7.70 (s, 1H), 7.50 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.18 (t, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 9.5

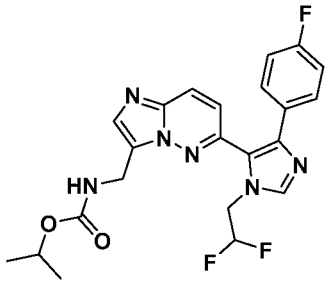
Hz, 1H), 6.39 (m, 1H), 6.18 (t, *J* = 5.9 Hz, 1H), 5.76 (s, 1H), 4.89 - 4.72 (m, 2H), 4.59 (d, *J* = 5.5 Hz, 2H), 1.21 (s, 9H).

[0479] **Example 200′**: methyl ((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)carbamate



[0480] To a solution of intermediate **196A′** (30 mg, 0.081 mmol) in THF (1 mL) were added Hunig's base (0.028 mL, 0.161 mmol) and methyl carbonochloridate (11.42 mg, 0.121 mmol). The reaction mixture was stirred at RT for 1 h and concentrated. The residue was dissolved in a mixture of DMF and methanol, purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **200′** (21.2 mg, 60 % yield). MS (ES): *m/z* = 431.1 $[M+H]^+$; HPLC Ret. Time 1.046 min. and 1.362 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.14 - 7.96 (m, 2H), 7.82 - 7.66 (m, 2H), 7.50 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.18 (t, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 9.5 Hz, 1H), 6.37 (m, 1H), 4.88 - 4.72 (m, 2H), 4.62 (d, *J* = 5.5 Hz, 2H), 2.55 (s, 3H).

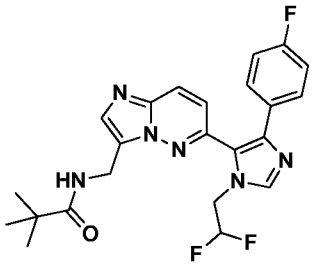
Example 201′: *iso*propyl ((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)carbamate



[0481] To a solution of intermediate **196A′** (30 mg, 0.081 mmol) in THF (1 mL) were added Hunig's base (0.028 mL, 0.161 mmol) and isopropyl carbonochloridate (0.121 mL, 0.121 mmol, 1M solution in toluene). The reaction mixture was stirred at RT overnight, quenched with MeOH and concentrated. The residue was dissolved in a mixture of DMF and methanol and purified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **201′** (25.6 mg, 69 % yield). MS (ES):

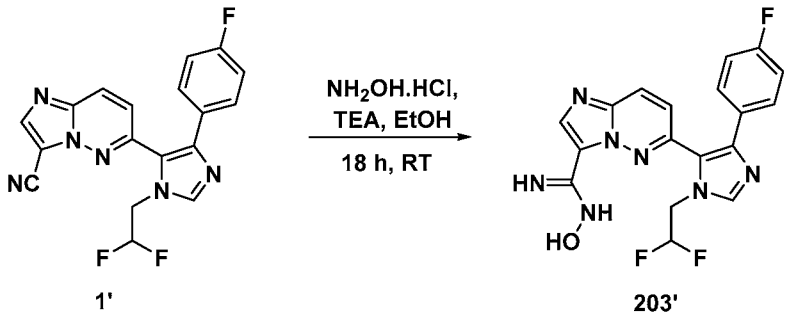
m/z = 459.1 $[M+H]^+$; HPLC Ret. Time 1.223 min. and 1.568 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.14 - 7.92 (m, 2H), 7.73 (s, 1H), 7.60 (br. s., 1H), 7.50 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.18 (t, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.5 Hz, 1H), 6.38 (m, 1H), 4.89 - 4.73 (m, 3H), 4.60 (d, *J* = 5.5 Hz, 2H), 3.39 (d, *J* = 7.0 Hz, 1H), 1.15 (d, *J* = 6.2 Hz, 6H).

Example 202′: *N*-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)pivalamide



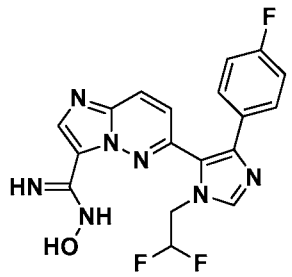
[0482] To a solution of intermediate **196A′** (30 mg, 0.081 mmol) in CH_2Cl_2 (5 mL) were added pyridine (0.013 mL, 0.161 mmol) and pivaloyl chloride (14.57 mg, 0.121 mmol). The reaction mixture was stirred at RT for 1 h, quenched with MeOH and concentrated. The residue was dissolved in a mixture of DMF and methanol andpurified via preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **202′** (22.5 mg, 61 % yield). MS (ES): *m/z* = 457.1 $[M+H]^+$; HPLC Ret. Time 1.21 min. and 1.579 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.09 (d, *J* = 9.5 Hz, 1H), 8.05 - 7.96 (m, 2H), 7.68 (s, 1H), 7.48 (dd, *J* = 8.6, 5.7 Hz, 2H), 7.18 (t, *J* = 9.0 Hz, 2H), 6.95 (d, *J* = 9.2 Hz, 1H), 4.79 (d, *J* = 3.3 Hz, 2H), 4.68 (d, *J* = 5.5 Hz, 2H), 1.11 (s, 9H).

Scheme 13



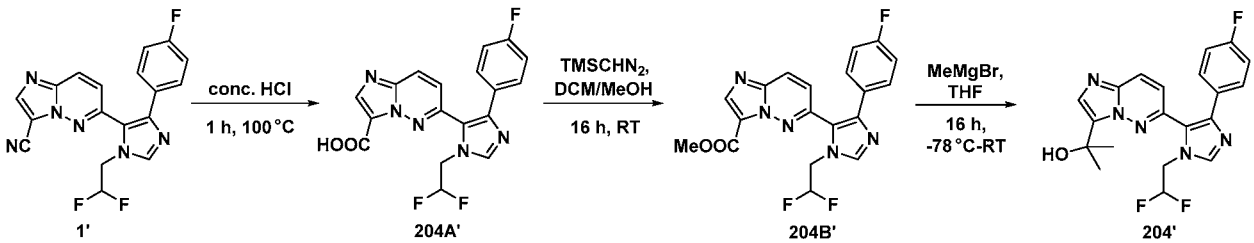
1' 203'

Example 203′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-*N*-hydroxyimidazo[1,2-*b*]pyridazine-3-carboximidamide

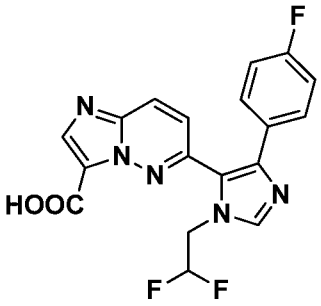


[0483] To a suspension of Example **1′** (0.045 g, 0.122 mmol) in EtOH (1.2 mL) was added TEA (0.026 mL, 0.183 mmol) and hydroxylamine hydrochloride (9.34 mg, 0.134 mmol). The reaction mixture was stirred at RT for 18 h and then purified via preparative HPLC. Fractions containing the product were combined and evaporated to afford Example **203′** (0.043 g, 83 % yield). MS (ES): *m/z* = 402.1 $[M+H]^+$; HPLC Ret. Time 0.943 min. and 1.269 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.13 (d, *J* = 9.2 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 2H), 7.51 (dd, *J* =8.8, 5.5 Hz, 2H), 7.18 (t, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 9.5 Hz, 1H), 6.46 (s, 1H), 6.02 (s, 2H), 4.76 (t, *J* = 15.2 Hz, 2H).

Scheme 14



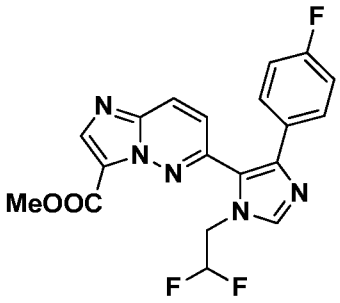
Intermediate 204A′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxylic acid, 3 TFA



[0484] A solution of Example **1′** (1.145 g, 3.11 mmol) in conc. HCl (0.77 mL, 9.33 mmol) was heated in an oil bath at 100 °C for 1 h. The reaction mixture was then cooled to RT, diluted with aq. acetonitrile and purified by reverse phase column chromatography (240 g reverse phase Commodity® column, eluting with a gradient of 0-50% acetonitrile in water

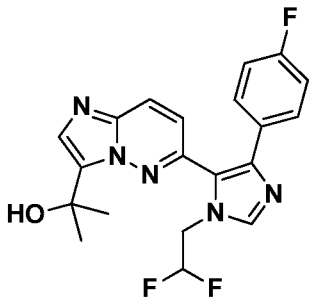
containing 0.1% TFA). Fractions containing the product were combined and evaporated to afford Example **204A′** (1.29 g, 57 % yield). MS (ES): *m/z* = 388.0 $[M+H]^+$; HPLC Ret. Time 1.032 min. (HPLC Method A).

Intermediate 204B′: methyl 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate



[0485] To a suspension of intermediate **204A′** (0.1 g, 0.258 mmol) in DCM (1.3 mL) and MeOH (1.3 mL) was added TMS-diazomethane (0.775 mL, 1.549 mmol, 2M solution in hexanes). During the addition, bubbling was observed and the reaction mixture became homogenous. The reaction mixture was stirred at RT for 16 h and then concentrated under reduced pressure. The residue was purified by silica gel chromatography (12 g RediSep® column, eluting with 96-100 % EtOAc in hexanes). Fractions containing the product were combined and evaporated to afford intermediate **204B′** (0.063 g, 61 % yield) as a pale yellow solid. MS (ES): *m/z* = 402.0 $[M+H]^+$; HPLC Ret. Time 0.72 min. (HPLC Method C).

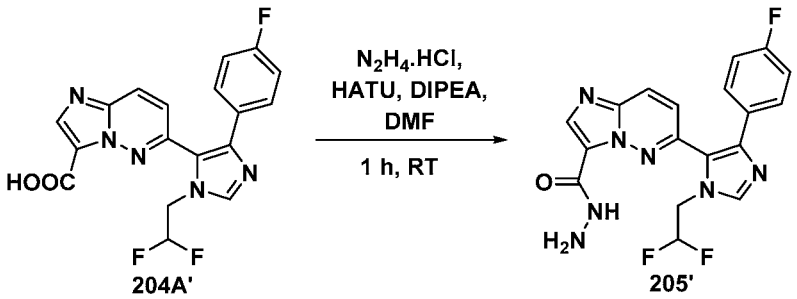
Example 204′: 2-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)propan-2-ol



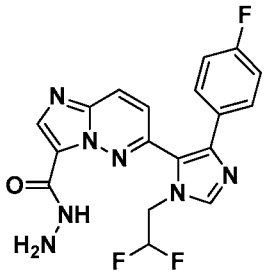
[0486] To a -78 °C solution of intermediate **204B′** (0.045 g, 0.112 mmol) in THF (1.12 mL) was added, dropwise, methylmagnesium bromide (0.187 mL, 0.561 mmol, 3M solution in Et_2O). The reaction mixture was gradually allowed to warm to RT, stirred for 18 h, and quenched with satd. aq. NH_4Cl solution. The resulting two layers were separated and the aq. layer back-extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was

concentrated under reduced pressure to give an oil, which was purified via preparative HPLC. Fractions containing the product were combined and evaporated to afford Example **204′** (0.03 g, 71.6 % yield). MS (ES): *m/z* = 402.1 $[M+H]^+$; HPLC Ret. Time 1.064 min. and 1.386 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.08 (d, *J* = 9.2 Hz, 1H), 8.03 (s, 1H), 7.71 (s, 1H), 7.53 - 7.43 (m, 2H), 7.17 (t, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 9.5 Hz, 1H), 6.38 (s, 1H), 4.85 - 4.70 (m, 2H), 1.65 (s, 6H).

Scheme 15



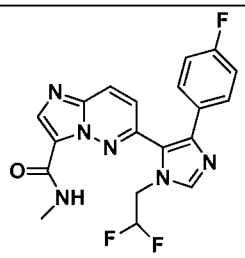
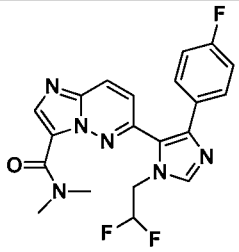
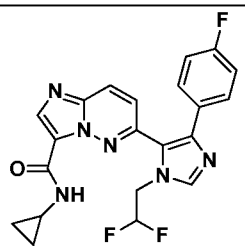
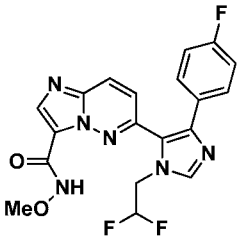
Example 205′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbohydrazide



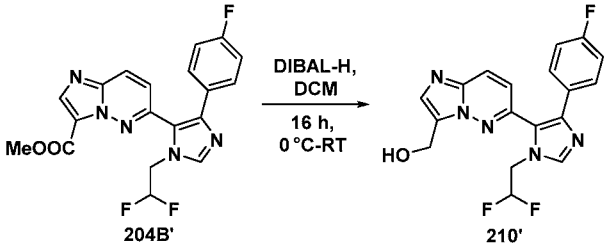
[0487] A solution of intermediate **204A′** (0.045 g, 0.062 mmol), hydrazine hydrochloride (8.45 mg, 0.123 mmol), HATU (0.047 g, 0.123 mmol) and DIPEA (0.065 mL, 0.370 mmol) in DMF (0.62 mL) was stirred at RT for 1 h. The mixture was then purified via preparative HPLC. Fractions containing the product were combined and evaporated to afford Example **205′** (0.011 g, 41.8 % yield). MS (ES): *m/z* = 402.3 $[M+H]^+$; HPLC Ret. Time 0.978 min. and 1.204 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.30 (s, 1H), 8.22 (d, *J* = 9.5 Hz, 1H), 8.05 (s, 1H), 7.52 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.22 - 7.08 (m, 3H), 4.86 - 4.68 (m, 2H), 4.04 (s, 2H).

[0488] Compounds shown in **Table 13** have been synthesized analogous to Example **205′** by amide bond coupling between intermediate **204A′** and corresponding amines.

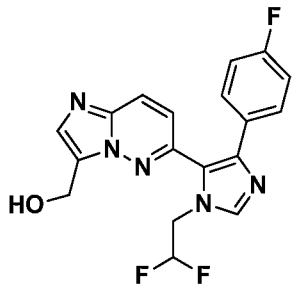
Table 13

Ex.	Structure	Name	$[M+H]^+$	Ret. Time (min.)	HPLC Method
206′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-*N*-methylimidazo[1,2-*b*]pyridazine-3-carboxamide	401.3	1.348, 1.107	A B
207′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-N,N-dimethylimidazo[1,2-*b*]pyridazine-3-carboxamide	415.2	1.078, 1.30	A B
208′		N-cyclopropyl-6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide	427.05	1.447, 1.195	A B
209′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-*N*-methoxyimidazo[1,2-*b*]pyridazine-3-carboxamide	417.3	1.342, 1.066	A B

Scheme 16

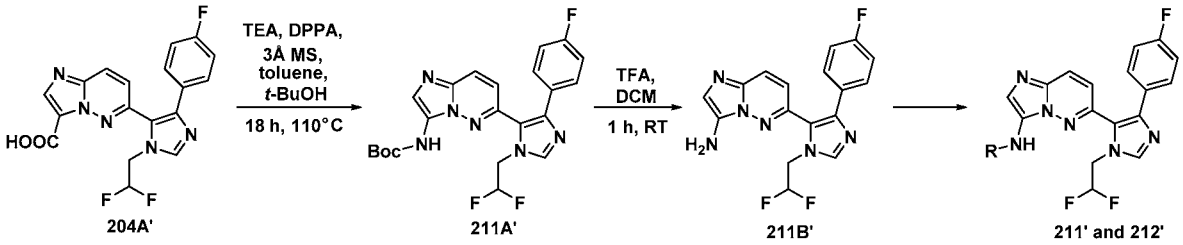


Example 210′: (6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methanol

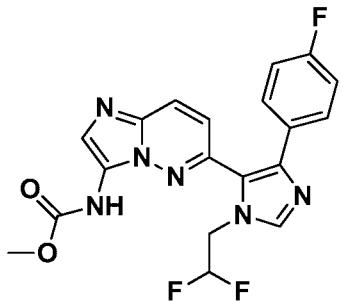


[0489] To a 0 °C solution of intermediate **204B′** (0.133 g, 0.331 mmol) in DCM (3.31 mL) was added DIBAL-H (1.16 mL, 1.16 mmol, 1M solution in hexanes). The reaction was allowed to stir at RT for 16 h, quenched with satd. aq. sodium potassium tartrate at RT. After the mixture was stirred for 10 min, it was extracted with DCM (2 x 10 mL). The combined organic layers were washed with water, brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and theresidue was purified by preparative HPLC. Fractions containing the product were combined and evaporated to afford Example **210′** (0.018 g, 51.4 % yield). MS (ES): *m/z* = 374.0 $[M+H]^+$; HPLC Ret. Time 1.007 min. and 1.340 min. (HPLC Methods A and B, respectively); ^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.09 (d, *J* = 9.2 Hz, 1H), 8.04 (s, 1H), 7.80 (s, 1H), 7.51 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.18 (t, *J* = 9.0 Hz, 2H), 6.96 (d, *J* = 9.5 Hz, 1H), 6.44 (s, 1H), 4.88 (d, *J* = 3.7 Hz, 2H), 4.83 - 4.71 (m, 2H).

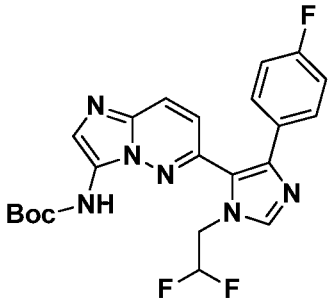
Scheme 17



Example 211′: methyl (6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)carbamate

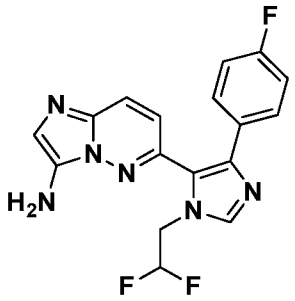


Intermediate 211A′: *tert*-butyl (6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)carbamate



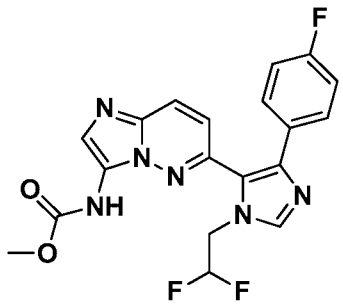
[0490] To a solution of intermediate **204A′** (0.37 g, 0.507 mmol) and TEA (0.32 mL, 2.283 mmol) in toluene (3 mL) and *t*-BuOH (3 mL) was added 3Å molecular sieves (0.6 g), followed by DPPA (0.492 mL, 2.283 mmol). The reaction mixture was refluxed in an oil-bath at 110 °C for 18 h, cooled to RT, and filtered. The filtrate was concentrated under reduced pressure and the residue was suspended in satd. aq. $NaHCO_3$ solution and extracted with a solution of 5 % MeOH in DCM (3 x 15 mL). The combined organic layers were washed with water, brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to afford an oil, which was purified by silica gel chromatography (24 g RediSep® column, eluting with a gradient of 80-100 % EtOAc in hexanes). Fractions containing the desired product were combined and evaporated to afford Example **211A′** (0.23 g, 99 % yield) as a bright yellow solid. MS (ES): *m/z* = 459.0 $[M+H]^+$; HPLC Ret. Time 0.73 min. (HPLC Method C).

Intermediate 211B′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-amine



[0491] To a solution of intermediate **211A′** (0.03 g, 0.065 mmol) in DCM (1.3 mL) was added TFA (0.050 mL, 0.654 mmol) and the reaction was stirred at RT for 1 h. The volatiles were concentrated under reduced pressure to afford a residue, which was basified with satd. aq. $NaHCO_3$ solution and extracted with a solution of 5 % MeOH in DCM (2 x 10 mL). The combined organic layers were washed with water, brine, dried, and concentrated to give an oil. The oil was purified via preparative HPLC. Fractions containing the product were combined and evaporated to afford intermediate **211B′** (0.023 g, 96 % yield) as a bright yellow solid. MS (ES): m/z = 359.0 $[M+H]^+$; HPLC Ret. Time 0.966 min. and 1.260 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.00 (s, 1H), 7.85 (d, J = 9.2 Hz, 1H), 7.49 (dd, J = 8.8, 5.5 Hz, 2H), 7.22 - 7.09 (m, 3H), 6.60 (d, J = 9.2 Hz, 1H), 6.45 (s, 1H), 5.63 (s, 2H), 4.82 - 4.69 (m, 2H).

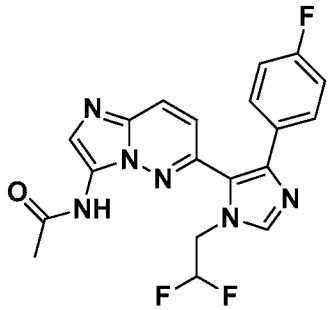
Example 211′: methyl (6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)carbamate



[0492] To a solution of intermediate **211B′** (0.03 g, 0.084 mmol) and DIPEA (0.044 mL, 0.251 mmol) in DMF (0.8 mL) was added methyl carbonochloridate (0.016 mL, 0.209 mmol). The reaction was stirred at RT for 1 h and then purified via preparative HPLC. Fractions containing the product were combined and evaporated to afford Example **211′** (0.007 g, 17 % yield). MS (ES): m/z = 417.1 $[M+H]^+$; HPLC Ret. Time 1.092 min. and 1.418 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.11 -

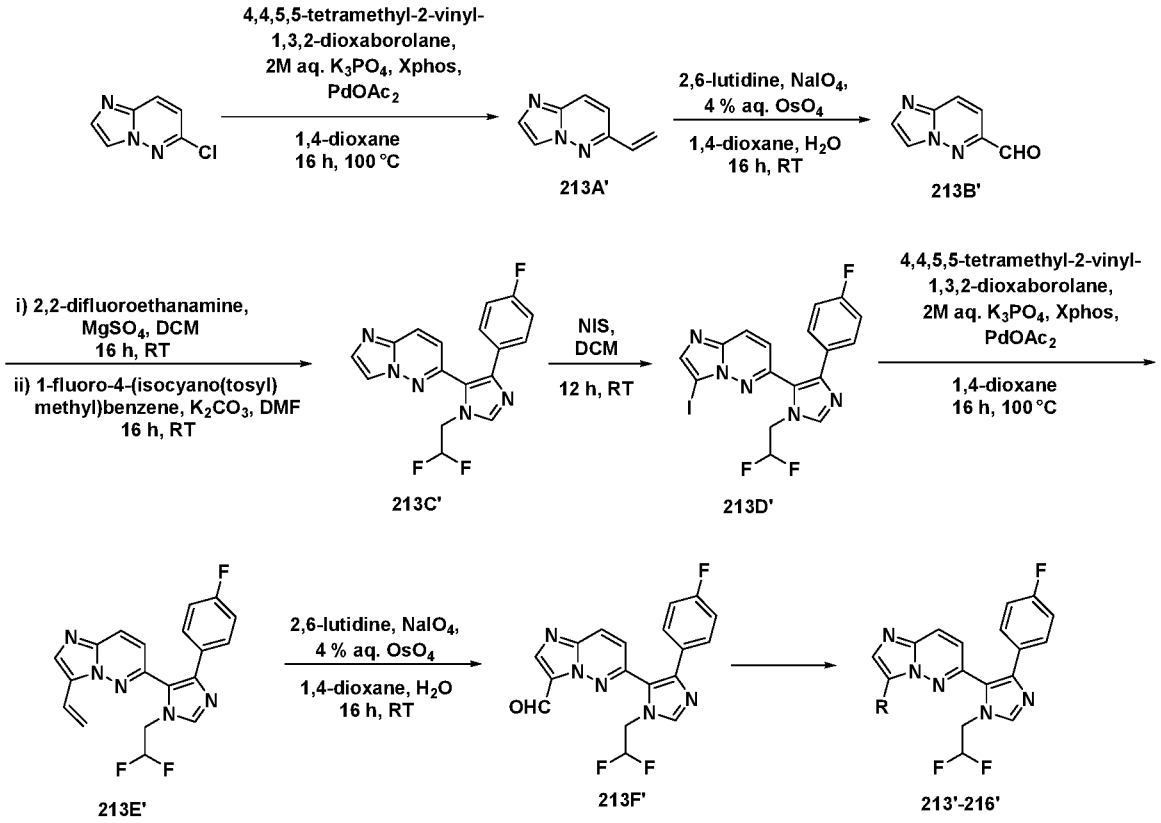
7.97 (m, 2H), 7.76 (s, 1H), 7.49 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.18 (t, *J* = 9.0 Hz, 2H), 6.93 (d, *J* = 9.2 Hz, 1H), 4.80 (t, *J* = 15.2 Hz, 2H), 3.72 (br. s., 1H), 2.55 (s, 3H).

Example 212′: *N*-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)acetamide

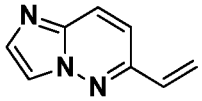


[0493] To a solution of intermediate **211B′** (0.03 g, 0.084 mmol) and DIPEA (0.058 mL, 0.335 mmol) in DMF (0.84 mL) was added acetyl chloride (0.209 mL, 0.209 mmol, 1M solution in DCM). Thereaction was stirred at RT for 1 h and purified via preparative HPLC. Fractions containing the product were combined and evaporated to afford Example **212′** (0.007 g, 21.8 % yield). MS (ES): *m/z* = 401.3 $[M+H]^+$; HPLC Ret. Time 0.972 min. and 1.290 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 10.45 (s, 1H), 8.13 - 7.97 (m, 2H), 7.88 (s, 1H), 7.50 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.17 (t, *J* = 8.8 Hz, 2H), 6.91 (d, *J* = 9.2 Hz, 1H), 6.39 (s, 1H), 4.86 - 4.69 (m, 2H), 2.19 (s, 3H).

Scheme 18



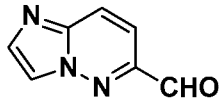
Intermediate 213A': 6-vinylimidazo[1,2-*b*]pyridazine



[0494] To a degassed solution of 6-chloroimidazo[1,2-*b*]pyridazine (7.1 g, 45.3 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (16.18 mL, 91 mmol) and Xphos (6.48 g, 13.59 mmol) in 2M aq. K_3PO_4 (68.0 mL, 136 mmol) and 1,4-dioxane (227 mL) was added $Pd(OAc)_2$ (1.017 g, 4.53 mmol). The reaction mixture was again degassed for 2 min. and the sealed tube was heated in an oil-bath at 100 °C for 16 h. The reaction mixture was then cooled to RT and concentrated under reduced pressure to give a residue that was suspended in water and extracted with a solution of 5 % MeOH in DCM (3 x 100 mL). The combined organic layers were washed with water, brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure to give a solid, which was purified by silica gel chromatography (220 g RediSep® column, eluting with a gradient of 10-90 % EtOAc in hexanes). Fractions containing the product were combined and evaporated to afford intermediate **213A'** (5.38 g, 82 % yield) as a pale yellow solid. MS (ES): *m/z* = 146.1 $[M+H]^+$; ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.28 - 8.21 (m, 1H), 8.11 (d, *J* = 9.5 Hz,

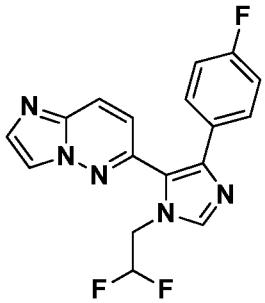
1H), 7.76 (d, *J* = 1.0 Hz, 1H), 7.60 (d, *J* = 9.5 Hz, 1H), 6.83 (dd, *J* = 17.8, 11.0 Hz, 1H), 6.32 (d, *J* = 17.8 Hz, 1H), 5.76 (d, *J* = 2.0 Hz, 1H).

Intermediate 213B′: imidazo[1,2-*b*]pyridazine-6-carbaldehyde



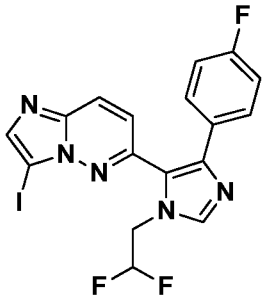
[0495] Intermediate **213B′** was synthesized analogous to intermediate **1D′** (Scheme **1**) by reacting intermediate **213A′** with $NaIO_4/OsO_4$. The crude product was purified by silica gel chromatography (220 g RediSep® column, eluting with a gradient of 10-90 % EtOAc in hexanes). Fractions containing the product were combined and evaporated to afford Example **213B′** (3.85 g, 70.6 % yield) as a yellow solid. MS (ES): *m/z* = 148.1 $[M+H]^+$; HPLC Ret. Time 0.972 min. and 1.232 min. (HPLC Method D); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.99 (s, 1H), 8.55 (s, 1H), 8.31 (d, *J* = 9.3 Hz, 1H), 8.03 (d, *J* = 1.3 Hz, 1H), 7.62 (d, *J* = 9.5 Hz, 1H).

Intermediate 213C′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine



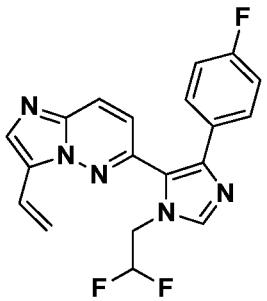
[0496] Intermediate **213C′** was synthesized analogous to Example **1′** (Scheme **1**) by treating intermediate **213B′** with 2,2-difluoroethanamine to first form the corresponding imine, followed by reacting the intermediate imine with commercially available 1-fluoro-4-(isocyano(tosyl)methyl)benzene. The crude product was purified by silica gel chromatography (120 g RediSep® column, eluting with a gradient of 20-100 % EtOAc in hexanes). Fractions containing the product were combined and evaporated to afford intermediate **213C′** (2.98 g, 88 % yield) as a semi-solid. MS (ES): *m/z* = 344.1 $[M+H]^+$; HPLC Ret. Time 0.56 min. (HPLC Method C); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.40 (s, 1H), 8.12 (dd, *J* = 9.5, 0.5 Hz, 1H), 8.03 (s, 1H), 7.87 (d, *J* = 1.3 Hz, 1H), 7.55 - 7.44 (m, 2H), 7.24 - 7.11 (m, 2H), 6.99 (d, *J* = 9.5 Hz, 1H), 6.38 (t, *J* = 3.4 Hz, 1H), 4.73 (dd, *J* = 15.5, 3.1 Hz, 2H).

Intermediate 213D′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-3-iodoimidazo[1,2-*b*]pyridazine



[0497] To a solution of intermediate **213C′** (2.4 g, 6.99 mmol) in DCM (46 mL) and MeOH (23 mL) was added NIS (1.651 g, 7.34 mmol). The reaction mixture was stirred at RT for 12 h, concentrated to dryness and the residue was purified by silica gel chromatography (120 g RediSep® column, eluting with a gradient of 60-100 % EtOAc in hexanes). Fractions containing the product were combined and evaporated to afford intermediate **213D′** (2.21 g, 67.4 % yield) as a yellow solid. MS (ES): *m/z* = 469.9 $[M+H]^+$; HPLC Ret. Time 0.77 min. (HPLC Method C).

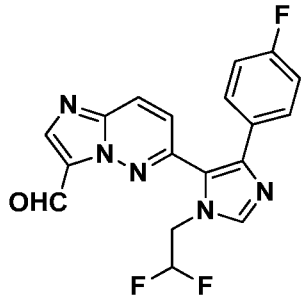
Intermediate 213E′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-3-vinylimidazo[1,2-*b*]pyridazine



[0498] To a degassed solution of intermediate **213D′** (2.622 g, 5.59 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.954 mL, 11.18 mmol) and Xphos (0.799 g, 1.676 mmol) in 2M aq. K_3PO_4 (8.38 mL, 16.76 mmol) and 1,4-dioxane (27.9 mL) was added $Pd(OAc)_2$ (0.125 g, 0.559 mmol). The mixture was degassed again for 2 min. and the sealed tube was heated in an oil-bath at 100 °C for 16 h. The reaction was cooled to RT and concentrated under reduced pressure. The residue was suspended in water and extracted with a solution of 5 % MeOH in DCM (3 x 25 mL). The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. Thefiltrate was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (80 g RediSep® column, eluting with 100 % EtOAc). Fractions containing the product were combined and evaporated to afford Example **213E′** (1.127 g, 54.6 % yield) as a yellowish

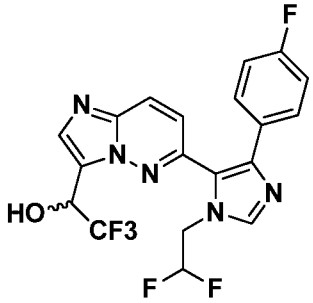
brown semi-solid. MS (ES): *m/z* = 370.2 $[M+H]^+$; HPLC Ret. Time 2.283 min. (HPLC Method D).

Intermediate 213F′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbaldehyde



[0499] To a solution of intermediate **213E′** (1.126 g, 3.05 mmol) in 1,4-dioxane (21.8 mL) and water (7.3 mL) were added 2,6-lutidine (0.71 mL, 6.10 mmol), sodium periodate (2.61 g, 12.19 mmol) and a 4 % aq. solution of OsO_4 (0.72 mL, 0.091 mmol). The reaction mixture was stirred at RT for 16 h, diluted with water and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography (80 g RediSep® column, eluting with 100 % EtOAc). Fractions containing the product were combined and evaporated to afford intermediate **213F′** (0.793 g, 70.1 % yield) as a brown solid. MS (ES): *m/z* = 372.0 $[M+H]^+$; HPLC Ret. Time 0.68 min. (HPLC Method C); ^1H NMR (400 MHz, DMSO-d_6) δ ppm 10.22 (s, 1H), 8.60 (s, 1H), 8.29 (d, *J* = 9.5 Hz, 1H), 8.08 (s, 1H), 7.61 - 7.49 (m, 2H), 7.27 (d, *J* = 9.5 Hz, 1H), 7.19 (t, *J* = 8.9 Hz, 2H), 6.65 (t, *J* = 3.8 Hz, 1H), 4.82 (dd, *J* = 14.8, 3.5 Hz, 2H).

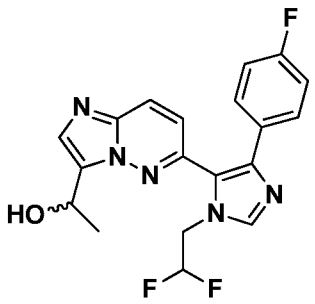
Example 213′: 1-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)-2,2,2-trifluoroethanol



[0500] To an ice-cold solution of intermediate **213F′** (0.04 g, 0.108 mmol) in THF (1.0 mL) was added trimethyl(trifluoromethyl)silane (0.024 mL, 0.162 mmol). The reaction mixture was then stirred at RT for 2 h, solvent was evaporated and the residue was and then

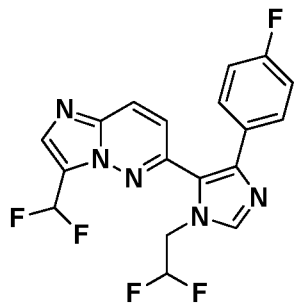
purified by preparative HPLC. Fractions containing the product were combined and evaporated to afford Example **213′** (0.016 g, 33.0 % yield) as a solid. MS (ES): *m/z* = 442.0 $[M+H]^+$; HPLC Ret. Time 1.211 min. and 1.470 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.17 (d, *J* = 9.5 Hz, 1H), 8.06 (s, 1H), 7.94 (s, 1H), 7.50 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.18 (t, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 9.2 Hz, 1H), 5.84 (q, *J* = 7.1 Hz, 1H), 4.86 - 4.71 (m, 2H).

Example 214′: 1-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)ethanol



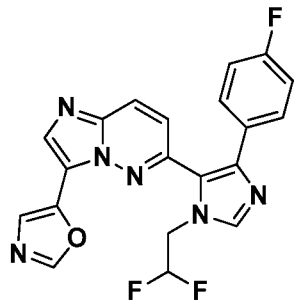
[0501] To an ice-cold solution of intermediate **213F′** (0.05 g, 0.135 mmol) in THF (1.35 mL) was slowly added methylmagnesium bromide (0.090 mL, 0.269 mmol, 3M solution in Et_2O), The reaction mixture was stirred at RT for 3 h., quenched with satd. aq. NH_4Cl solution and diluted with EtOAc. The two layers were separated and the aq. layer was back-extracted with EtOAc. The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. Thefiltrate was concentrated under reduced pressure and the resulting residuewas purified via preparative HPLC. Fractions containing the product were combined and evaporated to afford Example **214′** (0.045 g, 87 % yield) as a solid. MS (ES): *m/z* = 388.0 $[M+H]^+$; HPLC Ret. Time 0.988 min. and 1.298 min. (HPLC Methods A and B, respectively).

Example 215′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-3-(difluoromethyl)imidazo[1,2-*b*]pyridazine



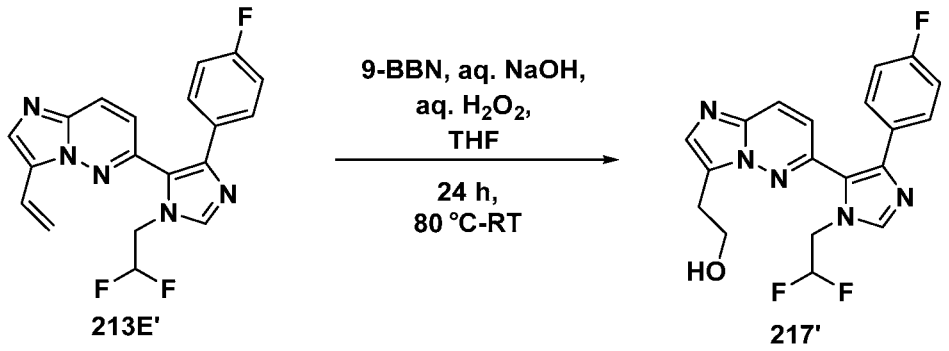
[0502] To an ice-cold solution of intermediate **213F′** (0.04 g, 0.108 mmol) in DCM (1.2 mL) was added DAST (0.043 mL, 0.323 mmol). The reaction mixture was stirred at RT for 16 h and carefully quenched with satd. aq. $NaHCO_3$ solution. The two layers were separated and the aq. layer was back-extracted with a solution of 5 % MeOH in DCM (2 x 10 mL). The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the resulting residue was purified via preparative HPLC. Fractions containing the product were combined and evaporated to afford Example **215′** (0.037 g, 88.1 % yield) as a solid. MS (ES): *m/z* = 394.05 $[M+H]^+$; HPLC Ret. Time 1.04 min. and 1.081 min. (HPLC Methods A and B, respectively); ^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.21 (d, *J* = 9.5 Hz, 1H), 8.16 (s, 1H), 8.06 (s, 1H), 7.60 (s, 1H), 7.58 - 7.45 (m, 2H), 7.19 (t, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 9.5 Hz, 1H), 6.40 (s, 1H), 4.87 - 4.71 (m, 2H).

Example 216′: 5-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)oxazole

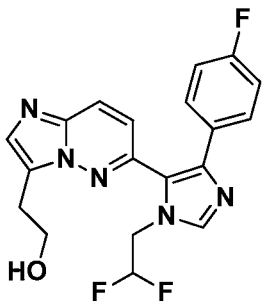


[0503] A suspension of intermediate **213F′** (0.04 g, 0.108 mmol), TosMIC (0.024 g, 0.124 mmol) and potassium carbonate (0.017 g, 0.124 mmol) in MeOH (1.08 mL) was refluxed in an oil-bath for 4 h. The methanol was evaporated under reduced pressure and the residue was purified via preparative HPLC. Fractions containing the product were combined and evaporated to afford Example **216′** (0.036 g, 81.36 % yield). MS (ES): *m/z* = 411.0 $[M+H]^+$; HPLC Ret. Time 1.339 min. (HPLC Method B); ^1H NMR (500 MHz, DMSO-d_6) δ 8.60 (s, 1H), 8.32 - 8.22 (m, 2H), 8.08 (s, 1H), 7.74 (s, 1H), 7.52 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.26 - 7.08 (m, 3H), 6.30 (s, 1H), 4.91 - 4.72 (m, 2H).

Scheme 19

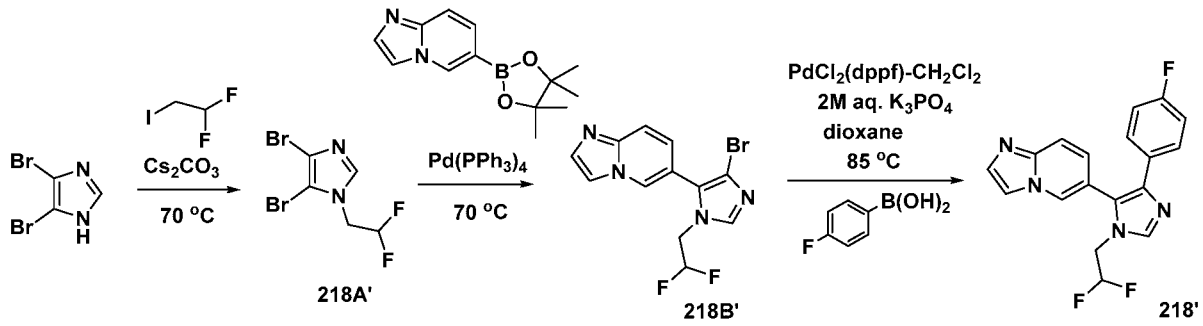


Example 217′: 2-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)ethanol

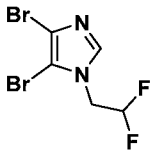


[0504] To a stirred solution of intermediate **213E′** (20 mg, 0.054 mmol) in THF (5 mL) was added 9-BBN (0.217 mL, 0.108 mmol, 0.5M solution in THF). The reaction mixture was heated at 80 °C for 14 h and cooled to RT. Following the sequential addition of 3M aq. solution of NaOH (0.108 mL, 0.325 mmol) and 30 % aq. solution of H_2O_2 (0.111 mL, 1.083 mmol), the resultant mixture was stirred at RT for an additional 14 h. The volatiles were evaporated under reduced pressure and the resulting residue was diluted with water and extracted with ethyl acetate (2 x 5 mL). The combined organic layers were washed with water and brine, dried over anhydrous $MgSO_4$, and filtered. The filtrate was concentrated under reduced pressure and the residue was purified via preparative HPLC. Fractions containing the product were combined and evaporated to afford Example **217′** (1.2 mg, 5.72 % yield) as a solid. MS (ES): *m/z* = 388.1 $[M+H]^+$; HPLC Ret. Time 1.018 min. and 1.336 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.11 - 7.97 (m, 2H), 7.72 (s, 1H), 7.49 (dd, *J* = 8.6, 5.7 Hz, 2H), 7.17 (t, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 9.2 Hz, 1H), 4.92 - 4.81 (m, 1H), 4.81 - 4.69 (m, 2H), 3.84 - 3.74 (m, 2H), 3.15 (t, *J* = 6.6 Hz, 2H).

Scheme 20

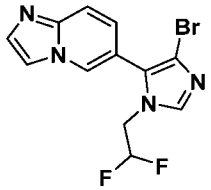


Intermediate 218A′: 4,5-dibromo-1-(2,2-difluoroethyl)-1*H*-imidazole



[0505] To a solution of 4,5-dibromo-1*H*-imidazole (0.37 g, 1.64 mmol) in acetonitrile (15 mL) were added 1,1-difluoro-2-iodoethane (0.47 g, 2.46 mmol) and cesium carbonate (0.64 g, 1.97 mmol). The suspension was heated at 70 °C overnight and then allowed to cool to RT. The reaction mixture was passed through a pad of Celite® and washed with EtOAc. The combined filtrates were concentrated and the residue was purified by silica gel chromatography (80 g RediSep® column, eluting with a gradient from 10-65 % EtOAc in hexanes). Fractions containing the product were combined and evaporated to afford intermediate **218A′** (0.34 g, 72 % yield). MS (ES): *m/z* = 288/290 $[M+H]^+$; HPLC Ret. Time 0.68 min. (HPLC Method C); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.61 (s, 1H), 6.00 (t, *J* = 3.9 Hz, 1H), 4.36 (dd, *J* = 13.7, 3.9 Hz, 2H).

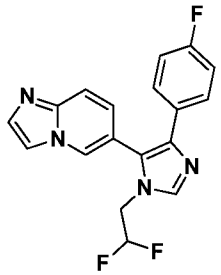
Intermediate 218B′: 6-(4-bromo-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-a]pyridine



[0506] To a vial were added intermediate **218A′** (104 mg, 0.359 mmol), imidazo[1,2-a]pyridin-6-ylboronic acid (58.1 mg, 0.359 mmol), potassium carbonate (149 mg, 1.076 mmol), THF (3 mL), and water (1 mL). The reaction mixture was purged with nitrogen and $Pd(Ph_3P)_4$ (41.5 mg, 0.036 mmol) was added. The reaction mixture was heated at 70 °C for 2 days, cooled to RT, diluted with water and extracted with DCM. The combined organic

layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated and the crude product was purified by silica gel chromatography (24 g RediSep® column, eluting with a gradient from 10-80 % B in DCM; B: 10 % MeOH in DCM). Fractions containing the product were combined and evaporated to afford intermediate **218B′** (65 mg, 0.199 mmol, 55.4 % yield). MS (ES): *m/z* = 327/329 $[M+H]^+$; HPLC Ret. Time 0.34 min. (HPLC Method C); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.33 - 8.18 (m, 1H), 7.81 - 7.66 (m, 3H), 7.63 (s, 1H), 7.07 (dd, *J* = 9.3, 1.8 Hz, 1H), 5.90 (t, *J* = 3.3 Hz, 1H), 4.27 (dd, *J* = 14.7, 3.3 Hz, 2H).

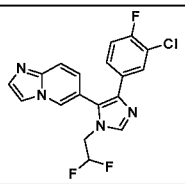
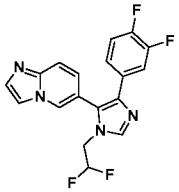
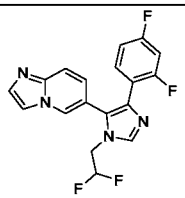
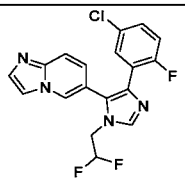
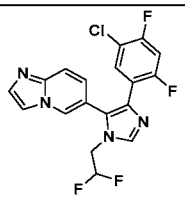
Example 218′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine



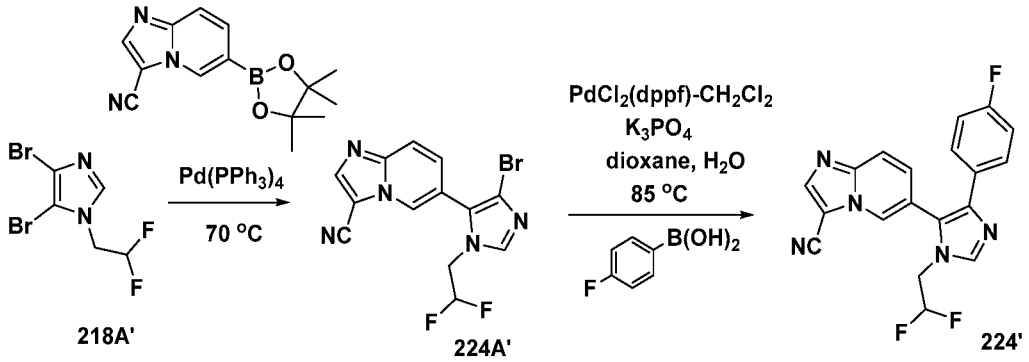
[0507] To a vial were added intermediate **218B′** (25 mg, 0.076 mmol), (4-fluorophenyl)boronic acid (16.04 mg, 0.115 mmol), 2M aq. solution of K_3PO_4 (48.7 mg, 0.229 mmol) and 1,4-dioxane (2 mL). The reaction mixture was purged with nitrogen and $PdCl_2$(dppf)-CH_2Cl_2 adduct (62.4 mg, 0.076 mmol) was added. After heating the reaction at 85 °C for 4 h, the dark mixture was cooled to RT, passed through a pad of Celite® and washed the filter-cake with DCM. The combined filtrates were concentrated under reduced pressure. The crude product was dissolved in a mixture of DMF and methanol and purified by preparative HPLC. Fractions containing the desired product were combined and evaporated to afford Example **218′** (17.7 mg, 67 % yield). MS (ES): *m/z* = 343.0 $[M+H]^+$; HPLC Ret. Time 0.920 min. and 1.342 min. (HPLC Methods A and B, respectively); ^1H NMR (500 MHz, DMSO-d_6) δ ppm 8.67 (s, 1H), 7.98 (s, 1H), 7.93 (s, 1H), 7.76 - 7.63 (m, 2H), 7.46 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.22 - 7.02 (m, 3H), 6.23 (s, 1H), 4.52 - 4.31 (m, 2H).

[0508] Compounds shown in **Table 14** have been prepared in a manner similar to Example **218′** using intermediate **218B′** and the corresponding boronic acids.

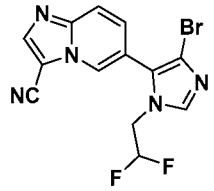
Table 14

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
219′		6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine	376.9	1.978 1.791	A B
220′		6-(1-(2,2-difluoroethyl)-4-(3,4-difluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine	361.1	0.964 1.499	A B
221′		6-(1-(2,2-difluoroethyl)-4-(2,4-difluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine	361.0	0.907 1.353	A B
222′		6-(4-(5-chloro-2-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine	376.9	0.940 1.426	A B
223′		6-(4-(5-chloro-2,4-difluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine	395.0	1.029 1.444	A B

Scheme 21

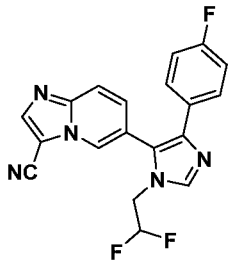


Intermediate 224A′: 6-(4-bromo-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile



[0509] To a pressure bottle were added intermediate **218A′** (420 mg, 1.449 mmol), (3-cyanoimidazo[1,2-a]pyridin-6-yl)boronic acid (271 mg, 1.449 mmol), potassium carbonate (601 mg, 4.35 mmol), THF (12 mL) and water (4 mL). The reaction mixture was purged with nitrogen and $Pd(Ph_3P)_4$ (167 mg, 0.145 mmol) was added. After purging the mixture again with nitrogen, reaction was heated at 70 °C for 36 h and cooled to RT, diluted with DCM and water. The layers were separated. The aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated and the crude product was purified by silica gel chromatography (40 g RediSep® column, eluting with a gradient from 40-100 % EtOAc in DCM, the 50-100 % B in DCM, B: 10 % MeOH in DCM)). Fractions containing the product were combined and evaporated to afford **224A′** (220 mg, 0.625 mmol, 43.1 % yield). MS (ES): *m/z* = 353.9 $[M+H]^+$; HPLC Ret. Time 0.68 min. (HPLC Method C); ^1H NMR (400 MHz, $CDCl_3$) δ ppm 8.50 - 8.40 (m, 1H), 8.28 (s, 1H), 7.97 - 7.87 (m, 1H), 7.70 (s, 1H), 7.43 (dd, *J* = 9.3, 1.5 Hz, 1H), 5.95 (t, *J* = 3.0 Hz, 1H), 4.30 (dd, *J* = 14.8, 3.0 Hz, 2H).

[0510] **Example 224′**: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile

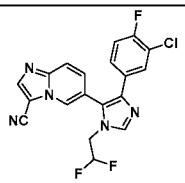
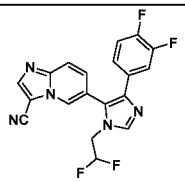
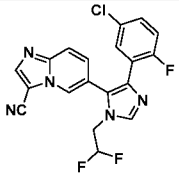
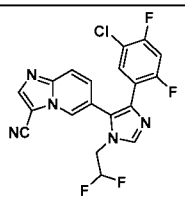


[0511] To a vial were added (4-fluorophenyl)boronic acid (14.9 mg, 0.106 mmol), intermediate **224A′** (25 mg, 0.07 mmol), a 2 M aq. solution of K_3PO_4 (0.1 mL, 0.213 mmol) and 1,4-dioxane (1 mL). The reaction mixture was purged with nitrogen for 2 min and $PdCl_2$(dppf)-CH_2Cl_2 adduct (10.67 mg, 0.013 mmol) was added. The reaction mixture was heated at 85 °C for 6 h. The dark reaction mixture was cooled to RT, passed through a pad of Celite®, washed with DCM and concentrated *in vacuo*. The crude product was dissolved in a

mixture of DMF and methanol and purified by preparative HPLC. Fractions containing the desired product were combined and dried under vacuum to afford Example **224′** (44.4 mg, 0.100 mmol, 63 % yield). MS (ES): *m/z* = 368.0 $[M+H]^+$; HPLC Ret. Time 1.233 min. and 1.408 min. (HPLC Methods A and B, respectively); ^{1}H NMR (500 MHz, DMSO-d_6) δ ppm 8.77 (s, 1H), 8.54 (s, 1H), 8.02 - 7.83 (m, 2H), 7.47 (dd, *J* = 8.8, 5.5 Hz, 2H), 7.39 (dd, *J* = 9.2, 1.5 Hz, 1H), 7.08 (t, *J* = 9.0 Hz, 2H), 6.20 (m, 1H), 4.59 - 4.37 (m, 2H).

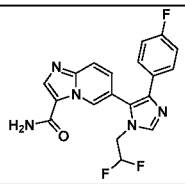
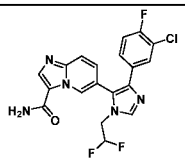
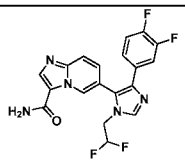
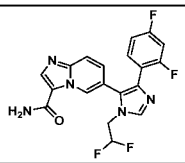
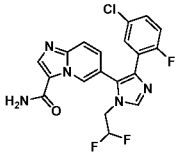
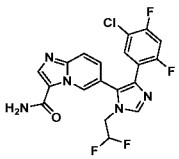
[0512] Compounds shown in **Table 15** have been prepared in a manner similar to Example **224′** using intermediate **224A′** and the corresponding boronic acids.

Table 15

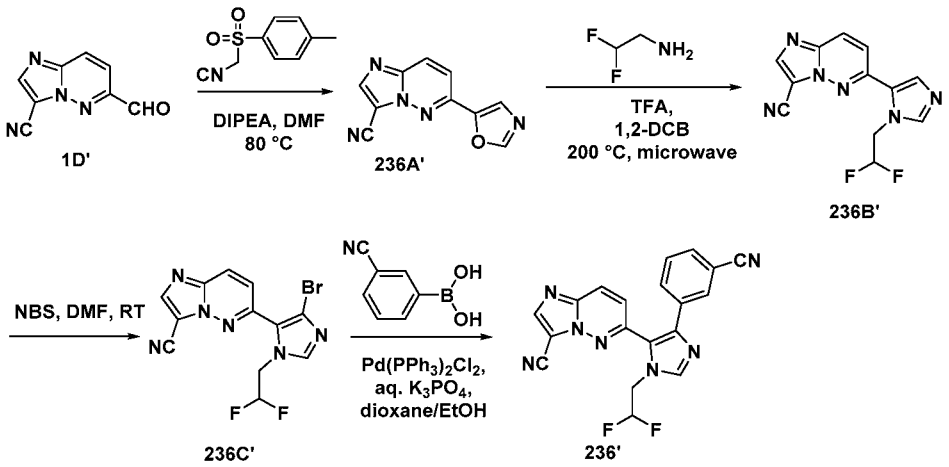
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
225′		6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	376.9	1.791 1.978	A B
226′		6-(1-(2,2-difluoroethyl)-4-(3,4-difluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	386.1	1.275 1.592	A B
227′		6-(1-(2,2-difluoroethyl)-4-(2,4-difluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	386.9	1.189 1.483	A B
228′		6-(4-(5-chloro-2-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	401.9	1.307 1.566	A B
229′		6-(4-(5-chloro-2,4-difluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile	419.9	1.029 1.444	A B

[0513] Compounds shown in **Table 16** have been prepared in a manner similar to Example **105′** (Scheme **6**) by heating the corresponding cyano compounds with TFA and sulfuric acid.

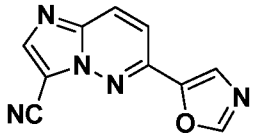
Table 16

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
230′		6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1H-imidazol-5-yl)imidazo[1,2-a]pyridine-3-carboxamide	386.1	0.823 1.187	A B
231′		6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	419.9	1.516 1.876	A B
232′		6-(1-(2,2-difluoroethyl)-4-(3,4-difluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	404.0	0.994 1.360	A B
233′		6-(1-(2,2-difluoroethyl)-4-(2,4-difluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	404.0	0.923 1.229	A B
234′		6-(4-(5-chloro-2-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	419.9	0.959 1.299	A B
235′		6-(4-(5-chloro-2,4-difluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	437.9	1.242 1.403	A B

Scheme 22

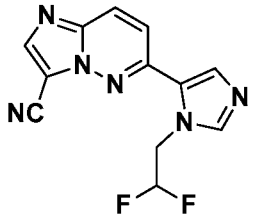


Intermediate 236A′: 6-(oxazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile



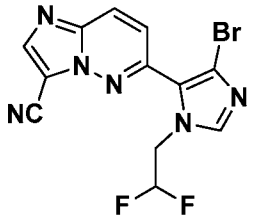
[0514] To a solution of intermediate **1D′** (1g, 5.81 mmol) in DMF (10 mL) was added DIPEA (2.029 mL, 11.62 mmol) and TosMIC (1.701 g, 8.71 mmol). The reaction mixture was heated at 80 °C for 2 h, quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure to give the crude residue, which was purified by silica gel chromatography (40 g CombiFlash® column, eluting with a gradient of 40-100 % EtOAc in petroleum ether) to afford intermediate **236A′** (0.6 g, 30.8 % yield). LCMS: *m/z* = 212.0 $[M+H]^+$; HPLC Ret. Time 0.67 min. (HPLC Method F).

Intermediate 236B′: 6-(1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile



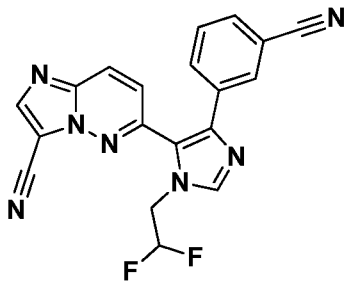
[0515] To a solution of intermediate **236A′** (400 mg, 1.894 mmol) in 1,2-dichlorobenzene (3 mL) was added 2,2-difluoroethanamine (0.267 mL, 3.79 mmol) and TFA (432 mg, 3.79 mmol). The reaction mixture was heated at 200 °C for 2 h in a CEM microwave instrument. The reaction mixture was quenched with 10 % aqueous NaOH solution and extracted with a solution of 10 % methanol in DCM. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give the crude residue which was purified by silica gel chromatography (120 g CombiFlash® column, eluting with a gradient of 0-20 % MeOH in DCM) to afford intermediate **236B′** (180 mg, 32.9 % yield). LCMS: *m/z* = 275.0 $[M+H]^+$; HPLC Ret. Time 0.75 min. (HPLC Method G).

Intermediate 236C′: 6-(4-bromo-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile



[0516] To a solution of intermediate **236B′** (250 mg, 0.912 mmol) in DMF (5 mL) was added NBS (195 mg, 1.094 mmol). The reaction mixture was stirred at RT for 18 h and partitioned between water and ethyl acetate. The aqueous layer was back-extracted with ethyl acetate (2 x 30 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to afford intermediate **236C′** (280 mg, 34.8 % yield). LCMS: *m/z* = 352.9 $[M+H]^+$; HPLC Ret. Time 0.75 min. (HPLC Method F).

Example 236′: 6-(4-(3-cyanophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile

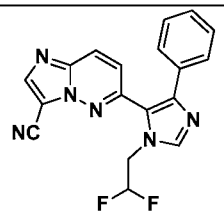
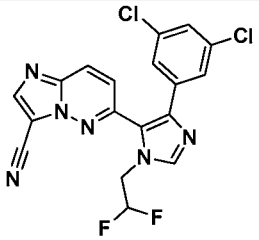
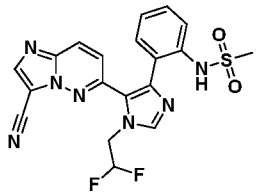
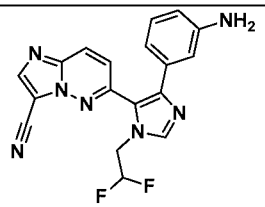
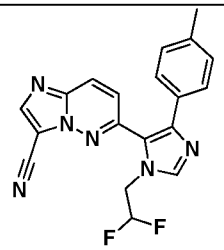


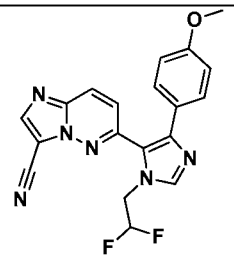
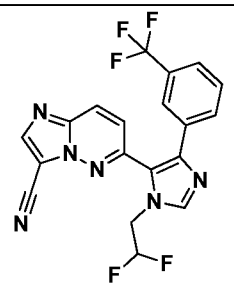
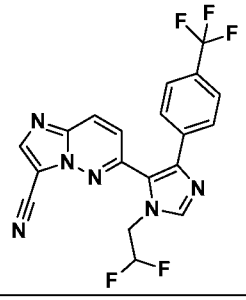
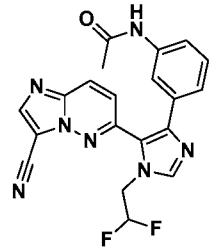
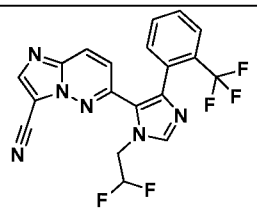
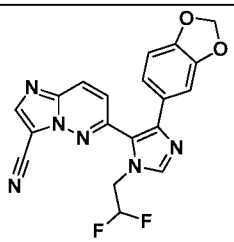
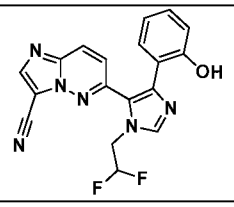
[0517] To a solution of intermediate **236C′** (30 mg, 0.085 mmol) in 1,4-dioxane (1 mL), ethanol (0.5 mL) water (0.5 mL) was added 3-cyanophenylboronic acid (18 mg, 0.127 mmol), and K_3PO_4 (54.1 mg, 0.255 mmol). The reaction mixture was degassed with argon for 5 minutes and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (6.22 mg, 8.50 µmol) was added. The reaction mixture was heated in a microwave instrument at 100 °C for 1 h. The reaction mixture was concentrated and the residue was partitioned between water and ethyl acetate. The aqueous layer was back-extracted with ethyl acetate (2 x 20 mL). The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give the crude residue, which was purified by preparative HPLC(Condition P). Fractions containing the desired product were combined and evaporated to afford Example **236′** (8.5 mg, 26.65 % yield). LCMS: *m/z* = 376.2 $[M+H]^+$; HPLC Ret. Time 1.329 min. (HPLC Method H); ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.66

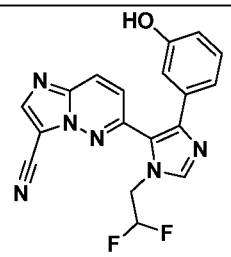
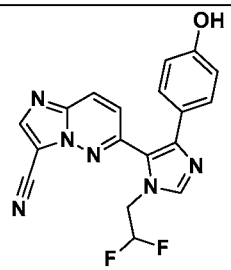
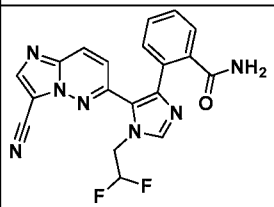
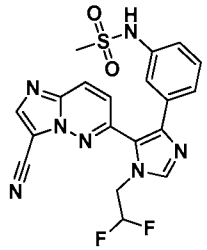
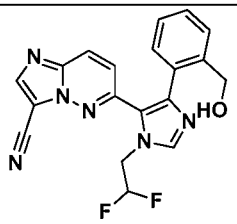
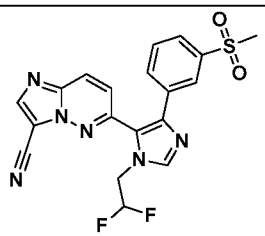
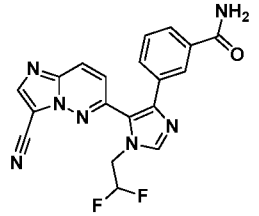
(s, 1H), 8.35 (d, J = 9.54 Hz, 1H), 8.14 (s, 1H), 7.98 (t, J = 1.51 Hz, 1H), 7.81 (ddd, J = 1.13, 7.91, 19.95 Hz, 2H), 7.54 (t, J = 7.78 Hz, 1H), 7.32 (d, J = 9.54 Hz, 1H), 6.27-6.59 (m, 1H), 4.80 (dt, J = 3.51, 15.31 Hz, 2H).

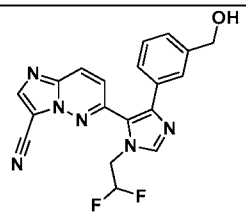
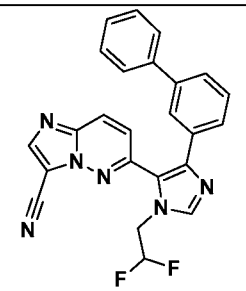
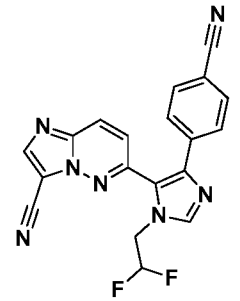
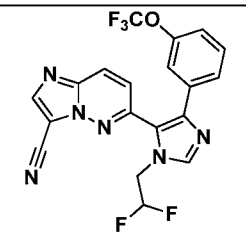
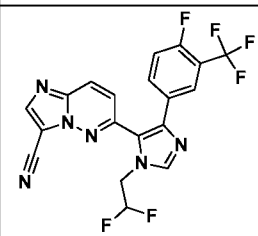
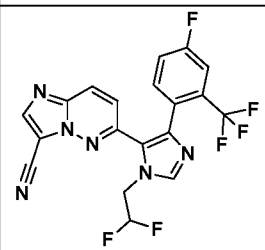
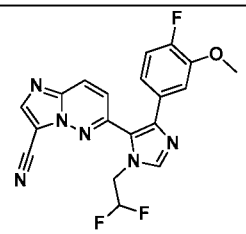
[0518] The compounds shown in **Table 17** have been prepared in a manner similar to Example **236′** by a Suzuki coupling between intermediate **236C′** and various aryl boronic acids/esters.

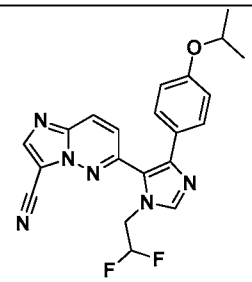
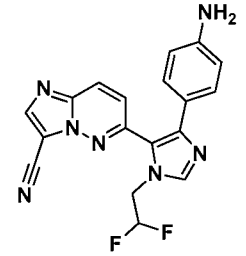
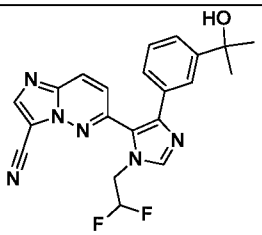
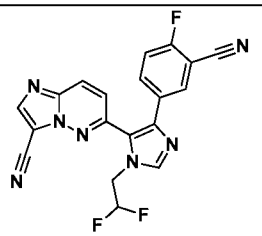
Table 17

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
237′		6-(1-(2,2-difluoroethyl)-4-phenyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	351.2	1.359 1.137	H I
238′		6-(4-(3,5-dichlorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	419.1	1.808 1.800	H I
239′		*N*-(2-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)phenyl)methanesulfonamide	444.2	1.378 1.171	H I
240′		6-(4-(3-aminophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	366.2	1.113 0.847	H I
241′		6-(1-(2,2-difluoroethyl)-4-(*p*-tolyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	365.2	1.515 1.252	H I

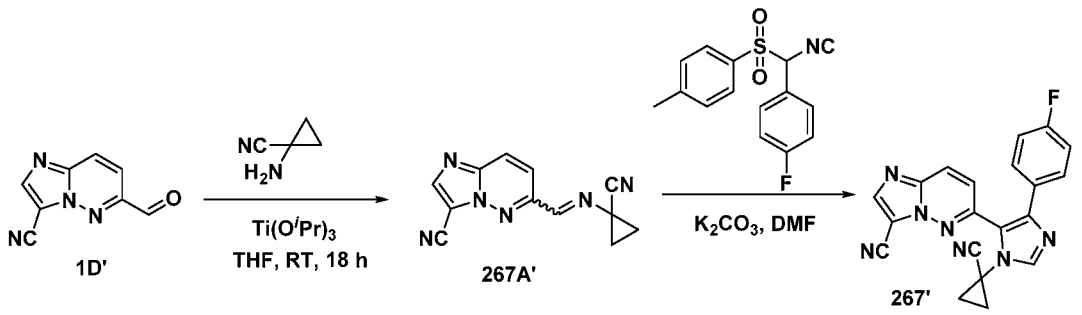
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
242′		6-(1-(2,2-difluoroethyl)-4-(4-methoxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	381.2	1.389 1.133	H I
243′		6-(1-(2,2-difluoroethyl)-4-(3-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	419.2	1.708 1.627	H I
244′		6-(1-(2,2-difluoroethyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	419.1	1.931 1.820	H I
245′		*N*-(3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)phenyl)acetamide	408.2	1.312 1.136	H I
246′		6-(1-(2,2-difluoroethyl)-4-(2-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	419.2	1.528 1.415	H I
247′		6-(4-(benzo[*d*][1,3]dioxol-5-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	395.2	1.330 1.090	H I
248′		6-(1-(2,2-difluoroethyl)-4-(2-hydroxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	367.2	1.422 1.014	H I

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
249′		6-(1-(2,2-difluoroethyl)-4-(3-hydroxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	367.1	1.336 1.124	H I
250′		6-(1-(2,2-difluoroethyl)-4-(4-hydroxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	367.2	1.134 0.902	H I
251′		2-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)benzamide	394.1	1.153 0.988	H I
252′		*N*-(3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)phenyl)methanesulfonamide	444.1	1.351 1.197	H I
253′		6-(1-(2,2-difluoroethyl)-4-(2-(hydroxymethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	381.2	1.226 0.994	H I
254′		6-(1-(2,2-difluoroethyl)-4-(3-(methylsulfonyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	429.2	1.179 1.102	H I
255′		3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)benzamide	394.2	0.971 0.848	H I

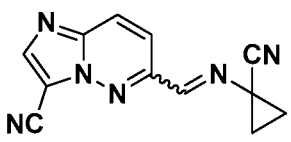
Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
256′		6-(1-(2,2-difluoroethyl)-4-(3-(hydroxymethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	381.2	1.105 0.939	H I
257′		6-(4-([1,1'-biphenyl]-3-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	427.2	1.799 1.625	H I
258′		6-(4-(4-cyanophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	376.2	1.318 1.263	H I
259′		6-(1-(2,2-difluoroethyl)-4-(3-(trifluoromethoxy)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	435.2	1.732 1.659	H I
260′		6-(1-(2,2-difluoroethyl)-4-(4-fluoro-3-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	437.2	1.739 1.674	H I
261′		6-(1-(2,2-difluoroethyl)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	437.2	1.556 1.491	H I
262′		6-(1-(2,2-difluoroethyl)-4-(4-fluoro-3-methoxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	399.2	1.435 1.275	H I

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
263′		6-(1-(2,2-difluoroethyl)-4-(4-isopropoxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	409.3	1.648 1.377	H I
264′		6-(4-(4-aminophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	366.2	1.070 0.761	H I
265′		6-(1-(2,2-difluoroethyl)-4-(3-(2-hydroxypropan-2-yl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	409.3	1.253 1.052	H I
266′		6-(4-(3-cyano-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	394.2	1.394 1.335	H I

Scheme 23

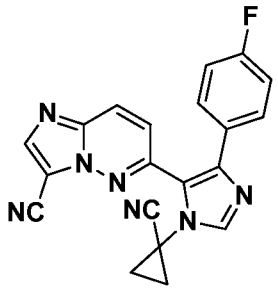


Intermediate 267A′: 6-(((1-cyanocyclopropyl)imino)methyl)imidazo[1,2-*b*]pyridazine-3-carbonitrile



[0519] To a solution of intermediate **1D′** (100 mg, 0.581 mmol) in THF (10 mL) was added 1-aminocyclopropanecarbonitrile.HCl (83 mg, 0.697 mmol) and titanium (IV) isopropoxide (0.187 mL, 0.639 mmol) at RT and the mixture was stirred for 2 h. To the reaction mixture was then added water and extracted with ethyl acetate (2 x 30 mL). The combined organic layers were dried over Na_2SO_4, filtered and the filtrate was concentrated to afford intermediate **267A′** (60 mg, 39.4 % yield) which was used in the next step without further purification LCMS: *m/z* = 237.3 $[M+H]^+$; HPLC Ret. Time 0.96 min. (HPLC Method G); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.68 (s, 1H), 8.58 (s, 1H), 8.43 (d, *J* = 9.54 Hz, 1H), 7.89 (d, *J* = 9.54 Hz, 1H), 1.96-2.03 (m, 2H), 1.73-1.81 (m, 2H) .

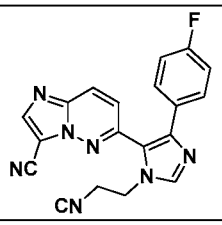
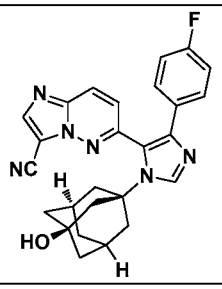
Example 267′: 6-(1-(1-cyanocyclopropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile, TFA



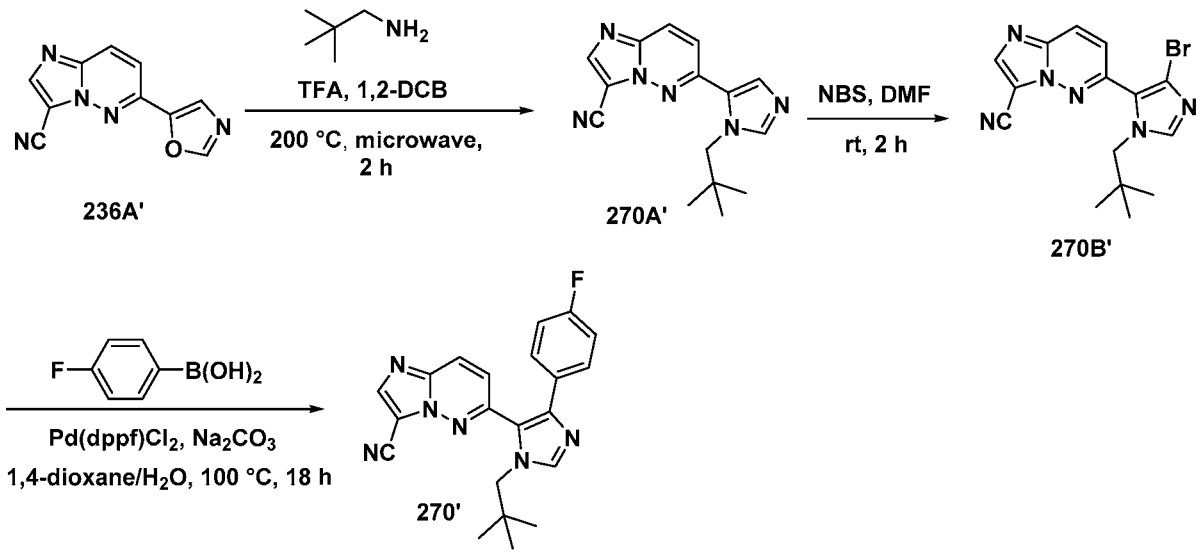
[0520] To a suspension of intermediate **267A′** (200 mg, 0.847 mmol) in DMF (5 mL) was added potassium carbonate (176 mg, 1.270 mmol) and 1-fluoro-4-(isocyano(tosyl)methyl)benzene (294 mg, 1.016 mmol) at RT. The reaction mixture was stirred at the same temperature for 16 h, diluted with water and extracted with ethyl acetate (2 x 20 mL). The combined organic layers were dried over Na_2SO_4, and filtered. The filtrate was concentrated and the crude product was purified by preparative HPLC (Condition P) to afford Example **267′** (1.2 mg, 0.290 % yield) as the TFA salt. LCMS: *m/z* = 370.0 $[M+H]^+$; HPLC Ret. Time 1.53 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.68 (s, 1H), 8.32-8.42 (m, 2H), 7.58 (dd, *J* = 5.50, 8.44 Hz, 2H), 7.31 (d, *J* = 9.54 Hz, 1H), 7.19 (t, *J* = 8.80 Hz, 2H), 1.84 (d, *J* = 7.83 Hz, 4H).

[0521] Compounds shown in **Table 18** have been prepared in a manner similar to Example **267′** using intermediate **1D′**, various amines and 1-fluoro-4-(isocyano(tosyl)methyl)benzene.

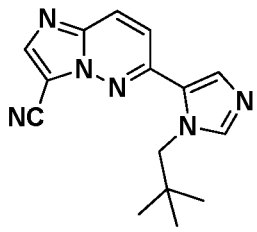
Table 18

Ex.	Structure	Name	$[M+H]^+$	Ret Time (min.)	HPLC Method
268′		6-(1-(2-cyanoethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	358.0	1.441 1.208	H I
269′		6-(4-(4-fluorophenyl)-1-((*1r,3s,5R,7S*)-3-hydroxyadamantan-1-yl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile	455.3	1.398 1.084	H I

Scheme 24



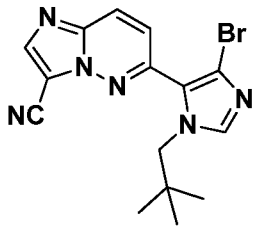
Intermediate 270A′: 6-(1-neopentyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile



[0522] Intermediate **270A′** was synthesized by treating intermediate **236A′** with 2,2-dimethylpropan-1-amine and by employing the experimental procedure described for intermediate **236B′** in Scheme **22**. The crude compound was purified by silica gel chromatography (24 g CombiFlash® column, eluting with 5% MeOH in $CHCl_3$). Fractions

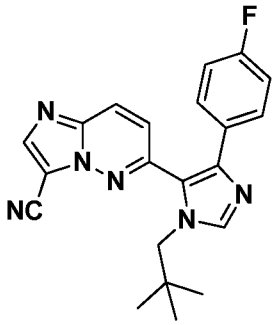
containing the desired product were combined and evaporated to afford intermediate **270A′** (160 mg, 60.3 % Yield). LCMS: *m/z* = 281.0 $[M+H]^+$; HPLC Ret. Time 2.11 min. (HPLC Method J).

Intermediate 270B′: 6-(4-bromo-1-neopentyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile



[0523] Intermediate **270B′** was synthesized by treating intermediate **270A′** with NBS and by employing the experimental procedure described for intermediate **236C′** in Scheme **21** .Intermediate **270B′** (195 mg). LCMS: *m/z* = 361.2 $[M+H]^+$; HPLC Ret. Time 1.28 min. (HPLC Method G).

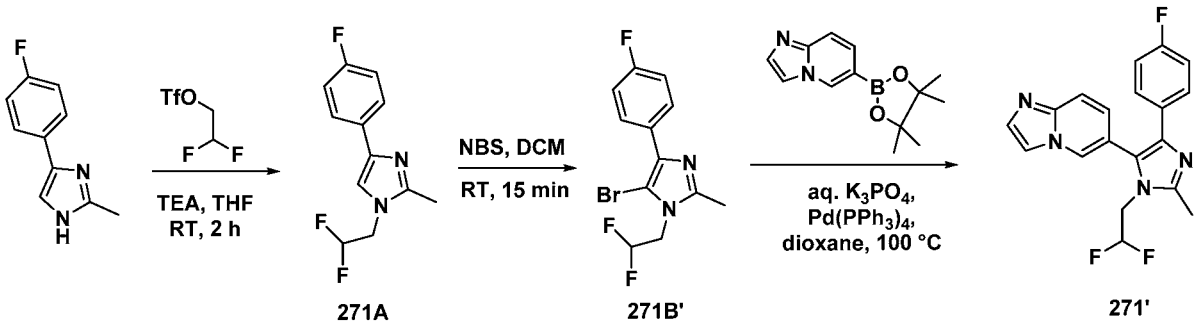
Example 270′: 6-(4-(4-fluorophenyl)-1-neopentyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile



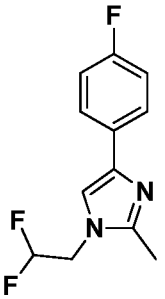
[0524] To a solution of intermediate **270B′** (100 mg, 0.278 mmol) and (4-fluorophenyl)boronic acid (58.4 mg, 0.418 mmol) in 1,4-dioxane (4 mL) and H_2O (0.2 mL) was added sodium carbonate (73.8 mg, 0.696 mmol) and the mixture was degassed for 5 minutes, then $PdCl_2$(dppf)-CH_2Cl_2 adduct (22.73 mg, 0.028 mmol) was also added. The reaction mixture was degassed again and heated at 100 °C for 12 h. The volatiles were removed under reduced pressure. The crude solid was dissolved in ethyl acetate and washed with H_2O. The aqueous layer was back-extracted with ethyl acetate. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to obtain a brown solid (250 mg). The crude compound was purified by preparative HPLC (Condition P) to afford Example **270′** (11.7 mg, 0.030 mmol, 21.8 % yield). LCMS: *m/z* = 375.3 $[M+H]^+$; HPLC Ret. Time 1.69 min.. (HPLC Method H); ^1H

NMR (400 MHz, DMSO-d_6) δ ppm 8.65 (s, 1H), 8.31 (d, J = 9.6 Hz, 1H), 7.99 (s, 1H), 7.50-7.53 (m, 2H), 7.30 (d, J = 9.6 Hz, 1H), 7.12-7.16 (m, 2H), 4.17 (s, 2H), 0.73 (s, 9H) ppm.

Scheme 25

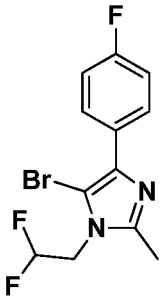


Intermediate 271A': 1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-2-methyl-1*H*-imidazole



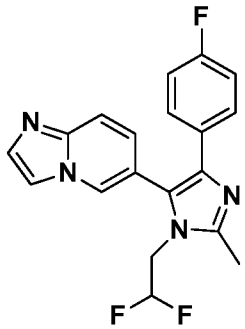
[0525] To a solution of 4-(4-fluorophenyl)-2-methyl-1*H*-imidazole (**reference**: WO 2014100533 A1) (0.35 g, 1.986 mmol) in THF (5 mL) was added TEA (0.554 mL, 3.97 mmol). The reaction mixture was cooled to 0 °C and 2,2-difluoroethyl trifluoromethanesulfonate (0.4 mL, 2.98 mmol) was added dropwise. The reaction was stirred at RT for 2 h, concentrated under reduced pressure and the resulting residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude residue, which was purified by silica gel chromatography (24 g CombiFlash® column, eluting with a gradient of 4 % MeOH in $CHCl_3$). Fractions containing the desired product were combined and evaporated to afford intermediate **271A'** (0.3 g, 62.9 % yield) as a yellow solid. LCMS m/z = 241.2 $[M+H]^+$; HPLC Ret. Time 1.731 min. (HPLC Method J).

Intermediate 271B′: 5-bromo-1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-2-methyl-1*H*-imidazole



[0526] To a solution of intermediate **271A′** (0.27 g, 1.124 mmol) in DCM (5 mL) at 0 °C was added NBS (0.220 g, 1.236 mmol) portion wise. The reaction mixture was stirred at RT for 15 min. diluted with water and extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to afford intermediate **271B′** (0.3 g, 84 % yield) as a white solid. LCMS: *m/z* = 321.0 $[M+H]^+$; HPLC Ret. Time 1.19 min. (HPLC Method G).

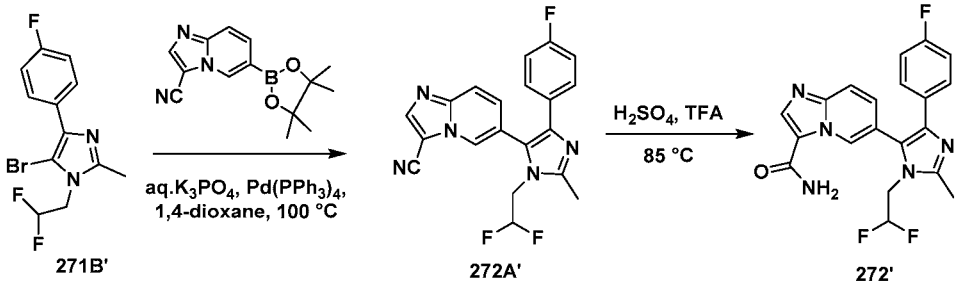
Example 271′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine



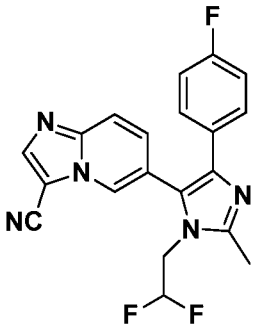
[0527] To a solution of intermediate **271B′** (0.16 g, 0.501 mmol) in 1,4-dioxane (2 mL) was added imidazo[1,2-*a*]pyridin-6-ylboronic acid (**reference**: CN 103275112 A) (0.162 g, 1.003 mmol) and K_3PO_4 (0.752 mL, 1.504 mmol) and the mixture was degassed with argon for 5 minutes. Then $Pd(Ph_3P)_4$ (0.058 g, 0.050 mmol) was added and the reaction mixture was heated at 100 °C for 4 h. The reaction mixture was diluted with water and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude compound, which was purified by preparative HPLC (Condition N). Fractions containing the desired product were combined and evaporated to afford Example **271′** (19 mg, 11 % yield). LCMS *m/z* = 357.1 $[M+H]^+$; HPLC Ret. Time 1.387 min. (HPLC Method H); ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.26

(s, 1H), 7.96 (s, 1H), 7.69-7.65 (m, 2H), 7.41 (q, J = 16.00 Hz, 2H), 7.13-7.03 (m, 3H), 6.32-6.05 (m, 1H), 4.36-4.29 (m, 2H), 2.45-2.4 (m, 3H).

Scheme 26

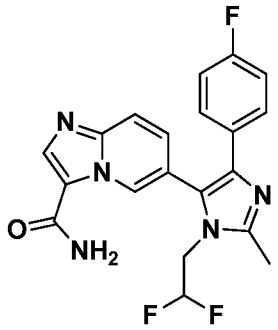


Intermediate 272A′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile



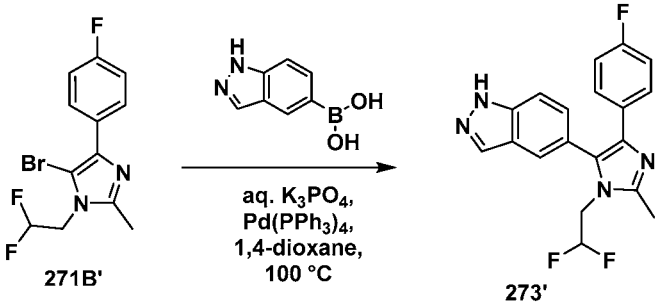
[0528] Intermediate **272A′** was synthesized by reacting intermediate **271B′** with 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile (**reference**: WO 2014/055955 A1) and by employing the experimental procedure described for Example **271′** in Scheme **25**. The crude compound was purified by preparative HPLC (Condition P). Fractions containing the desired product were combined and evaporated to afford Example **272A′** (150 mg, 78 % yield). LCMS: *m/z* = 382.1 $[M+H]^+$; HPLC Ret. Time 1.52 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.71 (s, 1H), 8.52 (s, 1H), 7.92-7.89 (m, 1H), 7.44-7.39 (m, 3H), 7.06-7.01 (m, 2H), 6.28-6.01 (m, 1H), 4.44-4.37 (m, 2H), 2.46(m, 3H).

Example 272′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

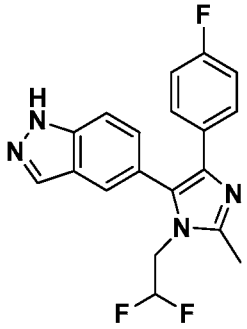


[0529] A solution of intermediate **272A′** (0.1 g, 0.262 mmol) in H_2SO_4 (0.063 ml, 1.180 mmol) and TFA (0.263 mL, 3.41 mmol) was heated at 85 °C for 2 h. The reaction mixture was diluted with water and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated to give the crude compound which was purified by preparative HPLC (Condition P). Fractions containing the desired product were combined and evaporated to afford Example **272′** (2 mg, 2 % yield). LCMS: *m/z* = 400.1 $[M+H]^+$; HPLC Ret. Time 1.35 min. (HPLC Method H); ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.44 (s, 1H), 8.40 (s, 1H), 8.0(bs, 1H), 7.84 (d, *J* = 12.00 Hz, 1H), 7.41-7.36 (m, 4H), 7.06-7.01 (m, 2H), 6.31-6.04 (m, 1H), 4.38-4.25 (m, 2H) 2.45(m, 3H).

Scheme 27

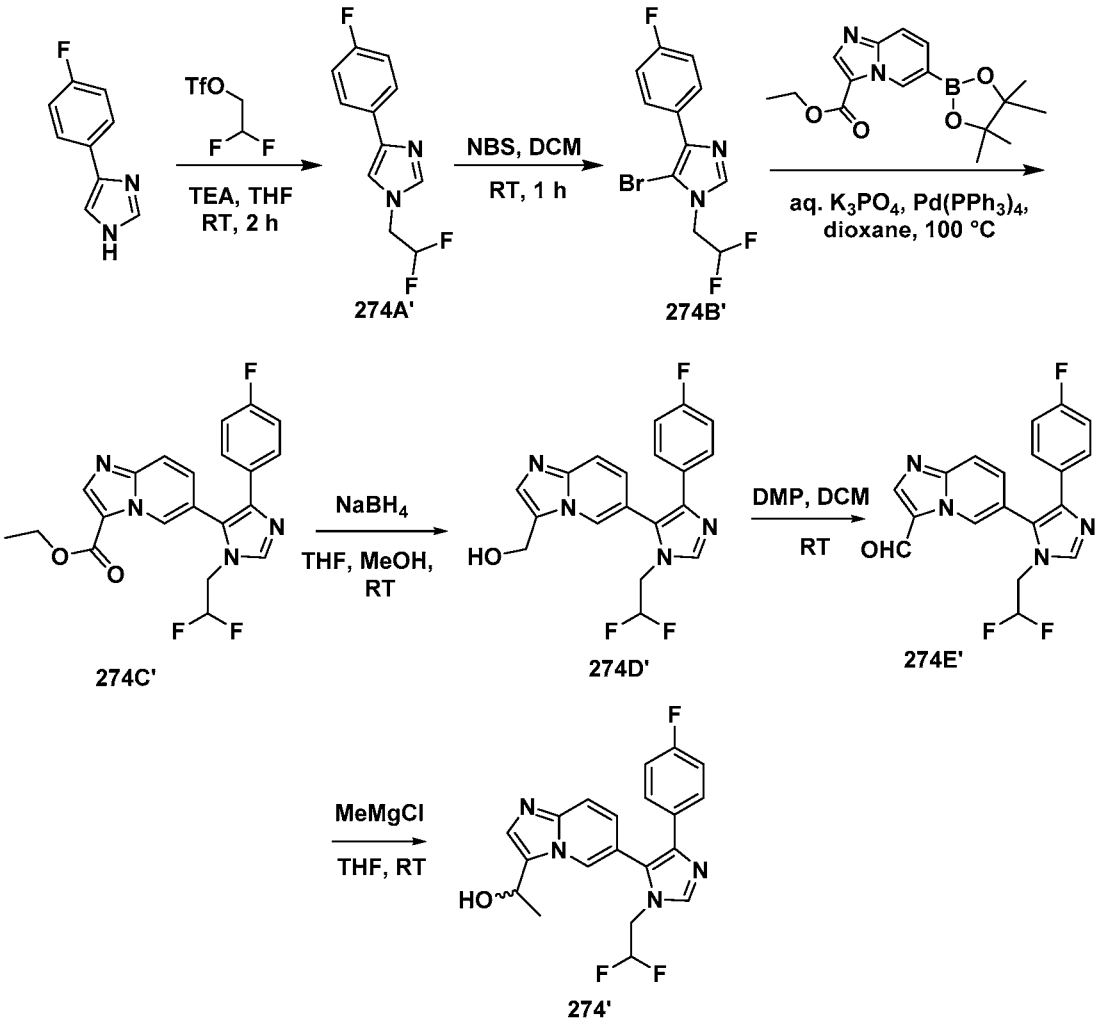


Example 273′: 5-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-2-methyl-1*H*-imidazol-5-yl)-1*H*-indazole

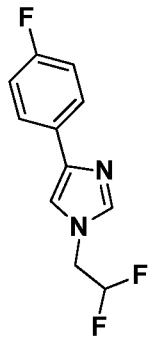


[0530] Example **273′** was synthesized by reacting intermediate **271B′** with (1*H*-indazol-5-yl)boronic acid (**reference**: WO 2012/078777 A1) and by employing the experimental procedure described for Example **271′** in Scheme **25**. The crude compound was purified by preparative HPLC (Condition P). Fractions containing the desired product were combined and evaporated to afford Example **273′** (5.1 mg, 5 % yield). LCMS: *m/z* = 357.1 $[M+H]^+$; HPLC Ret. Time 1.533 min. (HPLC Method H); ^{1}H NMR 400 MHz, DMSO-d_6) δ ppm 13.27 (s, 1H), 8.14 (s, 1H), 7.77 (s, 1H), 7.71-7.60 (m, 1H), 7.33-7.23 (m, 3H), 6.99-6.95 (m, 2H), 6.25-5.97 (m, 1H), 4.26-4.10 (m, 2H), 2.45 (s, 3H).

Scheme 28

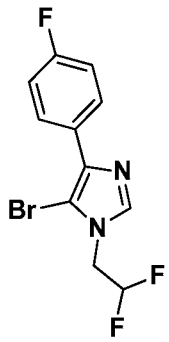


Intermediate 274A′: 1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazole



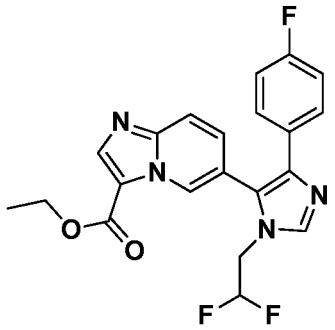
[0531] Intermediate **274A′** was synthesized by reacting 4-(4-fluorophenyl)-1*H*-imidazole with 2,2-difluoroethyl trifluoromethanesulfonate and by employing the experimental procedure described for intermediate **271A′** in Scheme **25**. The crude product was purified by silica gel chromatography (40 g CombiFlash® column, eluting with a gradient of 3 % MeOH in $CHCl_3$). Fractions containing the desired product were combined and evaporated to afford intermediate **274A′** (3.0 g, 71.7 % yield) as a brown oil. LCMS: *m/z* = 227.0 $[M+H]^+$; HPLC Ret. Time 1.89 min. (HPLC Method J).

Intermediate 274B′: 5-bromo-1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazole



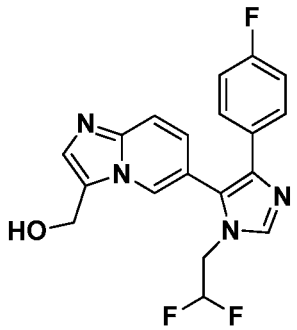
[0532] Intermediate **274B′** was synthesized by reacting intermediate **274A′** with NBS and by employing the experimental procedure described for intermediate **271B′** in Scheme **25**. Intermediate **274B′** (3.5 g, 86 % yield) as a brown oil. LCMS: *m/z* = 307.0 [M+H[$^+$; HPLC Ret. Time 2.395 min. (HPLC Method J).

Intermediate 274C′: ethyl 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxylate



[0533] To a solution of 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-*a*] pyridine-3-carboxylate (**reference**: WO 2013033203 A1) (1.554 g, 4.92 mmol) in 1,4-dioxane (10 mL) was added intermediate **274B′** (1 g, 3.28 mmol) and K_2CO_3 (4.92 mL, 9.83 mmol). The mixture was degassed with argon for 5 minutes and $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.268 g, 0.328 mmol) was added. The reaction mixture was heated at 100 °C for 4 h, diluted with water and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. Thefiltrate was concentrated under reduced pressure to give the crude compound, which was purified by preparative HPLC (Condition P). Fractions containing the desired product were combined and evaporated to afford intermediate **274C′** (815 mg, 60 % yield). LCMS: *m/z* = 415.1 $[M+H]^+$; HPLC Ret. Time 1.72 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.21 - 9.15 (m, 1H), 8.37 (s, 1H), 7.98 - 7.90 (m, 2H), 7.51 - 7.41 (m, 3H), 7.12 - 7.02 (m, 2H), 6.40 - 6.07 (m, 1H), 4.48 - 4.29 (m, 4H), 1.30 (s, 3H).

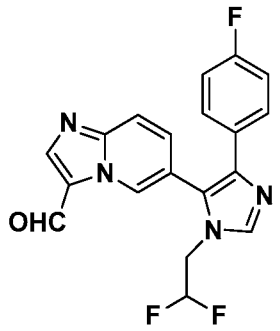
Intermediate 274D′: (6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl)methanol



[0534] To a solution of intermediate **274C′** (0.1 g, 0.241 mmol) in MeOH (1.5 mL) and THF (2.5 mL) at 0 °C was added $NaBH_4$ (10.96 mg, 0.290 mmol). The reaction mixture was stirred at RT for 1 h, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give the crude compound, which was purified by preparative HPLC

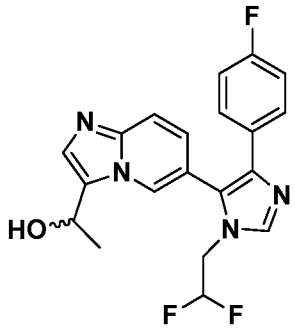
(Condition P). Fractions containing the desired product were combined and evaporated to afford intermediate **274D′** (6.4 mg, 7.12 % yield). LCMS: *m/z* = 373.1 $[M+H]^+$; HPLC Ret. Time 1.19 min. (HPLC Method H). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.52 - 8.49 (m, 1H), 7.95 - 7.93 (m, 1H), 7.73 - 7.66 (m, 1H), 7.61 - 7.57 (m, 1H), 7.51 - 7.44 (m, 2H), 7.16 - 7.04 (m, 3H), 6.37 - 6.05 (m, 1H), 5.23 - 5.16 (m, 1H), 4.82 - 4.77 (m, 2H), 4.47 - 4.34 (m, 2H).

Intermediate 274E′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbaldehyde



[0535] To a solution of intermediate **274D′** (0.2 g, 0.537 mmol) in DCM (1 mL) at 0 °C was added DMP (0.342 g, 0.806 mmol). The reaction mixture was stirred at RT for 1 h, diluted with water and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to afford intermediate **274E′** (0.2 g, crude). LCMS: *m/z* = 371.4 $[M+H]^+$; HPLC Ret. Time 0.97 min. (HPLC Method G).

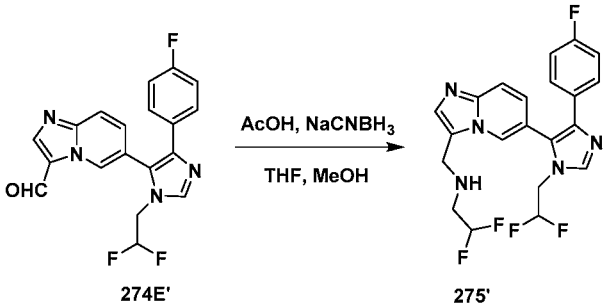
Example 274′: 1-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl)ethanol



[0536] To a solution of intermediate **274E′** (0.1 g, 0.270 mmol) in THF (2 mL) at 0 °C was added methylmagnesium chloride (0.900 mL, 2.70 mmol, 3M solution in THF). The reaction mixture was stirred at RT for 2 h, quenched with aqueous NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4,

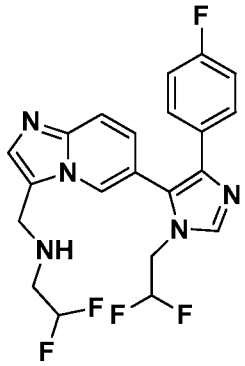
filtered and the filtrate was concentrated under reduced pressure to give the crude product, which was purified via preparative HPLC (condition P). Fractions containing the desired product were combined and evaporated to afford Example **274′** (5.2 mg, 4.98 % yield). LCMS: *m/z* = 387.1 $[M+H]^+$; HPLC Ret. Time 1.33 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.52 - 1.59 (m, 3 H) 4.33 - 4.46 (m, 2 H) 5.08 - 5.16 (m, 1 H) 5.32 - 5.37 (m, 1 H) 6.05 - 6.38 (m, 1 H) 7.03 - 7.19 (m, 3 H) 7.43 - 7.50 (m, 2 H) 7.56 - 7.63 (m, 1 H) 7.67 - 7.72 (m, 1 H) 7.92 - 7.96 (m, 1 H) 8.51 - 8.56 (m, 1 H).

Scheme 29



274E′ 275′

Example 275′: *N*-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl)methyl)-2,2-difluoroethanamine

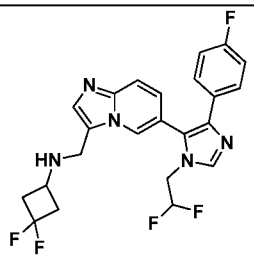


[0537] To a solution of intermediate **274E′** (0.1 g, 0.270 mmol) in THF (1 mL) and MeOH (1 mL) was added 2,2-difluoroethanamine (0.024 g, 0.297 mmol) and acetic acid (0.015 mL, 0.270 mmol). The reaction mixture was stirred at RT for 16 h. After that the reaction was cooled to 0 °C, $NaCNBH_3$ (0.051 g, 0.810 mmol) was added and the mixture was stirred at RT for 5 h. The reaction mixture was quenched with aq. $NaHCO_3$ and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by preparative HPLC (Condition P). Fractions containing the desired product were combined and evaporated to afford Example **275′** (6.0 mg, 5.10 % yield). LCMS: *m/z* = 436.2 $[M+H]^+$; HPLC Ret. Time 1.59 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ

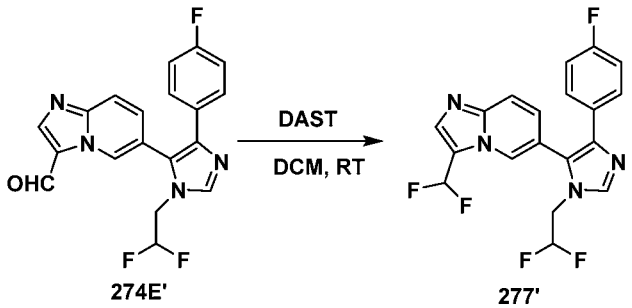
ppm 2.8 - 2.9 (m, 2 H) 4.18 (s, 2 H) 4.38 - 4.46 (m, 2H) 5.77 - 6.36 (m, 2 H) 7.08 (t, J = 8.83 Hz, 2 H) 7.17 (d, J = 9.17 Hz, 1 H) 7.49 (dd, J = 8.56, 5.75 Hz, 2 H) 7.65 (s, 1 H) 7.71 (d, J = 9.23 Hz, 1 H) 7.96 (s, 1 H) 8.65 (s, 1 H).

[0538] Compound shown in **Table 19** has been prepared in a manner similar to Example **275′** using intermediate **274E′**, amine and $NaCNBH_3$.

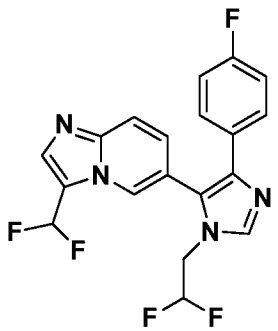
Table 19

Ex.	Structure	Name	$[M+H]^+$	Ret. Time (min.)	HPLC Method
276′		*N*-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl)methyl)-3,3-difluorocyclobutanamine	462.1	1.716 0.935	H I

Scheme 30



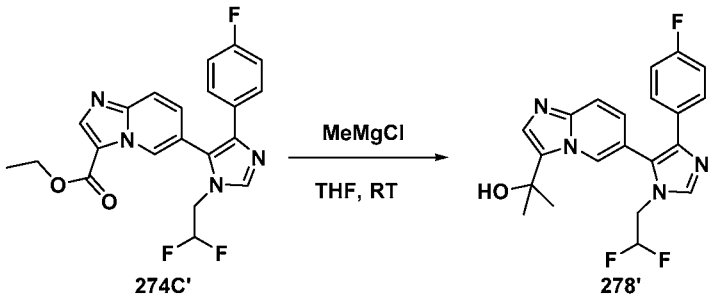
Example 277′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-3-(difluoromethyl)imidazo [1,2-*a*]pyridine



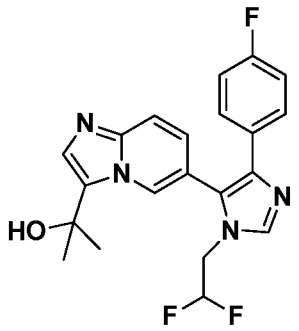
[0539] To a solution of intermediate **274E′** (0.1 g, 0.270 mmol) in DCM (2 mL) at 0 °C was added DAST (0.071 mL, 0.540 mmol). The reaction mixture was stirred at RT for 2 h, quenched with aqueous $NaHCO_3$ solution and extracted with DCM. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure to give the crude product, which was purified by preparative HPLC (Condition L).

Fractions containing the desired product were combined and evaporated to afford Example **277′** (0.026 g, 24.54 % yield). LCMS *m/z* = 393.1 $[M+H]^+$; HPLC Ret. Time 1.65 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.64 - 8.68 (m, 1 H) 8.04 - 8.11 (m, 2 H) 7.83 - 7.88 (m, 1 H) 7.39 - 7.49 (m, 2 H) 6.92 - 7.23 (m, 4 H) 6.07 - 6.39 (m, 1 H) 4.36 - 4.50 (m, 2 H).

Scheme 31

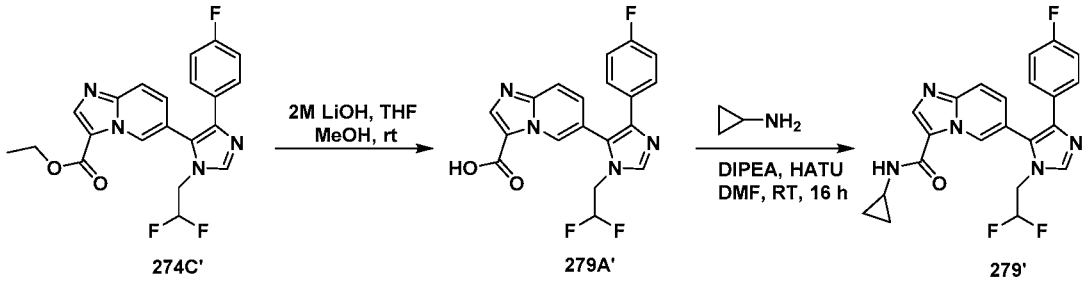


Example 278′: 1-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl)ethanol

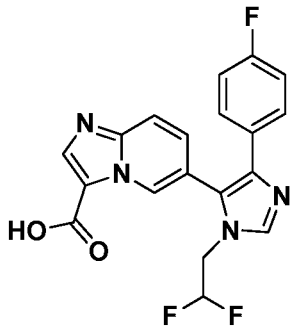


[0540] To a solution of intermediate **274C′** (0.1 g, 0.241 mmol) in THF (2 mL) at 0 °C was added methylmagnesium chloride (0.804 mL, 2.413 mmol; 3M solution in THF). The reaction was warmed to RT, stirred for 2 h, quenched with aqueous NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give the crude product, which was purified by preparative HPLC (Condition N). Fractions containing the desired product were combined and evaporated to afford Example **278′** (4.2 mg, 4.35 % yield). LCMS: *m/z* = 401.1 $[M+H]^+$; HPLC Ret. Time 1.35 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.07 - 9.01 (m, 1H), 8.10 - 7.99 (m, 3H), 7.79 - 7.72 (m, 1H), 7.51 - 7.42 (m, 2H), 7.14 - 7.04 (m, 2H), 6.43 - 6.09 (m, 1H), 5.7 (s, 1H), 4.50 - 4.36 (m, 2H), 1.64 - 1.59 (m, 6H).

Scheme 32

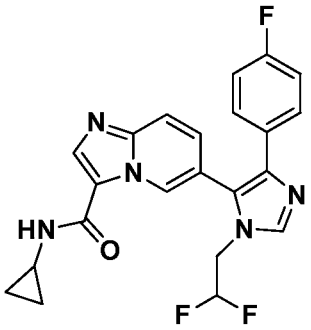


Intermediate 279A′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxylic acid



[0541] To a solution of intermediate **274C′** (0.2 g, 0.483 mmol) in THF (4 mL) and MeOH (2 mL) was added 2M aq. LiOH (0.724 mL, 1.448 mmol) solution. The reaction mixture was stirred at RT for 16 h concentrated to dryness, and the resulting residue was suspended in water and acidified with 1.5 N aq. HCl. The solid precipitated out was filtered and dried to afford intermediate **279A′** (0.15 g, 80 % yield) as a pale yellow solid. LCMS: *m/z* = 387.2 $[M+H]^+$; HPLC Ret. Time 1.87 min. (HPLC Method J).

Example 279′: *N*-cyclopropyl-6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

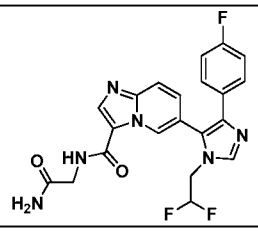


[0542] To a solution of intermediate **279A′** (0.05 g, 0.129 mmol) in DMF (1 mL) was added cyclopropanamine (0.011 g, 0.194 mmol), DIPEA (0.068 mL, 0.388 mmol) and HATU (0.098 g, 0.259 mmol). The reaction mixture was stirred at RT for 16 h, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over

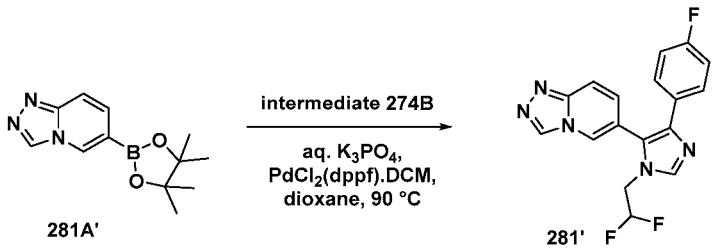
Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give the crude product, which was purified by preparative HPLC (Condition L). Fractions containing the desired product were combined and evaporated to afford Example **279′** (0.015 g, 27.2 % yield). LCMS: *m/z* = 426.2 $[M+H]^+$; HPLC Ret. Time 1.29 min. (HPLC Method H); ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.53 (d, *J* = 0.79 Hz, 1 H) 8.6 - 8.61 (m, 1 H) 8.41 (s, 1 H) 8.29 (s, 1 H) 7.86 - 7.91 (m, 1 H) 7.42 - 7.48 (m, 3 H) 7.08 - 7.15 (m, 2 H) 6.09 - 6.41 (m, 1 H) 4.39 - 4.52 (m, 2 H) 2.76 - 2.87 (m, 1 H) 0.71 - 0.77 (m, 2 H) 0.53 - 0.60 (m, 2 H).

[0543] The compound shown in **Table 20** has been prepared in a manner similar to Example **279′** by amide bond coupling between intermediate **279A′** and the amine.

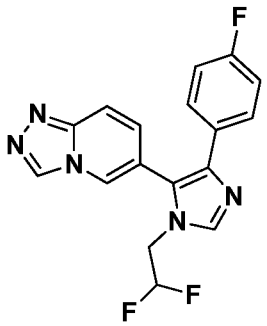
Table 20

Ex.	Structure	Name	$[M+H]^+$	Ret. Time (min.)	HPLC Method
280′		*N*-(2-amino-2-oxoethyl)-6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	443.2	0.989 0.597	H I

Scheme 33



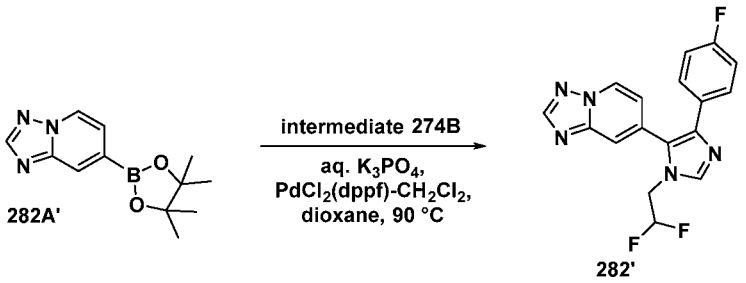
Example 281′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[4,3-*a*]pyridine



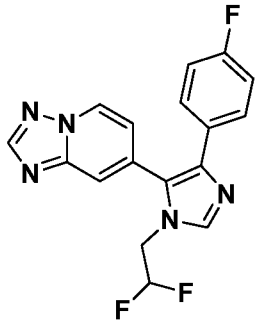
[0544] Example **281′** was synthesized by reacting intermediate **281A′** (**reference**: WO2013086397 A1) with intermediate **274B′** and by employing the experimental procedure described for Example **271′** in Scheme **25**.. The crude compound was purified by preparative

HPLC (Condition O). Fractions containing the desired product were combined and evaporated to afford Example **281′** (0.02 g, 0.058 mmol, 17.77 % yield). LCMS *m/z* = 344.1 $[M+H]^+$; HPLC Ret. Time 1.13 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.26 (s, 1H), 8.68 (s, 1H), 7.94 (s, 2H), 7.52 - 7.43 (m, 2H), 7.26 - 7.18 (m, 1H), 7.09 (s, 2H), 6.38 - 6.05 (m, 1H), 4.51 - 4.37 (m, 2H).

Scheme 34

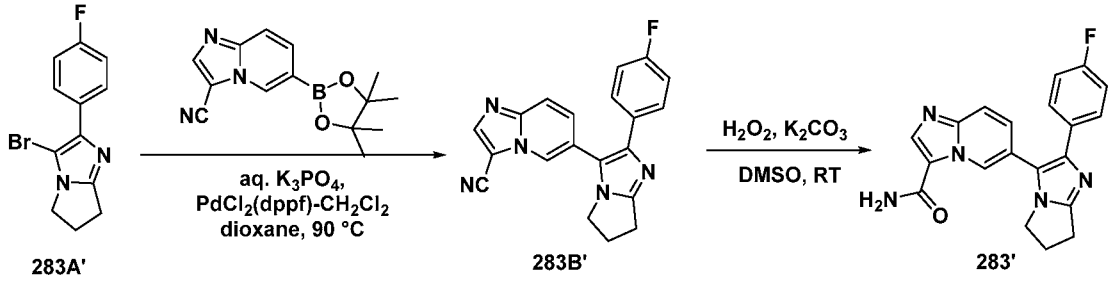


Example 282′: 7-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-[1,2,4]triazolo[1,5-*a*]pyridine

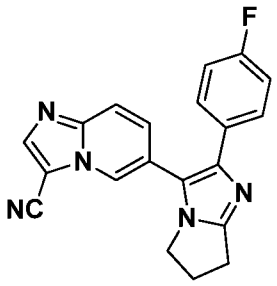


[0545] Example **282′** was synthesized by reacting intermediate **282A′** (**reference**: WO 2013086397 A1) with intermediate **274B′** and by employing the experimental procedure described for Example **271′** in Scheme **25**. The crude compound was purified by preparative HPLC (Condition O). Fractions containing the desired product were combined and evaporated to afford Example **282′** (0.023 g, 20.44 % yield). LCMS: *m/z* = 344.1 $[M+H]^+$; HPLC Ret. Time 1.31 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.04 (d, *J* = 6.8 Hz, 1H), 8.60 (s, 1H), 7.97 (s, 2H), 7.43 (dd, *J* = 8.8, 5.6 Hz, 2H), 7.09 (t, *J* = 8.9 Hz, 3H), 6.38 - 6.05 (m, 1H), 4.54 - 4.41 (m, 2H).

Scheme 35

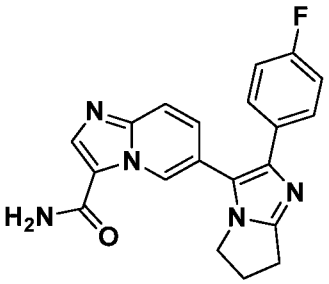


Intermediate 283B′: 6-(2-(4-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-3-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile



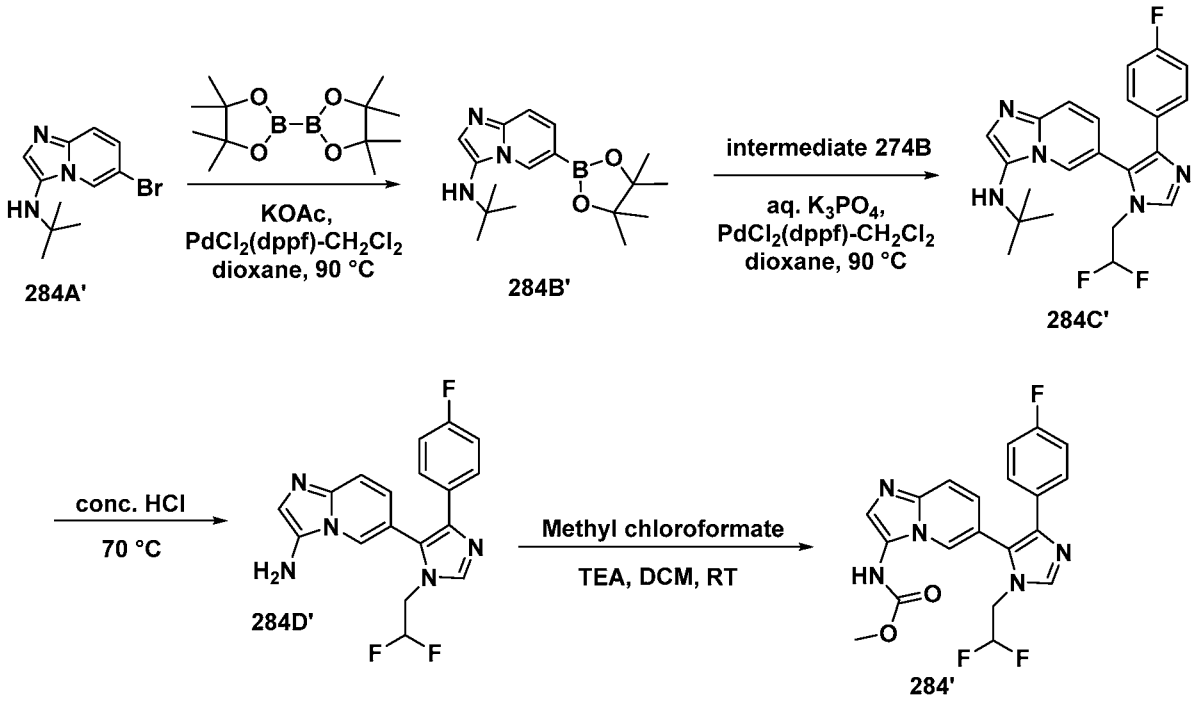
[0546] Compound **283′** was synthesized by reacting 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile (**reference**: WO 2014/055955 A1) and intermediate **283A′** (**reference**: WO 2014100533 A1) by employing the experimental procedure described in Scheme **25** for Example **271′**. The crude compound was purified by preparative HPLC (Condition P). Fractions containing the desired product were combined and evaporated to afford intermediate **283B′** (156 mg, 64.57 % yield). LCMS *m/z* = 344.1 $[M+H]^+$; HPLC Ret. Time 1.139 min. (HPLC Method H); ^{1}H NMR 400 MHz, DMSO-d_6) δ ppm 8.72 (s, 1H), 8.50 (s, 1H), 7.87-7.89 (m, 1H), 7.48-7.52 (m, 2H), 7.43-7.45 (m, 1H), 7.10 (t, J = 16.00 Hz, 2H), 4.03 (t, J = 12.00 Hz, 2H), 2.88 (t, J = 16.00 Hz, 2H), 2.55-2.61 (m, 2H).

Compound 283′: 6-(2-(4-fluorophenyl)-6,7-dihydro-5*H*-pyrrolo[1,2-*a*]imidazol-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

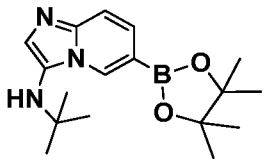


[0547] To a solution of intermediate **283B'** (0.2 g, 0.582 mmol) in DMSO (1 mL) was added K_2CO_3 (0.282 g, 2.039 mmol). The mixture was cooled to 0 °C and 30 % aq. solution of H_2O_2 (0.535 mL, 17.47 mmol) was added. The reaction mixture was stirred at RT for 2 h. It was then diluted with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure to give the crude product, which was purified by preparative HPLC (Condition N). Fractions containing the desired product were combined and evaporated to afford Example **283'** (9 mg, 4.28 % yield). LCMS: *m/z* = 362.1 $[M+H]^+$; HPLC Ret. Time 1.256 min. (HPLC Method H); ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.53 - 9.57 (m, 1 H) 8.35 - 8.39 (m, 1 H) 8.0 (bs, 1H) 7.73 - 7.80 (m, 1 H) 7.45 - 7.52 (m, 2 H) 7.36 - 7.41 (m, 2 H) 7.04 - 7.12 (m, 2 H) 3.92 - 3.99 (m, 2 H) 2.82 - 2.91 (m, 2 H) 2.54 - 2.60 (m, 2 H).

Scheme 36



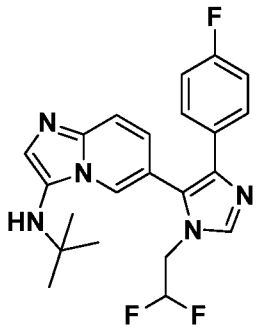
Intermediate 284B': *N*-(*tert*-butyl)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-*a*]pyridin-3-amine



[0548] To a solution of intermediate **284A'** (**reference**: WO2013/64984 A1) (1.2 g, 4.48 mmol) in dioxane (10 mL) was added 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3-dioxolane)

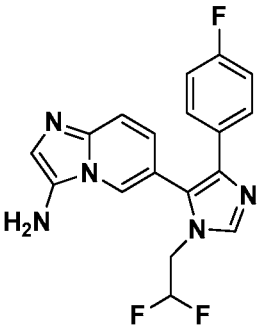
(1.136 g, 4.48 mmol), K_3PO_4 (1.318 g, 13.43 mmol) and $PdCl_2(dppf)$-CH_2Cl_2 adduct (0.110 g, 0.134 mmol). After degassing with argon, the reaction mixture was heated at 90 °C for 16 h. The reaction mixture was filtered through a pad of Celite® and the pad was washed with DCM (500 mL). The combined filtrates were concentrated under reduced pressure to afford **284B′** as a dark brown oil, which was used in the next step without further purification. LCMS: *m/z* = 316.1 $[M+H]^+$; HPLC Ret. Time 0.82 min. (HPLC Method G).

Intermediate 284C′: *N*-(*tert*-butyl)-6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-amine



[0549] Intermediate **284C′** was synthesized by reacting intermediate **284B′** with intermediate **274B′** and by employing the experimental procedure described for Example **271′** in Scheme **25**. The crude compound was purified by preparative HPLC (Condition P). Fractions containing the desired product were combined and evaporated to afford intermediate **284C′** (305 mg, 45 % yield). LCMS: *m/z* = 414.3 $[M+H]^+$; HPLC Ret. Time 1.60 min. (HPLC Method H); ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.35 - 8.41 (m, 1 H) 7.90 - 7.97 (m, 1 H) 7.59 - 7.66 (m, 1 H) 7.40 - 7.47 (m, 2 H) 7.27 - 7.32 (m, 1 H) 7.02 - 7.16 (m, 3 H) 6.05 - 6.37 (m, 1 H) 4.57 - 4.60 (m, 1 H) 4.31 - 4.44 (m, 2 H) 1.06 - 1.10 (m, 9 H).

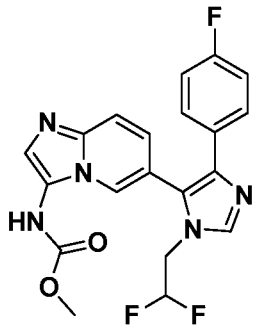
Intermediate 284D′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-amine



[0550] A solution of Example **284C′** (0.2 g, 0.484 mmol) in conc. aqueous HCl (1.2 mL, 4.84 mmol) was stirred at 70 °C for 1 h. The reaction mixture was basified using 10 % NaOH

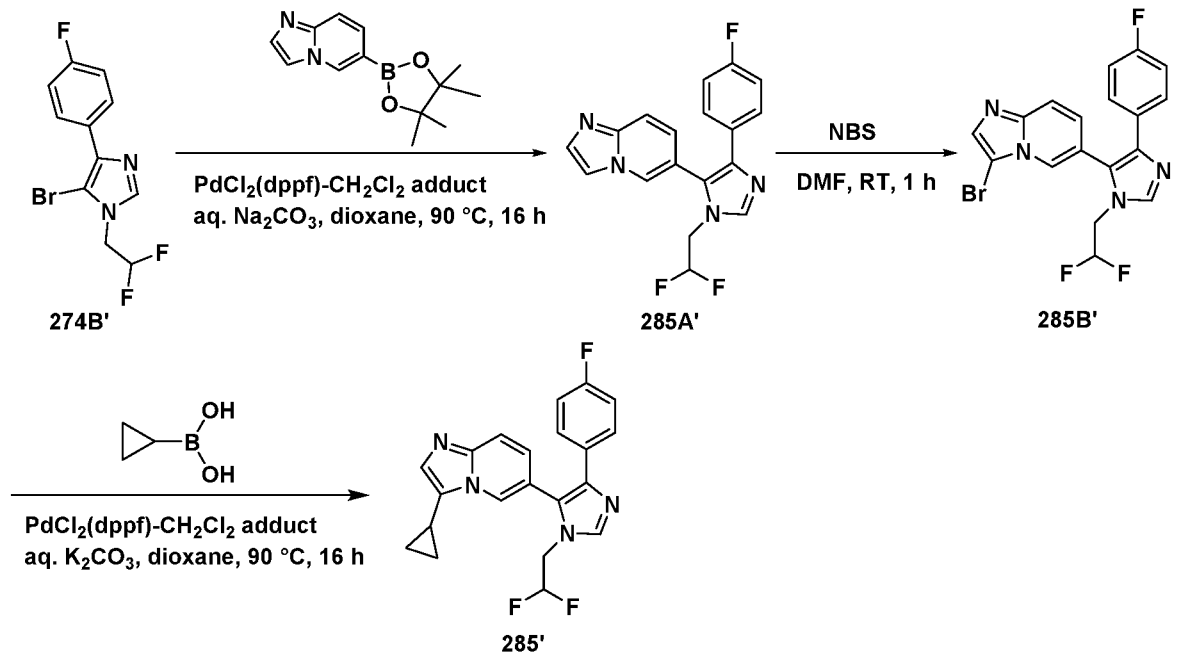
solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure to afford intermediate **284D′** (0.1 g, 57.9 % yield) as a red oil. LCMS: *m/z* = 358.3 $[M+H]^+$; HPLC Ret. Time 0.87 min. (HPLC Method G).

Example 284′: methyl (6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl)carbamate

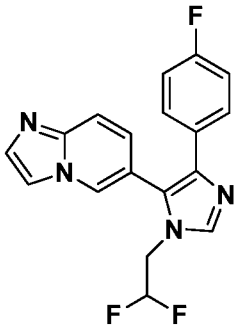


[0551] To a solution of intermediate **284D′** in DCM (1 mL) was added TEA (0.047 mL, 0.336 mmol). The reaction mixture was cooled to 0 °C and methyl chloroformate (8.67 µL, 0.112 mmol) was added. The reaction mixture was stirred at RT for 1 h, quenched with aq. $NaHCO_3$ solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give the crude compound, which was purified by preparative HPLC (Condition P). Fractions containing the desired product were combined and evaporated to afford Example **284′** (6.0 mg, 13 % yield). LCMS: *m/z* = 416.3 $[M+H]^+$; HPLC Ret. Time 1.26 min. (HPLC Method H); ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.6 (bs, 1H), 8.31 - 8.36 (m, 1 H) 7.94 (s, 1 H) 7.65 - 7.70 (m, 1 H) 7.52 (s, 3 H) 7.06 - 7.14 (m, 3 H) 6.06 - 6.39 (m, 1 H) 4.32 - 4.45 (m, 2 H) 3.64 - 3.70 (m, 3 H).

Scheme 37

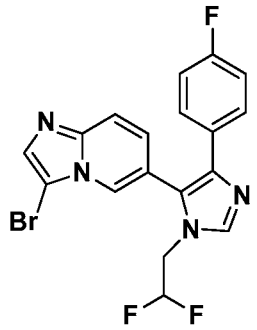


Intermediate 285A′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine



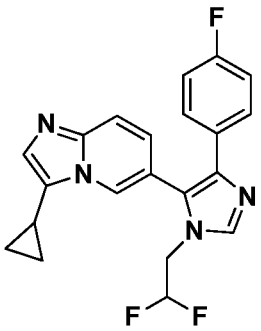
[0552] Intermediate **285A′** was synthesized by reacting 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-*a*]pyridine (**reference**: CN 103275112 A) with intermediate **274B′** and by employing the experimental procedure described for Example **271′** in Scheme **25**. The crude product was purified by silica gel chromatography (40 g CombiFlash® column, eluting with a gradient of 4 % MeOH in $CHCl_3$). Fractions containing the desired product were combined and evaporated to afford intermediate **285A′** (0.4 g, 35.7 % yield) as a pale yellow solid. LCMS: *m/z* = 343.0 [M+H[$^+$]; HPLC Ret. Time 1.345 min. (HPLC Method J).

Intermediate 285B′: 3-bromo-6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine



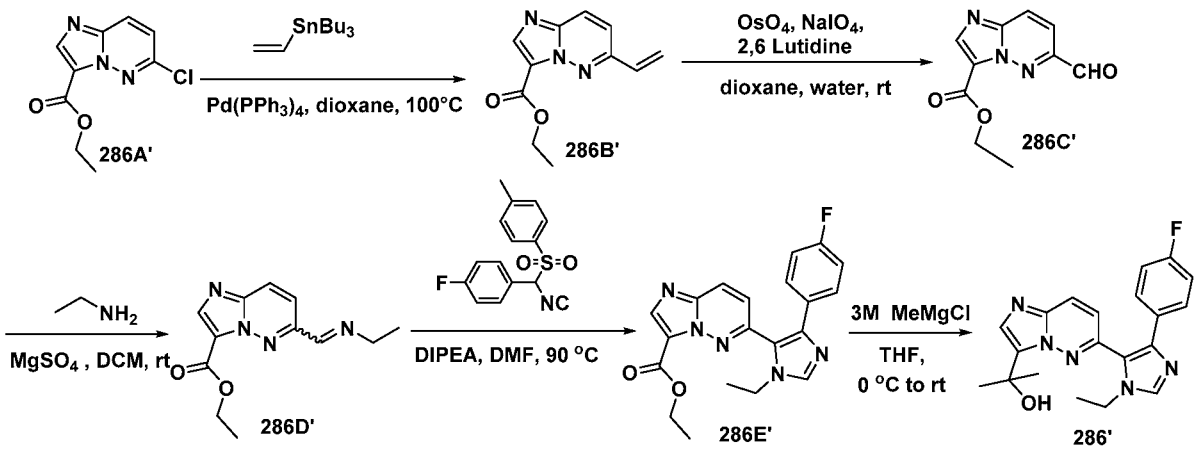
[0553] Intermediate **285B′** was synthesized by reacting Example **285A′** with NBS and by employing the experimental procedure described for intermediate **236C′** in Scheme **22.** Intermediate **285B′** was obtained as a brown oil. LCMS: *m/z* = 423.2 $[M+H]^+$; HPLC Ret. Time 1.08 min. (HPLC Method G).

Example 285′: 3-cyclopropyl-6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine

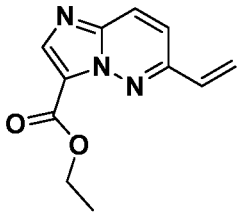


[0554] Example **285′** was synthesized by a Suzuki coupling reaction between intermediate **285B′** and cyclopropylboronic acid and by employing the experimental procedure described for Example **271′** in Scheme **25**. The crude compound was purified by preparative HPLC (Condition N). Fractions containing the desired product were combined and evaporated to afford Example **285′** (5 mg, 3.67 % yield). LCMS: *m/z* = 383.2 $[M+H]^+$; HPLC Ret. Time 1.49 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.54 (dd, *J* = 1.51, 1.00 Hz, 1 H) 7.95 (s, 1 H) 7.66 (dd, *J* = 9.22, 0.88 Hz, 1 H) 7.50 (dd, *J* = 9.00, 5.62 Hz, 2 H) 7.42 (d, *J* = 0.88 Hz, 1 H) 7.05 - 7.17 (m, 3 H) 6.08 - 6.41 (m, 1 H) 4.37 - 4.49 (m, 2 H) 1.95 - 2.04 (m, 1 H) 0.96 (dd, *J* = 8.16, 2.13 Hz, 2 H) 0.66 (dd, *J* = 5.05, 2.10 Hz, 2 H).

Scheme 38

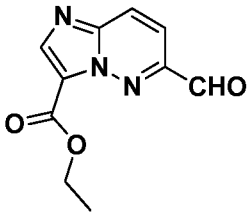


Intermediate 286B′: ethyl 6-vinylimidazo[1,2-*b*]pyridazine-3-carboxylate



[0555] To a solution of intermediate **286A′** (**reference**: WO 2015026574 A1) (3.0 g, 13.30 mmol) in 1,4-dioxane (10 mL) was added tributyl(vinyl)tin (4.68 mL, 15.96 mmol). The mixture was degassed with argon for 5 minutes and $Pd(PPh_3)_4$ (0.768 g, 0.665 mmol) was added. The reaction mixture was heated at 100 °C for 12 h and concentrated under reduced pressure to give the crude residue, whichwas purified by silica gel chromatography (80 g CombiFlash® column, eluting with a gradient of 20-30 % EtOAc in petroleum ether). Fractions containing the desired product were combined and evaporated to afford intermediate **286B′** (3.0 g, 8.98 mmol, 67.5 % yield) as a pale yellow solid. LCMS: *m/z* = 218.0 $[M+H]^+$; HPLC Ret. Time 1.528 min. (HPLC Method J).

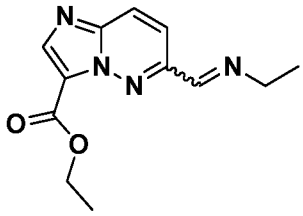
Intermediate 286C′: ethyl 6-formylimidazo[1,2-*b*]pyridazine-3-carboxylate



[0556] To a solution of intermediate **286B′** (2.0g , 18.41 mmol) in dioxane (60 mL) and water (17.4 mL) were added 2,6-lutidine (2.145 mL, 18.41 mmol), sodium periodate (7.88 g, 36.8 mmol), and 4 % aq. solution of osmium tetroxide (2.312 mL, 0.184 mmol). The reaction

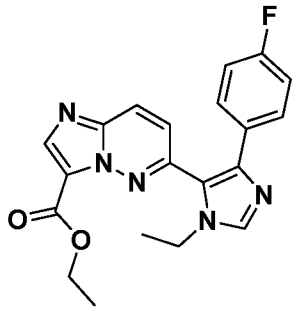
mixture was stirred at RT for 4 h, diluted with water and DCM. The layers were separated. The aqueous layer was extracted with DCM. The combined organic layers were washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated and the residue was purified by silica gel chromatography (40 g RediSep® column, eluting with a gradient from 40-50 % EtOAc in hexanes). Fractions containing the product were combined and evaporated to afford **286C′** (1.2 g, 5.47 mmol, 59.5 % yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 10.02 (d, J = 0.8 Hz, 1H), 8.58 (s, 1H), 8.47 (dd, J = 9.4, 0.8 Hz, 1H), 7.83 (d, J = 9.4 Hz, 1H), 4.40 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.2 Hz, 3H).

Intermediate 286D′: ethyl 6-((ethylimino)methyl)imidazo[1,2-*b*]pyridazine-3-carboxylate



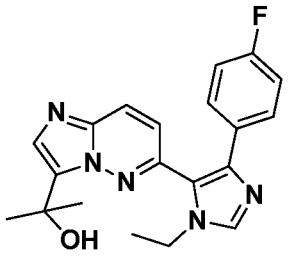
[0557] Intermediate **286D′** was synthesized from intermediate **286C′** and ethylamine by employing the experimental procedure described for intermediate **1E** in Scheme **1**. Intermediate **286D′** (0.2 g, 80 % yield) was obtained as an off white solid. LCMS: *m/z* = 247.0 $[M+H]^+$; HPLC Ret. Time 0.98 min. (HPLC Method G).

Intermediate 286E′: ethyl 6-(1-ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxylate



[0558] Intermediate **286E′** was synthesized by reacting **286D′** with 1-fluoro-4-(isocyano(tosyl)methyl)benzene and by employing the experimental procedure described for Example **1′** in Scheme **1**. Intermediate **286E′** (154 mg, 33.0 % yield). LCMS: *m/z* = 380.3 $[M+H]^+$; HPLC Ret. Time 1.10 min. (HPLC Method G).

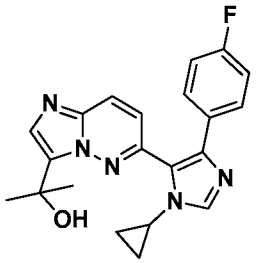
Example 286′: 2-(6-(1-ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)propan-2-ol



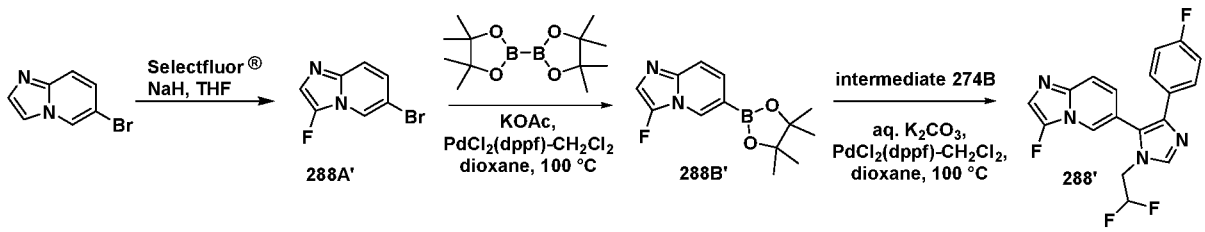
[0559] Example **286′** was synthesized from intermediate **286E′** by employing the experimental procedure described for Example **278′** in Scheme **31**. The crude residue was purified by preparative HPLC (Condition L). Fractions containing the desired product were combined and evaporated to afford Example **286′** (48.8 mg, 38.6 % yield). LCMS: *m/z* = 366.1 $[M+H]^+$; HPLC Ret. Time 1.397 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.11 (d, *J* = 9.5 Hz, 1H), 8.04 (s, 1H), 7.72 (s, 1H), 7.48 - 7.41 (m, 2H), 7.17 - 7.09 (m, 2H), 7.04 (d, *J* = 9.5 Hz, 1H), 5.38 (br. s., 1H), 4.19 (q, *J* = 7.2 Hz, 2H), 1.63 (s, 6H), 1.24 (t, *J* = 7.1 Hz, 3H).

[0560] The compound shown in **Table 21** has been prepared in a manner similar to Example **286′** using intermediate **286C′**, cyclopropylamine, 1-fluoro-4-(isocyano(tosyl)methyl)benzene and then reacting with MeMgBr.

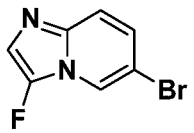
Table 21

Ex.	Structure	Name	$[M+H]^+$	Ret. Time (min.)	HPLC Method
287′		2-(6-(1-cyclopropyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)propan-2-ol	378.1	1.462 0.935	H I

Scheme 39

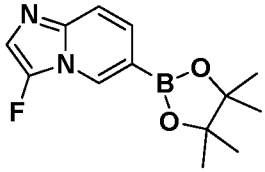


Intermediate 288A′: 6-bromo-3-fluoroimidazo[1,2-*a*]pyridine



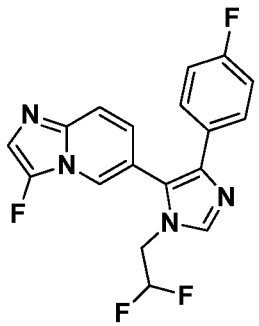
[0561] To a solution of 6-bromoimidazo[1,2-*a*]pyridine (0.1 g, 0.508 mmol) in THF (10 mL) at 0 °C was added NaH (0.018 g, 0.750 mmol, 60 % in mineral oil). The reaction mixture was stirred at RT for 30 min. and to it was added Selectfluor® (0.387 g, 1.092 mmol) in acetonitrile (5 mL). The reaction mixture was stirred at RT for 18 h, quenched with saturated aq. NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the filtrate concentrated under reduced pressure to give intermediate **288A′** (110 mg, 40.3 % yield). LCMS: *m/z* = 215.3 $[M+H]^+$; HPLC Ret. Time 1.06 min. (HPLC Method G).

Intermediate 288B′: 3-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-*a*]pyridine



[0562] Intermediate **288B′** was synthesized by reacting intermediate **288A′** with 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3-dioxolane) and by employing the experimental procedure described for intermediate **284B′** in Scheme **36**. Intermediate **288B′** (230 mg, 75 % yield). LCMS: *m/z* = 263.4 $[M+H]^+$; HPLC Ret. Time 1.28 min. (HPLC Method G).

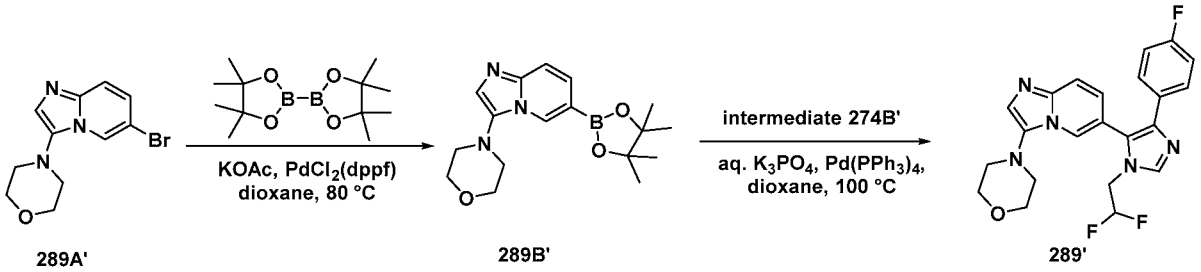
Example 288′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-3-fluoroimidazo[1,2-*a*]pyridine



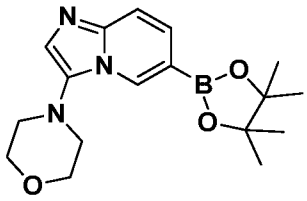
[0563] Example **288′** was synthesized by reacting intermediate **288B′** with intermediate **274B′** and by employing the experimental procedure described for intermediate **274C′** in Scheme **28**. The crude residue which was purified by preparative HPLC (Condition O). Fractions containing the desired product were combined and evaporated to afford Example

288′. LCMS: *m/z* = 361.1 $[M+H]^+$; HPLC Ret. Time 1.55 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.45 (s, 1H), 7.92 (s, 1H), 7.65 - 7.59 (m, 1H), 7.51 - 7.41 (m, 3H), 7.13 - 7.01 (m, 3H), 6.38 - 6.01 (m, 1H), 4.43 (dd, *J* = 16.0, 3.1 Hz, 1H).

Scheme 40

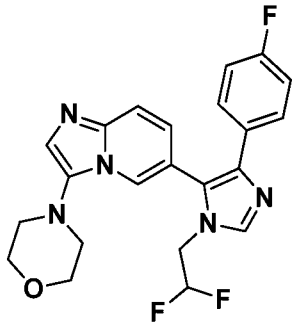


Intermediate 289B′: 4-(6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-*a*]pyridin-3-yl)morpholine



[0564] Intermediate **289B′** was synthesized by reacting intermediate **289A′** (**reference**: *J. Med. Chem.* **2011**, *54*, 2455–2466) with 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3-dioxolane) and by employing the experimental procedure described for intermediate **284B′** in Scheme **36**.. LCMS: *m/z* = 330.5 $[M+H]^+$; HPLC Ret. Time 1.13 min. (HPLC Method G).

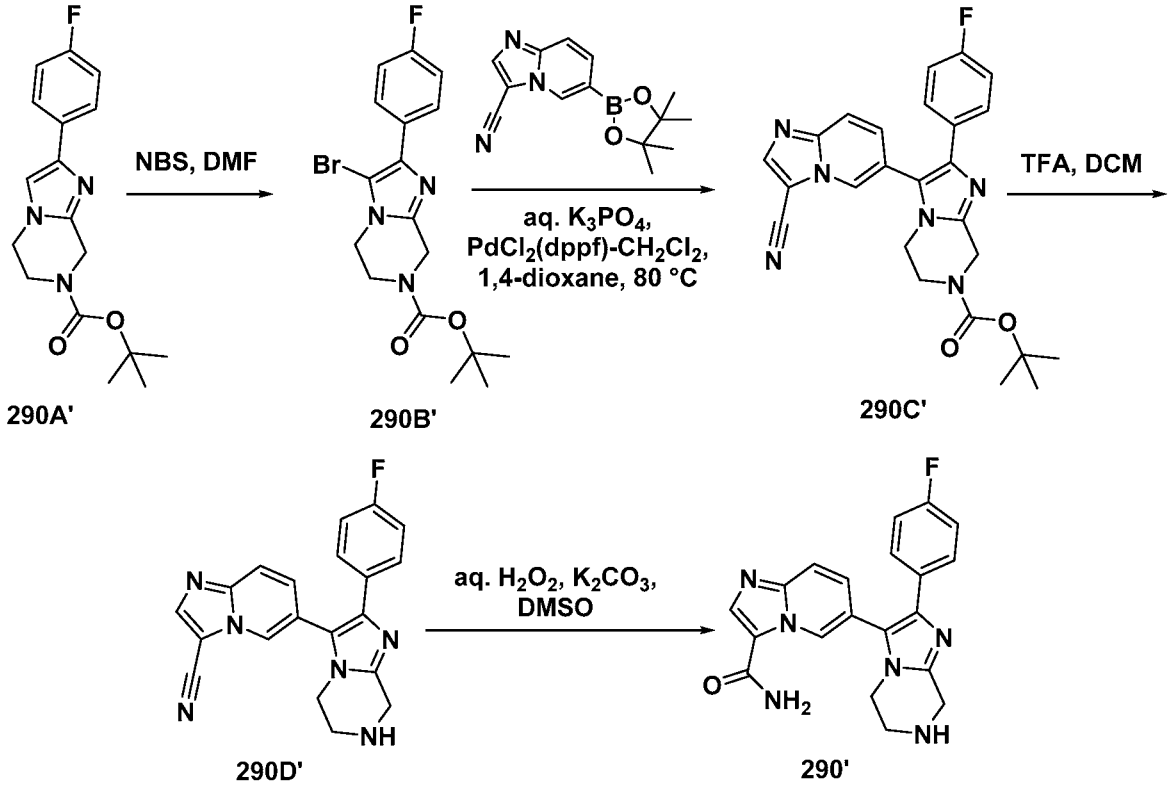
Example 289′: 4-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridin-3-yl)morpholine



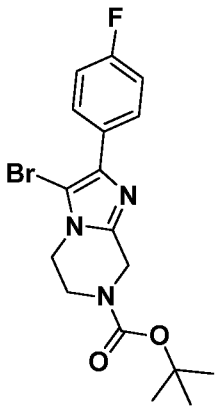
[0565] Example **289′** was synthesized by reacting intermediate **299B′** with intermediate **274B′** and by employing the experimental procedure described for Example **271′** in Scheme **25**. The crude compound was purified by preparative HPLC (Condition-P). Fractions containing the desired product were combined and evaporated to afford Example **289′**. LCMS: *m/z* = 428.1 $[M+H]^+$; HPLC Ret. Time 1.586 min. (HPLC Method H); ^{1}H NMR (400

MHz, DMSO-d_6) δ ppm 8.23 (s, 1H), 7.93 (s, 1H), 7.62 (d, J = 9.29 Hz, 1H), 7.45 (dd, J = 5.62, 8.80 Hz, 2H), 7.37 (s, 1H), 7.00-7.15 (m, 3H), 6.03-6.42 (m, 1H), 4.32-4.45 (m, 2H), 3.69-3.77 (m, 4H), 2.90-3.01 (m, 4H).

Scheme 41

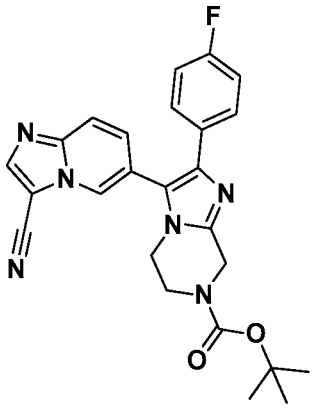


Intermediate 290B′: *tert*-butyl 3-bromo-2-(4-fluorophenyl)-5,6-dihydroimidazo[1,2-*a*]pyrazine-7(8*H*)-carboxylate



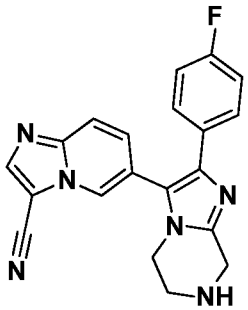
[0566] Intermediate **290B′** was synthesized by reacting intermediate **290A′** (**reference**: WO 2014100533 A1) and NBS by employing the experimental procedure described in Scheme **22** for intermediate **236C′** to afford intermediate **290B′** as a yellow solid. LCMS: *m/z* = 398.2 $[M+H]^+$; HPLC Ret. Time 3.21 min. (HPLC Method J).

Intermediate 290C′: *tert*-butyl 3-(3-cyanoimidazo[1,2-*a*]pyridin-6-yl)-2-(4-fluorophenyl)-5,6-dihydroimidazo[1,2-*a*]pyrazine-7(8*H*)-carboxylate



[0567] Intermediate **290C′** was synthesized by reacting 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile (**reference**: WO 2014/055955 A1) and intermediate **290B′** by employing the experimental procedure described in Scheme **25** for Example **271′**. The crude residue was purified by silica gel chromatography (24 g CombiFlash® column, eluting with a gradient of 60-100 % EtOAc in petroleum ether). Fractions containing the desired product were combined and evaporated to afford example **290C′** as a brown solid. LCMS: *m/z* = 459.1 $[M+H]^+$; HPLC Ret. Time 1.25 min. (HPLC Method G).

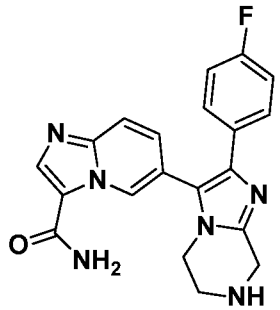
Intermediate 290D′: 6-(2-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-3-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile



[0568] To a solution of intermediate **290C′** (30 mg, 0.065 mmol) in DCM (2 mL) was added TFA (0.1 mL, 1.298 mmol) and the reaction mixture was stirred at RT for 15 h and then concentrated to give the crude residue. It was purified by preparative HPLC (Condition P). Fractions containing the desired product were combined and evaporated to afford example **290D′**. LCMS: *m/z* = 359.1 $[M+H]^+$; HPLC Ret. Time 1.37 min. (HPLC Method H); ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.73 - 8.75 (m, 1 H) 8.52 (s, 1 H) 7.92 (dd, *J* = 9.29, 0.98

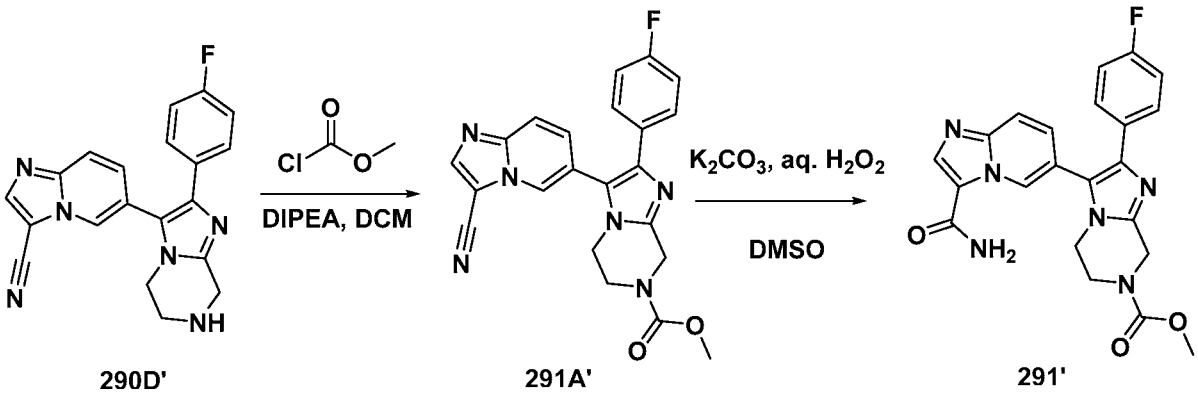
Hz, 1 H) 7.43 - 7.49 (m, 3 H) 7.02 - 7.09 (m, 2 H) 3.97 (s, 2 H) 3.73 (t, *J* = 5.26 Hz, 2 H) 3.06 (t, *J* = 5.26 Hz, 2 H).

Example 290′: 6-(2-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

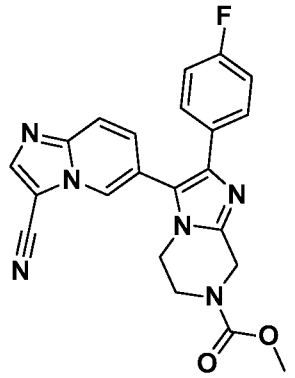


[0569] Example **290′** was synthesized by reacting intermediate **290D′** and K_2CO_3/ H_2O_2 by employing the experimental procedure described in Scheme **35** for example **283′**. The crude residue was purified by preparative HPLC (Condition P). Fractions containing the desired product were combined and evaporated to afford Example **290′**. LCMS: *m/z* = 377.1 $[M+H]^+$; HPLC Ret. Time 1.049 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (dd, *J* = 1.71, 0.98 Hz, 1 H) 8.40 (s, 1 H) 8.02 (br. s., 1 H) 7.82 (dd, *J* = 9.29, 0.98 Hz, 1 H) 7.39 - 7.47 (m, 3 H) 7.02 - 7.08 (m, 2 H) 3.95 (s, 2 H) 3.65 (t, *J* = 5.26 Hz, 2 H) 3.05 (t, *J* = 5.26 Hz, 2 H).

Scheme 42

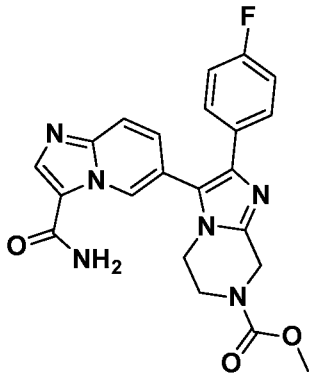


Intermediate 291A′: methyl 3-(3-cyanoimidazo[1,2-*a*]pyridin-6-yl)-2-(4-fluorophenyl)-5,6-dihydroimidazo[1,2-*a*]pyrazine-7(8*H*)-carboxylate



[0570] Intermediate **291A′** was synthesized from intermediate **290D′** by employing the experimental procedure described in Scheme **36** for example **284′**. The crude compound was purified by preparative HPLC (Condition P). Fractions containing the desired product were combined and evaporated to afford intermediate **291A′**. LCMS: *m/z* = 417.1 $[M+H]^+$; HPLC Ret. Time 1.539 min. (HPLC Method H).

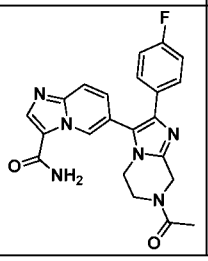
Example 291′: methyl 3-(3-carbamoylimidazo[1,2-*a*]pyridin-6-yl)-2-(4-fluorophenyl)-5,6-dihydroimidazo[1,2-*a*]pyrazine-7(8*H*)-carboxylate



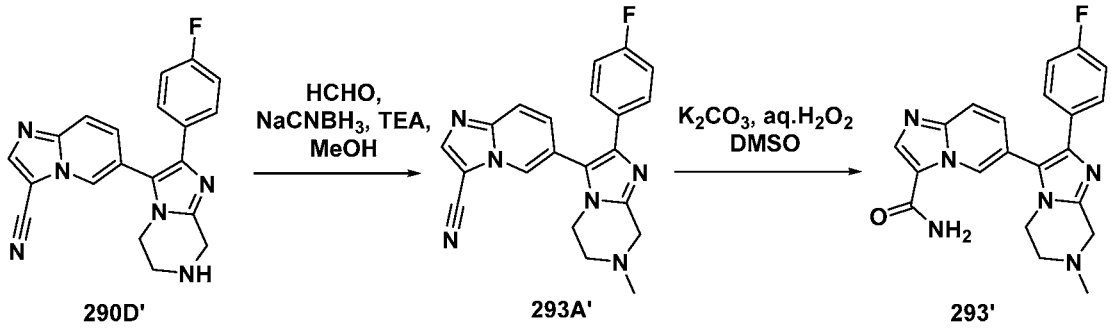
[0571] Example **291′** was synthesized from intermediate **291A′** by employing the experimental procedure described in Scheme **35** for example **283′**. The crude compound was purified by preparative HPLC (Condition P). Fractions containing the desired product were combined and evaporated to afford Example **291′**. LCMS: *m/z* = 435.1 $[M+H]^+$; HPLC Ret. Time 1.280 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (dd, *J* = 1.71, 0.98 Hz, 1 H) 8.40 (s, 1 H) 8.01 (br. s., 1 H) 7.84 (dd, *J* = 9.29, 0.98 Hz, 1 H) 7.42 - 7.48 (m, 3 H) 7.04 - 7.10 (m, 2 H) 4.71 (s, 2 H) 3.80 (br. s., 4 H) 3.69 (s, 3 H).

[0572] The compound shown in **Table 22** has been prepared similar to example **291′** using intermediate **291A′**, acetyl chloride and then the oxidation of the cyano group with K_2CO_3/H_2O_2.

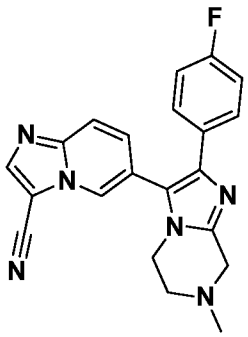
Table 22

Ex.	Structure	Name	$[M+H]^+$	Ret. Time (min.)	HPLC Method
292′		6-(7-acetyl-2-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide	419.2	0.935 0.600	H I

Scheme 43



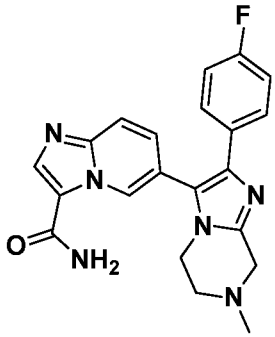
Intermediate 293A′: 6-(2-(4-fluorophenyl)-7-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-3-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile



[0573] To a solution of intermediate **290D′** (50 mg, 0.140 mmol) in methanol (5 mL) at 0 °C was added formaldehyde (0.021 mL, 0.279 mmol, 37 % aqueous solution), TEA (0.039 mL, 0.279 mmol) and sodium cyanoborohydride (17.54 mg, 0.279 mmol). The reaction mixture was stirred at RT for 1 h and then partitioned between water and DCM. The organic layer was washed with brine, dried over Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure to give the crude residue. It was purified by preparative HPLC (Condition P). Fractions containing the desired product were combined and evaporated to afford intermediate **293A′** (2.1 mg, 5.6 µmol, 3.1 % yield). LCMS: *m/z* = 373.2 $[M+H]^+$; HPLC Ret. Time 1.213 min. (HPLC Method I); ^1H NMR (400 MHz, DMSO-d_6) δ ppm 9.12

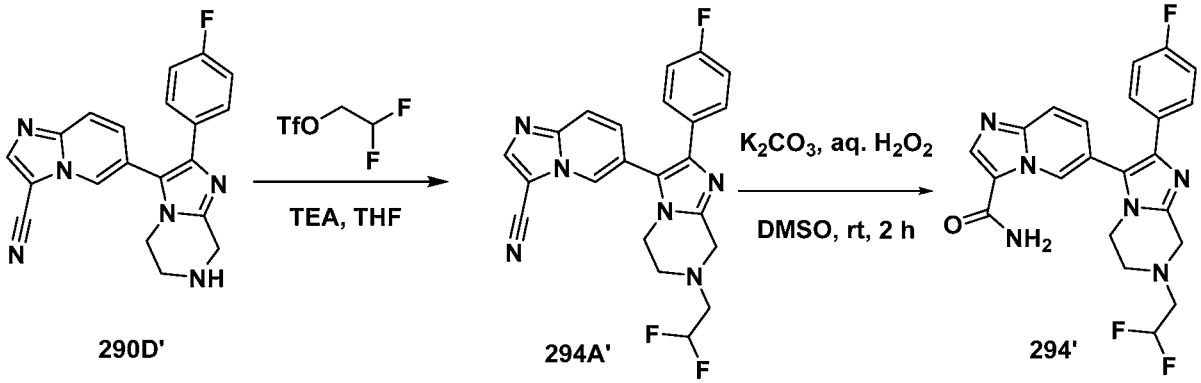
(s, 1H), 8.81 (s, 1H), 8.21 (d, J = 9.05 Hz, 1H), 7.68-7.78 (m, 3H), 6.95-7.20 (m, 4H), 7.22 (s, 1H), 4.02 (br. s., 4H), 2.91-2.95 (m, 2H), 2.26 (s, 3H).

Example 293′: 6-(2-(4-fluorophenyl)-7-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide

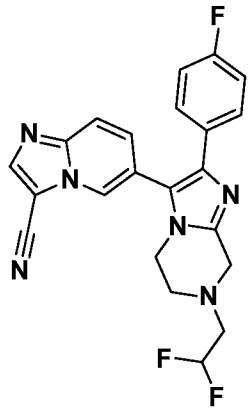


[0574] Example **293′** was synthesized by reacting intermediate **293A′** and H_2O_2/K_2CO_3 by employing the experimental procedure described in Scheme **35** for Example **283′**. The crude compound was purified by preparative HPLC (Condition Q). Fractions containing the desired product were combined and evaporated to afford example **293′**. LCMS: *m/z* = 391.2 $[M+H]^+$; HPLC Ret. Time 0.982 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (s, 1H), 8.40 (s, 1H), 8.01 (br. s., 1H), 7.85 (d, J = 9.54 Hz, 1H), 7.43-7.47 (m, 3H), 7.07 (t, J = 9.05 Hz, 2H), 3.78 (br. s., 4H), 2.86 (br. s., 2H), 2.6 (s, 3H).

Scheme 44

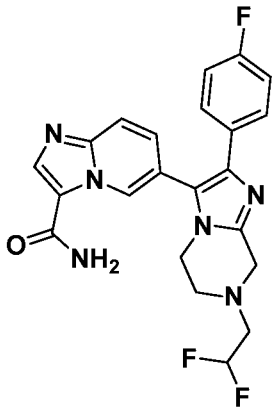


Intermediate 294A′: 6-(7-(2,2-difluoroethyl)-2-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-3-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile



[0575] Intermediate **294A′** was synthesized by reacting intermediate **290D′** and 2,2-difluoroethyl trifluoromethanesulfonate by employing the experimental procedure described in Scheme **25** for intermediate **271A′**. The crude residue which was purified by preparative HPLC (Condition P). Fractions containing the desired product were combined and evaporated to afford intermediate **294A′**. LCMS: *m/z* = 423.1 $[M+H]^+$; HPLC Ret. Time 1.731 min; (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.84 (s, 1H), 8.51 (s, 1H), 7.92 (d, *J* = 9.29 Hz, 1H), 7.44-7.48 (m, 3H), 7.06 (t, *J* = 8.93 Hz, 2H), 6.12-6.39 (m, 1H), 3.91 (s, 2H), 3.85 (t, *J* = 5.26 Hz, 2H), 2.99-3.08 (m, 4H).

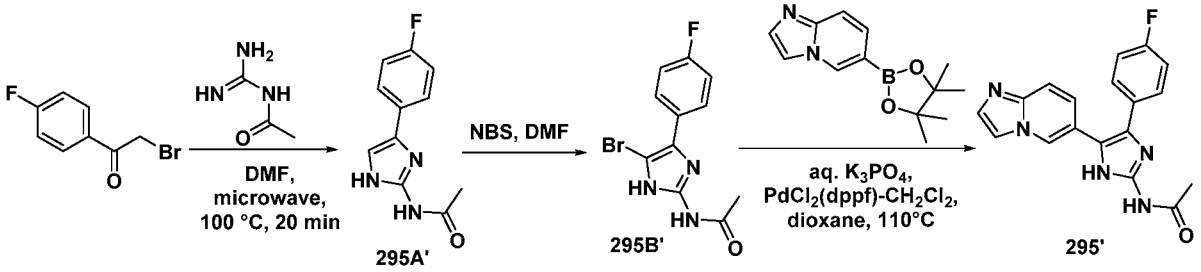
Example 294′: 6-(7-(2,2-difluoroethyl)-2-(4-fluorophenyl)-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyrazin-3-yl)imidazo[1,2-*a*]pyridine-3-carboxamide



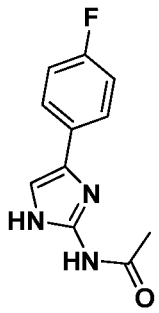
[0576] Example **294′** was synthesized by reacting intermediate **294A′** and H_2O_2/K_2CO_3 by employing the experimental procedure described in Scheme **35** for Example **283′**. The crude compound was purified by preparative HPLC (Condtion Q). Fractions containing the desired product were combined and evaporated to afford example **294′**. LCMS: *m/z* = 441.3 $[M+H]^+$; HPLC Ret. Time 1.160 min. (HPLC Method I). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.49 (dd, *J* = 1.71, 0.98 Hz, 1 H) 8.40 (s, 1 H) 8.01 (br. s., 1 H) 7.83 (dd, *J* = 9.17, 0.86

Hz, 1 H) 7.42 - 7.50 (m, 3 H) 7.03 - 7.10 (m, 2 H) 6.09 - 6.41 (m, 1 H) 3.92 (s, 2 H) 3.77 (t, *J* = 5.38 Hz, 2 H) 2.98 - 3.09 (m, 4 H).

Scheme 45

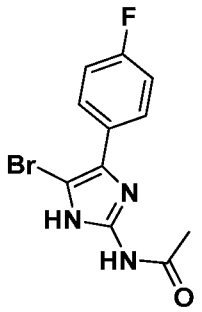


Intermediate 295A′: *N*-(4-(4-fluorophenyl)-1*H*-imidazol-2-yl)acetamide



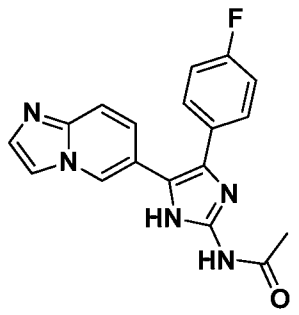
[0577] To a solution of 2-bromo-1-(4-fluorophenyl)ethanone (5.0 g, 23.04 mmol) in DMF (50 mL) was added *N*-carbamimidoylacetamide (6.99 g, 69.1 mmol). The reaction mixture was irradiated in a microwave oven at 100 °C for 20 min. The reaction mixture was concentrated and water was added to the residue. The solid thus obtained was filtered and dried under suction to afford intermediate **295A′** (4.0 g, 79 % yield). LCMS: *m/z* = 220.2 $[M+H]^+$; HPLC Ret. Time 1.396 min. (HPLC Method J).

Intermediate 295B′: *N*-(5-bromo-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)acetamide



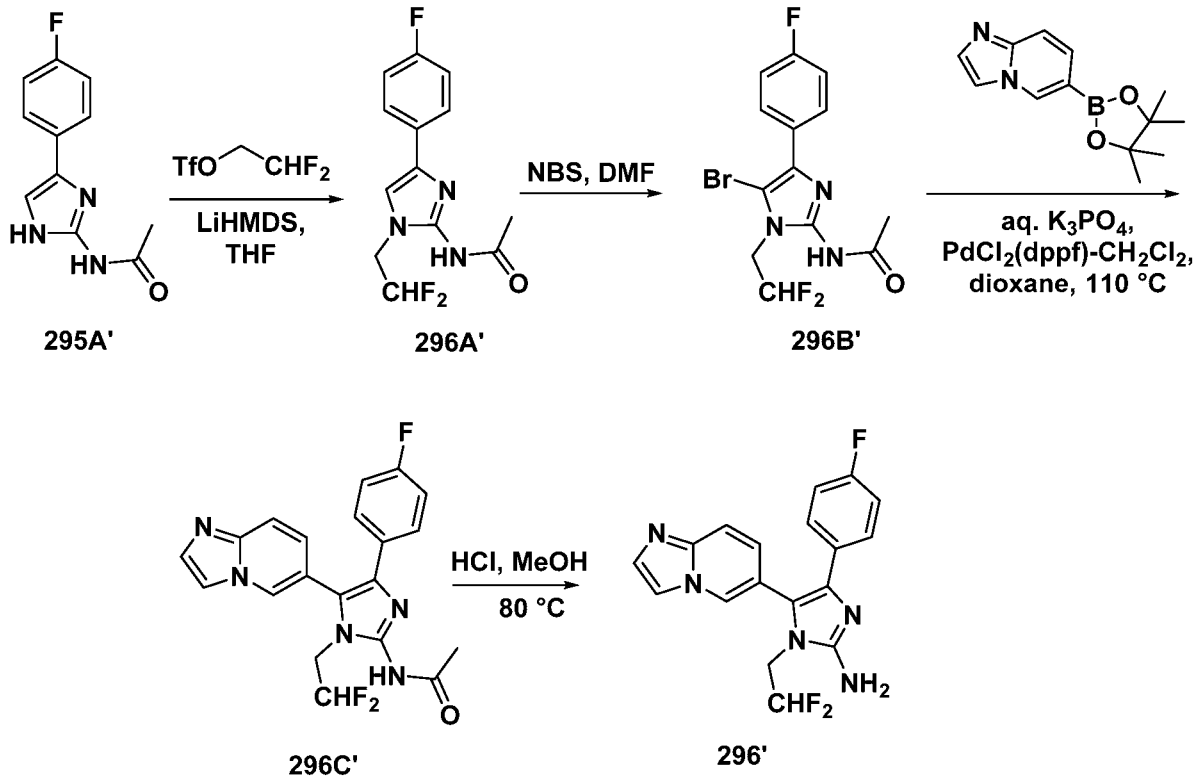
[0578] Intermediate **295B′** was synthesized by reacting intermediate **295A′** with NBS and by employing the experimental procedure described for intermediate **236C′** in Scheme **22**.. LCMS: *m/z* = 300.0 $[M+2H]^+$; HPLC Ret. Time 0.99 min. (HPLC Method G).

Example 295′: *N*-(4-(4-fluorophenyl)-5-(imidazo[1,2-*a*]pyridin-6-yl)-1*H*-imidazol-2-yl)acetamide

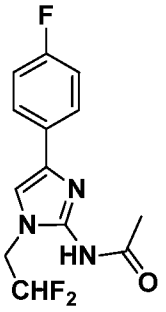


[0579] Example **295′** was synthesized by reacting intermediate **295B′** with 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-*a*]pyridine (**reference**: CN 103275112 A) and by employing the experimental procedure described for example **271′** in Scheme **25.**. The crude residue was purified by preparative HPLC (Condition R). Fractions containing the desired product were combined and evaporated to afford Example **295′** (2.2 mg, 1.88 % yield). LCMS: *m/z* = 336.1 $[M+H]^+$; HPLC Ret. Time 1.345 min; (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.63 (br. s., 1H), 7.96 (s, 1H), 7.57 (br. s., 1H), 7.54 - 7.46 (m, 3H), 7.23 - 7.09 (m, 3H), 2.10 (s, 3H).

Scheme 46

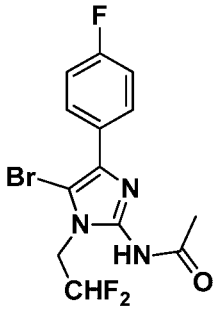


Intermediate 296A′: *N*-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)acetamide



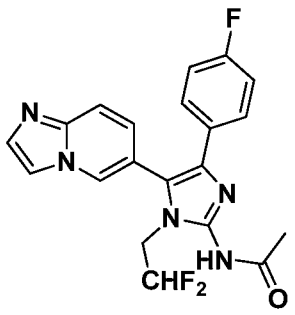
[0580] To a solution of intermediate **296A′** (800 mg, 3.65 mmol) in anhydrous THF (20 mL) at 0 °C was added LiHMDS (7.30 mL, 7.30 mmol, 1M solution in THF) dropwise. The reaction mixture was stirred at 0 °C for 15 min and 2,2-difluoroethyl trifluoromethanesulfonate (0.485 mL, 3.65 mmol) was added. The mixture was stirred at 0 °C for an additional 2 h, quenched with saturated aq. NH_4Cl solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. Thefiltrate was concentrated under reduced pressure to give the crude residue, which was purified by silica gel chromatography (24 g CombiFlash® column, eluting with a gradient of 30-50 % EtOAc in petroleum ether). Fractions containing the desired product were combined and evaporated to afford intermediate **296A′** (600 mg, 58.0 % yield). LCMS: *m/z* = 282.0 $[M-H]^+$; HPLC Ret. Time 1.410 min. (HPLC Method J).

Intermediate 296B′: *N*-(5-bromo-1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)acetamide



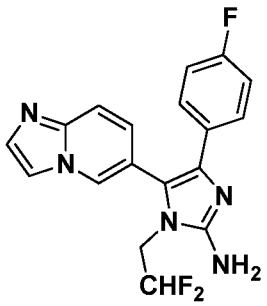
[0581] Intermediate **296B′** was synthesized by reacting intermediate **296A′** with NBS and by employing the experimental procedure described for intermediate **236C′** in Scheme **22**.. LCMS: *m/z* = 362.0 $[M+H]^+$; HPLC Ret. Time 1.988 min. (HPLC Method J).

Intermediate 296C′: *N*-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-5-(imidazo[1,2-*a*]pyridin-6-yl)-1*H*-imidazol-2-yl)acetamide



[0582] Intermediate **296C′** was synthesized by reacting 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-*a*]pyridine (**reference**: CN 103275112 A) with intermediate **296B′** and by employing the experimental procedure described for Example **236′ in** Scheme **22**. The crude compound was purified by preparative HPLC (Condition R). Fractions containing the desired product were combined and evaporated to afford intermediate **296C′** (20 mg, 18.14 % yield). LCMS: *m/z* = 400.1 $[M+H]^+$; HPLC Ret. Time 1.257 min. (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 8.97 (s, 1H), 7.95 (s, 1H), 7.75 (d, *J* = 9.3 Hz, 1H), 7.62 (s, 1H), 7.32-7.42 (m, 2H), 7.12-7.22 (m, 3H), 5.98-6.26 (m, 1H), 4.24 (t, *J* = 14.7 Hz, 2H), 2.37 (s, 3H).

Example 296′: 1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-5-(imidazo[1,2-*a*]pyridin-6-yl)-1*H*-imidazol-2-amine, 2 HCl

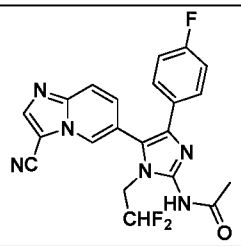


[0583] A solution of intermediate **296C′** (45 mg, 0.113 mmol) and HCl (0.2 mL, 6.58 mmol) in MeOH (10 mL) was heated at 80 °C for 5 h. The reaction mixture was concentrated to give the crude residue, which was purified by preparative HPLC (HPLC Method O). Fractions containing the desired product were combined and evaporated to afford Example **296′** (15.4 mg, 31.8 % yield). (Preparation of HCl salt of Example **296′**: 2 mL of 1M HCl was added to intermediate **296C′** and concentrated by Genevac and the analytical data was recorded as the bis HCl salt). LCMS: *m/z* = 358.1 $[M+H]^+$; HPLC Ret. Time 1.092 min; (HPLC Method H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 9.08 (s, 1 H) 8.34 (d, *J* = 2.01 Hz,

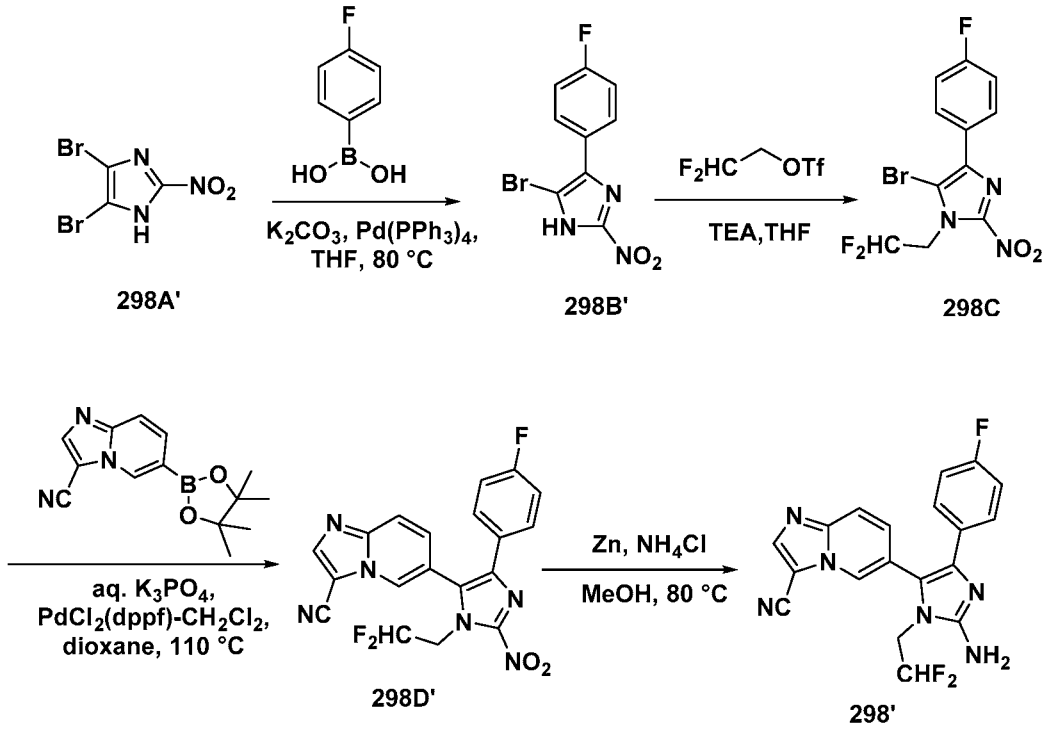
1 H) 8.15 - 8.22 (m, 1 H) 8.04 (d, *J* = 9.04 Hz, 1 H) 7.75 (d, *J* = 10.04 Hz, 1 H) 7.37 - 7.43 (m, 2 H) 7.34 (s, 1 H) 7.17 - 7.23 (m, 2 H) 7.09 (s, 1 H) 6.03 - 6.33 (m, 1 H) 4.36 - 4.47 (m, 2 H).

[0584] The compound shown in **Table 23** has been prepared in a manner similar to intermediate **296C′** using intermediate **296B′** and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile.

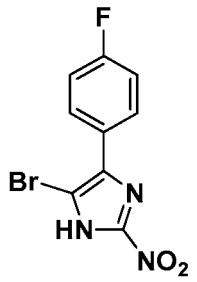
Table 23

Ex.	Structure	Name	$[M+H]^+$	Ret. Time (min.)	HPLC Method
297′		*N*-(5-(3-cyanoimidazo[1,2-*a*]pyridin-6-yl)-1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-2-yl)acetamide	425.1	1.403 1.339	H I

Scheme 47

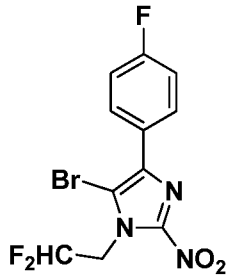


Intermediate 298B′: 5-bromo-4-(4-fluorophenyl)-2-nitro-1*H*-imidazole



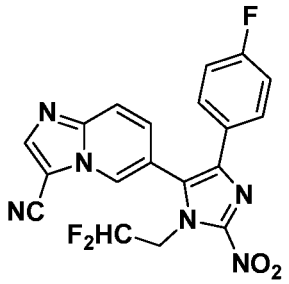
[0585] To a solution of intermediate **298A′** (**reference**: *Organic and Bio-Organic Chemistry (1972-1999)*, **1989**, *95–99)* (1.0 g, 3.69 mmol) in THF (150 mL) was added (4-fluorophenyl)boronic acid (1.033 g, 7.38 mmol) and K_2CO_3 (0.510 g, 3.69 mmol in 10 mL water). The reaction mixture was degassed with argon for 5 minutes and $Pd(PPh_3)_4$ (0.213 g, 0.185 mmol) was added. The reaction mixture was heated at 80 °C for 15 h. The solvent was then evaporated and the residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure to give the crude residue, which was purified by reverse phase silica chromatography (mobile phase A: 10 mM NH_4OAc:acetonitrile (95:5), mobile phase B: 10 mM NH_4OAc:acetonitrile (5:95), eluting with a gradient of 20-90% B). Fractions containing the desired product were combined and evaporated to afford intermediate **298B′** (500 mg, 23.67 % yield). LCMS: *m/z* = 286.1 $[M-H]^+$; HPLC Ret. Time 0.86 min. (HPLC Method G).

Intermediate 298C′: 5-bromo-1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-2-nitro-1*H*-imidazole



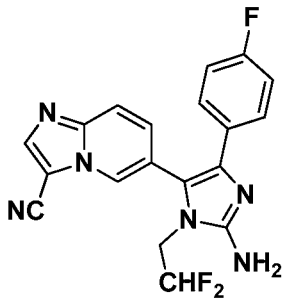
[0586] Intermediate **298C′** was synthesized by reacting intermediate **298B′** with NBS and by employing the experimental procedure described for intermediate **236C′** in Scheme **22**.. The crude residue was purified by silica gel chromatography (12 g CombiFlash® column, eluting with a gradient of 25-50 % EtOAc in petroleum ether). Fractions containing the desired product were combined and evaporated to afford intermediate **298C′**. LCMS: *m/z* = 352.0 $[M+2H]^+$; HPLC Ret. Time 2.520 min. (HPLC Method J).

Intermediate 298D′: 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-2-nitro-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile



[0587] Intermediate **298D′** was synthesized by reacting 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile (**reference**: WO 2014/055955 A1) with intermediate **298C′** and by employing the experimental procedure described for Example **271′** in Scheme **25**. The crude compound was purified by silica gel chromatography (12 g CombiFlash® column, eluting with a gradient of 5-10 % MeOH in $CHCl_3$). Fractions containing the desired product were combined and evaporated to afford intermediate **298D′** (60 mg, 25.5 % yield). LCMS: *m/z* = 413.1 $[M+H]^+$; HPLC Ret. Time 0.91 min. (HPLC Method F).

Example 298′: 6-(2-amino-1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*a*]pyridine-3-carbonitrile



[0588] To a solution of intermediate **298D′** (25 mg, 0.061 mmol) in methanol (2.5 mL) was added ammonium chloride (6.49 mg, 0.121 mmol) and zinc (39.6 mg, 0.606 mmol). The reaction mixture was stirred at 80 °C for 1 h, filtered through a Celite® pad, and the pad was washed with DCM. The combined filtrates were evaporated to give the crude residue, which was purified by preparative HPLC (HPLC Method M). Fractions containing the desired product were combined and evaporated to afford example **298′** (4.8 mg, 20.71 % yield). LCMS: *m/z* = 383.1 $[M+H]^+$; HPLC Ret. Time 1.451 min. (HPLC Method H); ^1H NMR (400 MHz, DMSO-d_6) δ ppm 8.61 (s, 1H), 8.50 (s, 1H), 7.88 (d, *J* = 9.05 Hz, 1H), 7.30-7.41 (m, 3H), 7.00 (t, *J* = 8.93 Hz, 2H), 5.86-6.28 (m, 3H), 4.12-4.27 (m, 2H).

Example 4: Biological assay

[0589] Assays for the compounds reproted below were conducted in 1536-well plates and 2 mL reactions are prepared from addition of HIS-TGF-βR1 T204D or HIS-TGF-βR2 WT, anti-HIS detection antibody, a labeled small molecule probe (K_d = <100 nM; k_{off} = <0.001 s^{-1}) and test compounds in assay buffer (20 mM HEPES pH 7.4, 10 mM $MgCl_2$, 0.015% Brij35, 4 mM DTT, and 0.05 mg/ml BSA). The reaction is incubated for 1 hour at room temperature and the HTRF signal was measured on an Envision plate reader (Ex: 340nm; Em: 520 nm / 495 nm). Inhibition data were calculated by comparison to no enzyme control reactions for 100% inhibition and vehicle-only reactions for 0% inhibition. The final concentration of reagents in the assay are 1 nM HIS-TGF-βR1 T204D or HIS-TGF-βR2 WT, 0.2 nM anti-HIS detection antibody, labeled small molecule prode (at K_d) and 0.5% DMSO. Dose response curves were generated to determine the concentration required inhibiting 50% of kinase activity (IC_{50}). Compounds were dissolved at 10 mM in dimethylsulfoxide (DMSO) and evaluated at eleven concentrations. IC_{50} values were derived by non-linear regression analysis.

No.	TGFbr1 IC50 (μM)	TGFBr2 IC50 (μM)
1′	0.0016	
2′	0.0023	2.2201
3′	0.0142	>15>15
4′	0.0068	-
5′	0.0055	-
6′	0.0050	10.2377
7′	0.0024	6.3338
8′	0.0179	>15
9′	0.0019	11.1563
10′	0.0025	7.1720
11′	0.0030	3.1990
12′	0.0021	-
13′	0.0170	>15
14′	0.0053	-
15′	0.0020	7.3009
16′	0.0023	>15
17′	0.0035	>15
18′	0.0105	0.1289

No.	TGFbr1 IC50 (μM)	TGFBr2 IC50 (μM)
19′	0.0099	>15
20′	0.0022	4.8708
21′	0.0019	4.4252
22′	0.0012	3.1110
23′	0.0019	9.4813
24′	0.0004	2.1937
25′	0.0026	3.7219
26′	0.0926	>15
27′	0.0006	2.2513
28′	0.0010	>15
29′	0.0064	>15
30′	0.0092	>15
31′	0.0019	3.7101
32′	0.0018	-
33′	0.0010	-
34′	0.0009	7.7063
35′	0.0026	11.0508
36′	0.0013	5.7988

No.	TGFbr1 IC50 (μM)	TGFBr2 IC50 (μM)
37′	0.0025	10.7414
38′	0.0010	>15
39′	0.0009	4.4730
40′	0.0006	3.0319
41′	0.0009	0.8753
42′	0.0018	11.5255
43′	0.0027	11.5430
44′	0.0012	5.0893
45′	0.0023	8.8598
46′	0.0015	17.2311
47′	0.0015	6.7145
48′	0.0031	>15
49′	0.0014	2.3019
50′	0.0023	>15
51′	0.0006	1.9862
52′	0.0009	6.8860
53′	0.0021	5.4685
54′	0.0008	5.9937

No.	TGFbr1 IC50 (μM)	TGFBr2 IC50 (μM)
55′	0.0067	>15
56′	0.0008	6.8237
57′	0.0015	9.3393
58′	0.0008	3.5799
59′	0.0011	7.5544
60′	0.0009	5.5574
61′	0.0008	6.4575
62′	0.0016	8.9964
63′	0.0009	8.7715
64′	0.0051	>15
65	0.0632	>15
66′	0.4185	>15
67′	0.0558	>15
68′	0.3007	>15
69′	0.1512	>15
70′	0.1226	>15
71′	0.1697	>15
72′	0.0678	>15
73′	0.0362	>15
74′	0.1519	>15
75′	0.1995	>15
76′	0.9993	>15
77′	0.0198	>15
78′	0.5684	>15
79′	0.0553	>15
80′	0.0310	>15
81′	0.0885	>15
82′	0.0716	>15
83′	0.1888	>15
84′	0.1212	>15
85′	0.1443	>15
86′	0.0947	>15
87′	0.0403	>15
88′	0.0193	>15
89′	0.1269	>15

No.	TGFbr1 IC50 (μM)	TGFBr2 IC50 (μM)
90′	0.1072	>15
91′	0.0188	>15
92′	0.2659	>15
93′	0.5763	>15
94′	0.0131	>15
95′	0.0768	>15
96′	0.0944	>15
97′	0.1396	>15
98′	0.0173	>15
99′	0.0657	>15
100′	0.0116	>15
101′	0.0232	>15
102	0.0024	0.5854
103′	0.0018	>15
104′	0.0005	3.9544
105	0.0009	2.9308
106′	0.0061	>15
107′	0.0019	7.6130
108′	0.0021	>15
109′	0.0025	2.2749
110′	0.0205	>15
111′	0.0008	3.3244
112′	0.0007	9.7831
113′	0.0009	3.3656
114′	0.0013	3.1522
115′	0.0046	>15
116′	0.0009	1.8896
117′	0.0006	9.8046
118′	0.0014	>15
119′	0.0004	5.8633
120′	0.0065	>15
121′	0.0011	>15
122′	0.0018	>15
123′	0.0042	1.8551
124′	0.0025	1.5908

No.	TGFbr1 IC50 (μM)	TGFBr2 IC50 (μM)
125′	0.0026	>15
126′	0.0074	>15
127′	0.0049	1.1498
128′	0.0015	8.4646
129′	0.0051	>15
130′	0.0021	>15
131′	0.0281	>15
132′	0.0047	>15
133′	0.0031	14.3697
134′	0.0039	7.3702
135′	0.0007	3.2657
136′	0.0124	>15
137′	0.0006	6.5998
138′	0.0007	5.9843
139′	0.0052	>15
140′	0.0028	9.7851
141′	0.0008	4.6352
142′	0.0016	>15
143′	0.0091	>15
144′	0.0041	>15
145′	0.0022	2.2237
146′	0.0017	7.1990
147′	0.0013	1.5180
148′	0.0011	2.6284
149′	0.0017	3.6157
150′	0.0012	1.1117
151′	0.0006	3.8554
152′	0.0011	>15
153′	0.0063	>15
154′	0.0023	>15
155′	0.0055	>15
156′	0.0043	9.2537
157′	0.0008	6.5893
158′	0.0027	>15
159′	0.0008	>15

No.	TGFbr1 IC50 (μM)	TGFBr2 IC50 (μM)
160′	0.0008	7.0201
161′	0.0067	>15
162′	0.0019	11.2231
163′	0.0319	>15
164′	0.0057	>15
165′	0.0049	>15
166′	0.0091	>15
167′	0.0006	4.6700
168′	0.0011	13.2538
169′	0.0213	>15
170′	0.0005	4.2962
171′	0.0084	>15
172′	0.0005	1.7386
173′	0.0066	>15
174′	0.0006	5.5480
175′	0.0020	>15
176′	0.0052	>15
177′	0.0011	9.0826
178′	0.0019	5.0774
179′	0.0022	>15
180′	0.0037	>15
181′	0.0060	>15
182′	0.0508	>15
183′	0.0216	>15
184′	0.0545	>15
185′	0.0301	>15
186′	0.2277	>15
187′	0.0033	>15
188′	0.0020	1.4660
189′	0.0016	3.5554
190′	0.0527	>15
191′	0.0727	>15
192′	0.2289	>15
193′	0.2269	>15
194′	0.0102	7.0868

No.	TGFbr1 IC50 (μM)	TGFBr2 IC50 (μM)
195′	0.4358	>15
196′	0.0238	>15
197′	0.0119	>15
198′	0.0053	>15
199′	0.0095	>15
200′	0.0120	>15
201′	0.0050	>15
202′	0.0438	>15
203′	0.0011	6.2222
204′	0.0012	>15
205′	0.0018	>15
206′	0.0009	>15
207′	0.0030	>15
208′	0.0012	>15
209′	0.0007	2.6841
210′	0.0022	7.7798
211′	0.0045	>15
212′	0.0093	>15
213′	0.0023	>15
214′	0.0011	>15
215′	0.0008	7.1973
216′	0.0009	7.0527
217′	0.0032	>15
218′	0.0627	>15
219′	0.0099	>15
220′	0.0414	>15
221′	0.0068	>15
222′	0.0029	>15
223′	0.0022	>15
224′	0.0667	>15
225′	0.0100	>15
226′	0.0732	>15
227′	0.0081	>15
228′	0.0037	>15
229′	0.0086	>15

No.	TGFbr1 IC50 (μM)	TGFBr2 IC50 (μM)
230′	0.0017	5.9767
231′	0.0006	6.3016
232′	0.0018	5.1875
233′	0.0010	>15
234′	0.0011	7.9394
235′	0.0010	>15
236	0.0021	>15
237′	0.0029	>15
238′	0.0397	>15
239′	0.5213	>15
240′	0.0143	>15
241′	0.1734	>15
242′	0.0050	>15
243′	0.0018	>15
244′	0.5459	>15
245′	0.0491	>15
246′	0.1435	>15
247′	0.0143	>15
248′	0.0007	0.1444
249′	0.0022	>15
250′	0.1359	>15
251′	0.0735	>15
252′	0.0077	>15
253′	0.0070	4.5788
254′	0.7517	>15
255′	0.8668	>15
256′	0.0050	>15
257′	0.0642	>15
258′	0.3560	>15
259′	0.0010	>15
260′	0.0088	>15
261′	0.0894	>15
262′	0.0052	>15
263′	0.1710	>15
264′	0.5161	>15

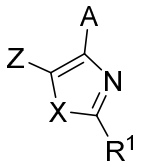
No.	TGFbr1 IC50 (μM)	TGFBr2 IC50 (μM)
265′	0.0098	>15
266′	0.0079	>15
267′	0.0003	1.7536
268′	0.0190	>15
269′	1.2000	>15
270′	0.0992	>15
271′	0.1723	>15
272′	0.0104	>15
273′	0.0296	>15
274′	0.1374	>15
275′	0.1208	>15
276′	0.9878	>15
277′	0.0209	>15
278′	0.1835	>15
279′	0.0095	>15

No.	TGFbr1 IC50 (μM)	TGFBr2 IC50 (μM)
280′	0.0032	>15
281′	0.5219	>15
282′	0.0129	>15
283′	0.0009	2.9356
284′	0.4262	>15
285′	0.0388	>15
286′	-	-
287′	-	-
288′	0.0567	>15
289′	0.3764	>15
290′	0.0216	>15
291′	0.0305	>15
292′	0.0408	>15
293′	0.0433	>15
294′	0.0272	>15

No.	TGFbr1 IC50 (μM)	TGFBr2 IC50 (μM)
295′	0.0550	>15
296′	0.1088	>15
297′	0.5418	>15
298′	0.0448	>15
190C′	0.0862	>15
195A′	0.2443	>15
195B′	0.0454	>15
196A′	0.0201	>15
213E′	0.0016	4.6759
272A′	0.2506	>15
274C′	0.0070	>15
274D′	0.0926	>15
283B′	0.0138	3.9581
284D′	0.0012	>15

Claims

1. A compound having the structure of formula (I°):



(I°)

or a pharmaceutically acceptable salt, or *N*-oxide thereof, or a solvate or hydrate thereof, wherein

X is -N(R′)-;

R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -(C_0-C_{12}alkyl)-Cak or -(C_0-C_6alkyl)-Hca, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, -OR^{S0}, C_1-C_6alkyl-OR^{S0}, -$C(O)OR^{S0}$, -$C(O)R^{S0}$, -$C(O)NR^{S0}_2$, -R^{S0} or cyano;

wherein each R^{S0} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, -OR^{S1}, -NR^{S1}_2, -SR^{S1} or -$N(R^{S1})C(O)R^{S1}$, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

wherein each R^{S1} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

or R′ and R^1 combined with the atoms to which they are attached form a five- to eight-membered ring;

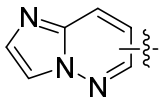
A is phenyl optionally substituted with one to five R^2 groups, wherein

each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl, -C_1-C_6alkoxy, -C_1-C_6haloalkoxy, -NO_2, -$N(R^{S2})C(O)R^{S2}$, -OR^{S2}, -$C(O)NR^{S2}_2$, -$N(R^{S2})S(O)_2R^{S2}$, -$S(O)_2R^{S2}$, -(C_0-C_6alkyl)-Ar or -CN, wherein each alkyl,

haloalkyl and alkoxy are optionally substituted with 1, 2, 3, or 4 groups that are each independently halogen, cyano, nitro, $-OR^{S2}$, $-SR^{S2}$, $-NR^{S2}_2$, $-C(O)OR^{S2}$, $-C(O)NR^{S2}_2$, $-C(O)R^{S2}$, $-S(O)R^{S2}$, $-S(O)_2R^{S2}$, $-S(O)OR^{S2}$, $-S(O)_2OR^{S2}$, $-S(O)NR^{S2}_2$, $-S(O)_2NR^{S2}_2$, $-OC(O)R^{S2}$, $-OC(O)OR^{S2}$, $-OC(O)NR^{S2}_2$, $-N(R^{S2})C(O)R^{S2}$, $-N(R^{S2})C(O)OR^{S2}$, $-N(R^{S2})C(O)NR^{S2}_2$, $-N(R^{S2})S(O)R^{S2}$, $-N(R^{S2})S(O)_2R^{S2}$, C_1-C_6alkyl, or C_1-C_6haloalkyl;

wherein each R^{S2} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

Z is



wherein

Z is optionally substituted by one or two $-R^Z$ groups that are each independently halogen, cyano, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, -C_1-C_6alkoxy, $-OR^{S3}$, $-SR^{S3}$, $-C(O)R^{S3}$, $-C(O)OR^{S3}$, $-C(O)NR^{S3}_2$, $-S(O)_2NR^{S3}_2$, $-S(O)_2R^{S3}$, $-OC(O)R^{S3}$, $-OC(O)OR^{S3}$, $-OC(O)NR^{S3}_2$, $-N(R^{S3})C(O)OR^{S3}$, $-N(R^{S3})S(O)_2R^{S3}$, $-OP(O)(OR^{S3})_2$ or $-CH_2$-$OP(O)(OR^{S3})$, wherein each alkyl, haloalkyl and alkoxy is optionally substituted by one or two $-R^{Z2}$ groups;

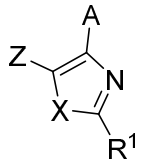
wherein each R^{S3} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, or cyano; and

each $-R^{Z2}$ is independently halogen, cyano, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, -C_1-C_6alkoxy, $-OR^{S4}$, $-SR^{S4}$, $-NR^{S4}_2$, $-C(O)R^{S4}$, $-C(O)OR^{S4}$, $-C(O)NR^{S4}_2$, $-S(O)_2NR^{S4}_2$, $-S(O)_2R^{S4}$, $-OC(O)R^{S4}$, $-N(R^{S4})C(O)R^{S4}$, $-OC(O)OR^{S4}$, $-OC(O)NR^{S4}_2$, $-N(R^{S4})C(O)OR^{S4}$,

$-N(R^{S4})C(O)NR^{S4}_2$, $-N(R^{S4})S(O)_2R^{S4}$, $-OP(O)(OR^{S4})_2$ or $-CH_2-OP(O)(OR^{S4})$; and

wherein each R^{S4} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with one or two C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

2. A compound according to claim 1 having the structure of formula (I):



(I)

or a pharmaceutically acceptable salt, or *N*-oxide thereof, or a solvate or hydrate thereof, wherein

X is -N(R′)-;

R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

R^1 is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6alkyloxy, $-OR^{S1}$, $-NR^{S1}_2$, $-SR^{S1}$, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

wherein each R^{S1} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

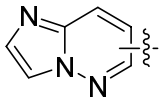
A is phenyl optionally substituted with one to five R^2 groups, wherein

each R^2 is independently halogen, -C_1-C_6alkyl, -C_1-C_6haloalkyl, -C_1-C_6alkoxy, $-NO_2$ or -CN, wherein each alkyl, haloalkyl and alkoxy are optionally substituted with 1, 2, 3, or 4 groups that are each independently halogen, cyano, nitro, $-OR^{S2}$, $-SR^{S2}$, $-NR^{S2}_2$, $-C(O)OR^{S2}$, $-C(O)NR^{S2}_2$, $-C(O)R^{S2}$,

-S(O)R^{S2}, -S(O)$_2R^{S2}$, -S(O)OR^{S2}, -S(O)$_2$OR^{S2}, -S(O)N$R^{S2}{}_2$, -S(O)$_2$N$R^{S2}{}_2$, -OC(O)R^{S2}, -OC(O)OR^{S2}, -OC(O)N$R^{S2}{}_2$, -N(R^{S2})C(O)R^{S2}, -N(R^{S2})C(O)OR^{S2}, -N(R^{S2})C(O)N$R^{S2}{}_2$, -N(R^{S2})S(O)R^{S2}, -N(R^{S2})S(O)$_2R^{S2}$, C_1-C_6alkyl, or C_1-C_6haloalkyl;

wherein each R^{S2} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

Z is



wherein

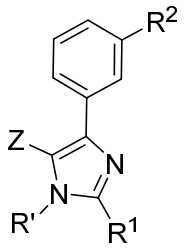
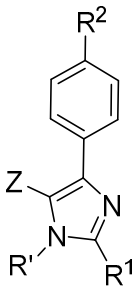
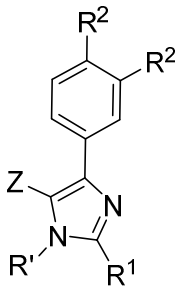
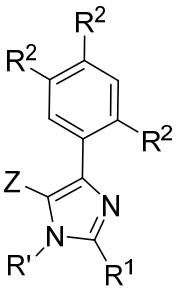
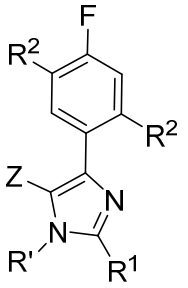
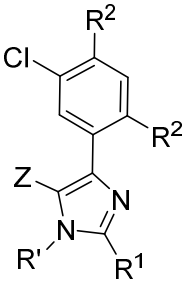
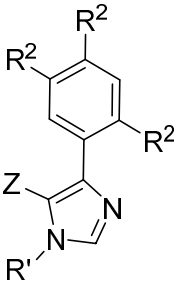
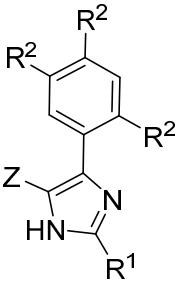
Z is optionally substituted by one or two -R^Z groups that are each independently halogen, cyano, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, -C_1-C_6alkoxy, -OR^{S3}, -SR^{S3}, -C(O)R^{S3}, -C(O)OR^{S3}, -C(O)N$R^{S3}{}_2$, -S(O)$_2$N$R^{S3}{}_2$, -S(O)$_2R^{S3}$, -OC(O)R^{S3}, -OC(O)OR^{S3}, -OC(O)N$R^{S3}{}_2$, -N(R^{S3})C(O)OR^{S3}, -N(R^{S3})S(O)$_2R^{S3}$, -OP(O)(OR^{S3})$_2$ or -CH_2-OP(O)(OR^{S3}), wherein each alkyl, haloalkyl and alkoxy is optionally substituted by one or two -R^{Z2} groups;

wherein each R^{S3} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano; and

each -R^{Z2} is independently halogen, cyano, $C_{1\text{-}6}$alkyl, $C_{1\text{-}6}$haloalkyl, -C_1-C_6alkoxy, -OR^{S4}, -SR^{S4}, -N$R^{S4}{}_2$, -C(O)R^{S4}, -C(O)OR^{S4}, -C(O)N$R^{S4}{}_2$, -S(O)$_2$N$R^{S4}{}_2$, -S(O)$_2R^{S4}$, -OC(O)R^{S4}, -N(R^{S4})C(O)R^{S4}, -OC(O)OR^{S4}, -OC(O)N$R^{S4}{}_2$, -N(R^{S4})C(O)OR^{S4}, -N(R^{S4})C(O)N$R^{S4}{}_2$, -N(R^{S4})S(O)$_2R^{S4}$, -OP(O)(OR^{S4})$_2$ or -CH_2-OP(O)(OR^{S4}); and

wherein each R^{S4} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano.

3. The compound of claim 1 or 2, wherein the compound has the structure of one of the following formulae:

<table>
<tr>
<td> 
(Ie)</td>
<td> 
(If)</td>
<td> 
(Ig)</td>
<td> 
(Ii)</td>
</tr>
<tr>
<td> 
(IIa)</td>
<td> 
(IIc)</td>
<td> 
or
(IId)</td>
<td> 
(IIe)</td>
</tr>
</table>

4. A compound according to claim 1 that is:

6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-*cis*-3-hydroxycyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(3,3-difluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-(3,3,3-trifluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(3,3-difluorocyclopentyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

(*S*)-6-(4-(4-fluorophenyl)-1-(1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-cyclopropyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(4,4-difluorocyclohexyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(2-fluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-(2-*iso*propoxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-(3-hydroxy-3-methylbutyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-(oxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(1-cyclopropyl-2-methoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-(2-hydroxycyclohexyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(3,3-difluoropropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-(3-fluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(2,2-difluoropropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(2-fluoro-2-methylpropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-isopropyl-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(bicyclo[1.1.1]pentan-1-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-(2-hydroxy-2-methylpropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-(3-(hydroxymethyl)cyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

(*R*)-6-(4-(4-fluorophenyl)-1-(4,4,4-trifluoro-1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

(*S*)-6-(4-(4-fluorophenyl)-1-(4,4,4-trifluoro-1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-(*tert*-pentyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-((tetrahydrofuran-2-yl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(2-fluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(3,3,3-trifluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-cyclopropyl-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(3-hydroxy-3-methylbutyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-((*cis*)-3-hydroxycyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(2-cyclobutylethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(1-methylcyclopropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

(*S*)-6-(4-(3-chloro-4-fluorophenyl)-1-((tetrahydrofuran-2-yl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(3-methyloxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(3-chloropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-((3-methyloxetan-3-yl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(tetrahydrofuran-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(2-methoxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-*iso*pentyl-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitril,

6-(4-(3-chloro-4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-isopropyl-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-ethyl-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(3-fluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(3,3,3-trifluoro-2-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(2-fluoro-2-methylpropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-cyclobutyl-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(bicyclo[1.1.1]pentan-1-yl)-4-(3-chloro-4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(2-chloroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(2-cyclopropylethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-((1-methylcyclopropyl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

(*R*)-6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclopentyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

(*S*)-6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclopentyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(3-fluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

(*S*)-6-(1-(1-fluorobutan-2-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3-chloro-4-fluorophenyl)-1-(3-fluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(1-(3,3-difluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(4-fluorophenyl)-1-(3,3,3-trifluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(1-(3,3-difluorocyclopentyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(1-cyclopropyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(1-(4,4-difluorocyclohexyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(1-(2-fluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(1-ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(2-fluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(3,3,3-trifluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-isopropyl-1H-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-ethyl-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(3,3-difluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(4-fluorophenyl)-1-*cis*-3-hydroxycyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(4-fluorophenyl)-1-(2-*iso*propoxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

(*S*)-6-(4-(4-fluorophenyl)-1-(1-hydroxybutan-2-yl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(4-fluorophenyl)-1-(oxetan-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(1-(3-fluorocyclobutyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

(*S*)-6-(1-(1-fluorobutan-2-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(1-(1,3-dihydroxypropan-2-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(1-(1-cyclopropyl-2-methoxyethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(4-fluorophenyl)-1-(3-hydroxy-3-methylbutyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(4-fluorophenyl)-1-methyl-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(4-fluorophenyl)-1-isopropyl-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(1-(bicyclo[1.1.1]pentan-1-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(1-(2,2-difluoropropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(3-hydroxy-3-methylbutyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-((*1s*,*3s*)-3-hydroxycyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(3-fluorocyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(3-hydroxypropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(2-(pyrrolidin-1-yl)ethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(tetrahydro-2*H*-pyran-4-yl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

(*S*)-6-(4-(3-chloro-4-fluorophenyl)-1-((tetrahydrofuran-2-yl)methyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(tetrahydrofuran-3-yl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(2-methoxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-isopentyl-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(3-chloropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(2-cyclobutylethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

6-(4-(3-chloro-4-fluorophenyl)-1-(2,2-difluoropropyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

1-(4-(4-fluorophenyl)-5-(imidazo[1,2-*b*]pyridazin-6-yl)-1*H*-imidazol-1-yl)cyclopropanecarbonitrile,

6-(1-(1-(difluoromethyl)cyclopropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine,

methyl 3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-4-(4-fluorophenyl)-1*H*-imidazol-1-yl)azetidine-1-carboxylate,

6-(1-(1-acetylazetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(1-(cyclopropanecarbonyl)azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

N-(*tert*-butyl)-3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-4-(4-fluorophenyl)-1*H*-imidazol-1-yl)azetidine-1-carboxamide,

6-(1-(1-(cyanomethyl)azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(1-(tert-butylcarbamoyl)azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methanamine,

N-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)acetamide,

N-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)cyclopropanecarboxamide,

1-(*tert*-butyl)-3-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)urea,

methyl ((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)carbamate,

*iso*propyl ((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)carbamate,

N-((6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methyl)pivalamide,

2-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)propan-2-ol,

6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-*N*-methylimidazo[1,2-b]pyridazine-3-carboxamide,

6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-N,N-dimethylimidazo[1,2-b]pyridazine-3-carboxamide,

N-cyclopropyl-6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methanol,

methyl (6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)carbamate,

1-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)-2,2,2-trifluoroethanol,

1-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)ethanol,

6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-3-(difluoromethyl) imidazo[1,2-b]pyridazine,

2-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)ethanol,

6-(4-(3-cyanophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(2,2-difluoroethyl)-4-phenyl-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(3,5-dichlorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

N-(2-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)phenyl)methanesulfonamide,

6-(1-(2,2-difluoroethyl)-4-(*p*-tolyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(2,2-difluoroethyl)-4-(4-methoxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(2,2-difluoroethyl)-4-(3-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(2,2-difluoroethyl)-4-(4-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

N-(3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)phenyl)acetamide,

6-(1-(2,2-difluoroethyl)-4-(2-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(2,2-difluoroethyl)-4-(2-hydroxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(2,2-difluoroethyl)-4-(3-hydroxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(2,2-difluoroethyl)-4-(4-hydroxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

2-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)benzamide,

N-(3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)phenyl)methanesulfonamide,

6-(1-(2,2-difluoroethyl)-4-(2-(hydroxymethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(2,2-difluoroethyl)-4-(3-(methylsulfonyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

3-(5-(3-cyanoimidazo[1,2-*b*]pyridazin-6-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-4-yl)benzamide,

6-(1-(2,2-difluoroethyl)-4-(3-(hydroxymethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-([1,1'-biphenyl]-3-yl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile ,

6-(4-(4-cyanophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile ,

6-(1-(2,2-difluoroethyl)-4-(3-(trifluoromethoxy)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile ,

6-(1-(2,2-difluoroethyl)-4-(4-fluoro-3-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile ,

6-(1-(2,2-difluoroethyl)-4-(4-fluoro-2-(trifluoromethyl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile ,

6-(1-(2,2-difluoroethyl)-4-(4-fluoro-3-methoxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile ,

6-(1-(2,2-difluoroethyl)-4-(4-isopropoxyphenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile ,

6-(1-(2,2-difluoroethyl)-4-(3-(2-hydroxypropan-2-yl)phenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile ,

6-(4-(3-cyano-4-fluorophenyl)-1-(2,2-difluoroethyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile ,

6-(1-(1-cyanocyclopropyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(1-(2-cyanoethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-((*1r,3s,5R,7S*)-3-hydroxyadamantan-1-yl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

6-(4-(4-fluorophenyl)-1-neopentyl-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

2-(6-(1-ethyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)propan-2-ol,

2-(6-(1-cyclopropyl-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)propan-2-ol,

6-(1-(azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carbonitrile,

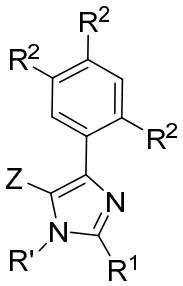
tert-butyl 3-(5-(3-carbamoylimidazo[1,2-*b*]pyridazin-6-yl)-4-(4-fluorophenyl)-1*H*-imidazol-1-yl)azetidine-1-carboxylate,

6-(1-(azetidin-3-yl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-b]pyridazine-3-carboxamide,

(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)methanamine, or

6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)-3-vinylimidazo[1,2-b]pyridazine.

5. A compound according to claim 1 having the structure of formula (II°):



(II°)

or a pharmaceutically acceptable salt, or *N*-oxide thereof, or solvate or hydrate thereof, wherein

R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_{12}alkyl)-Cak or -(C_0-C_6alkyl)-Hca, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, C_1-C_6alkyl-OR^{S0}, -OR^{S0}, -R^{S0} or cyano;

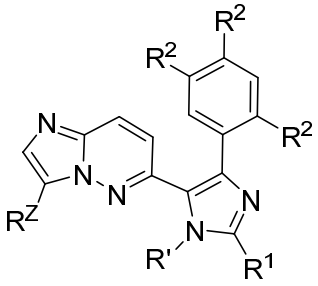
wherein each R^{S0} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

R^1 is hydrogen or C_1-C_6alkyl;

or R′ and R^1 combined with the atoms to which they are attached form a five- to eight-membered Hca; and

each R^2 is independently hydrogen, halogen, -C_1-C_6alkyl, -C_1-C_6alkyl-OR^{S2} or -OR^{S2}.

6. A compound according to claim 1 having the structure of formula (III°):



(III°)

or a pharmaceutically acceptable salt, or *N*-oxide thereof, or solvate or hydrate thereof, wherein

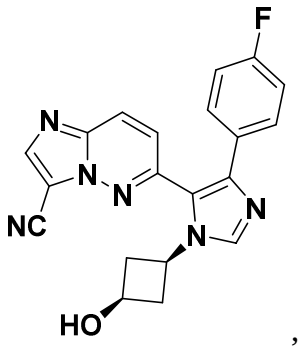
R′ is hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_{12}alkyl)-Cak or -(C_0-C_6alkyl)-Hca, each optionally substituted with 1 to 3 moieties that are each independently C_1-C_6alkyl, halogen, C_1-C_6haloalkyl, C_1-C_6alkyl-OR^{S0}, -OR^{S0}, -R^{S0} or cyano; wherein each R^{S0} is independently hydrogen, C_1-C_6alkyl, C_1-C_6haloalkyl, -(C_0-C_6alkyl)-Ar, -(C_0-C_6alkyl)-Het, -(C_0-C_6alkyl)-Cak, or -(C_0-C_6alkyl)-Hca, wherein Ar, Het, Cak, Hca, alkyl, and haloalkyl are optionally substituted with C_1-C_6alkyl, halogen, C_1-C_6haloalkyl or cyano;

R^1 is hydrogen or C_1-C_6alkyl;

or R′ and R^1 combined with the atoms to which they are attached form a five- to eight-membered Hca; and

each R^2 is independently hydrogen, halogen, -C_1-C_6alkyl, -C_1-C_6alkyl-OR^{S2} or -OR^{S2}.

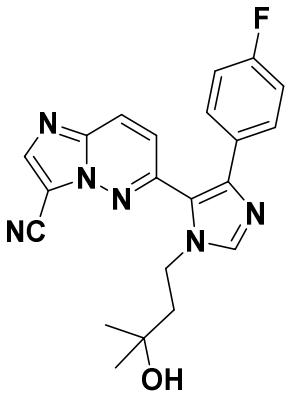
7. The compound according to claim 1 that is 6-(4-(4-fluorophenyl)-1-*cis*-3-hydroxycyclobutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile,



,

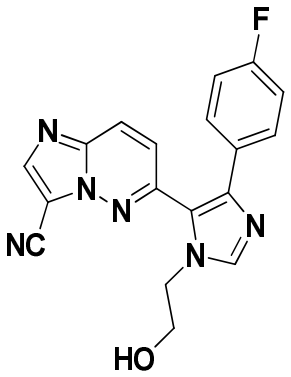
or a pharmaceutically acceptable salt thereof;

6-(4-(4-fluorophenyl)-1-(3-hydroxy-3-methylbutyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile,



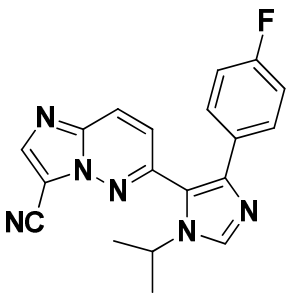
or a pharmaceutically acceptable salt thereof;

6-(4-(4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile,



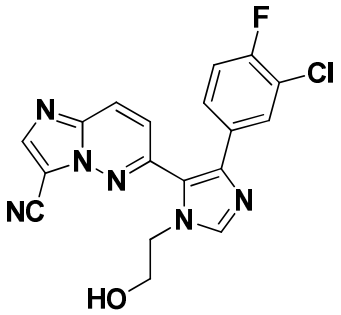
or a pharmaceutically acceptable salt thereof; or

6-(4-(4-fluorophenyl)-1-isopropyl-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile,



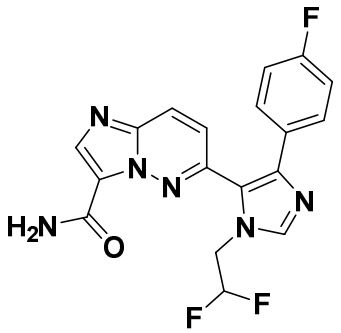
or a pharmaceutically acceptable salt thereof.

8. The compound according to claim 1 that is 6-(4-(3-chloro-4-fluorophenyl)-1-(2-hydroxyethyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carbonitrile,



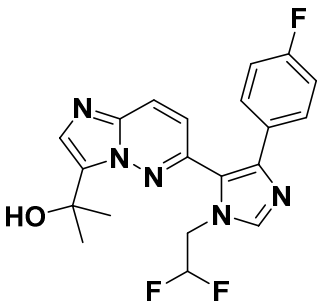
or a pharmaceutically acceptable salt thereof.

9. The compound according to claim 1 that is 6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazine-3-carboxamide,



or a pharmaceutically acceptable salt thereof; or

2-(6-(1-(2,2-difluoroethyl)-4-(4-fluorophenyl)-1*H*-imidazol-5-yl)imidazo[1,2-*b*]pyridazin-3-yl)propan-2-ol,



or a pharmaceutically acceptable salt thereof.

10. A pharmaceutical composition comprising a pharmaceutically acceptable diluent, carrier, or excipient and a compound according to any one of claims 1 –9.

11. A compound according to any of claims 1 –9, for use in therapy.

12. The compound for use of claim 11, wherein the disease or condition is mediated by or involves GDF-8, or wherein the disease or condition is mediated by or involves TGF-β.

13. The compound of claim 11 or claim 12, for use in treating pulmonary hypertension, chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcer, ocular disorder, corneal wound, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal or sub-dermal adhesion, kidney fibrosis, lung fibrosis, idiopathic pulmonary fibrosis, liver fibrosis, hepatitis B, hepatitis C, alcohol-induced hepatitis, cancer, haemochromatosis, primary biliary cirrhosis, restenosis, retroperitoneal fibrosis, mesenteric fibrosis, endometriosis, keloids, abnormal bone function, inflammatory disorder, scarring or photoaging of the skin; or

    for use in treating benign or malignant tumor, carcinoma of the brain, kidney, liver, adrenal gland, bladder, breast, stomach, gastric tumors, ovaries, colon, rectum, prostate, pancreas, lung, vagina or thyroid, sarcoma, glioblastomas, multiple myeloma or gastrointestinal cancer, colon carcinoma or colorectal adenoma, tumor of the neck and head, epidermal hyperproliferation, melanoma, psoriasis, prostate hyperplasia, neoplasia, neoplasia of epithelial character, leukemias, lymphomas, mammary carcinoma or leukemia; or

    for use in treating Cowden syndrome, Lhermitte-Dudos disease, Bannayan-Zonana syndrome, or other disease in which the PI3K/PKB pathway is aberrantly activated.

14. The compound according to any of claims 1 to 9, for use in the treatment of cancer wherein the compound is used in combination with one or more chemotherapeutic agents independently selected from the group consisting of antimetabolites, alkylating agents, coordination compounds, platinum complexes, DNA cross-linking compounds, inhibitors of transcription enzymes, tyrosine kinase inhibitors, protein kinase inhibitors, topoisomerase inhibitors, DNA minor-groove binding compounds, vinca alkyloids,

taxanes, antitumor antibiotics, hormones, aromatase inhibitors, enzymes, growth factor receptors antibodies, cytokines, cell surface markers antibodies, HDAC inhibitors, HSP 90 inhibitors, BCL-2 inhibitors, B-raf inhibitors, MEK inhibitors, mTOR inhibitors, proteasome inhibitors and monoclonal antibodies.

15. The compound for use according to claim 14 , wherein the one or more chemotherapeutic agents is independently selected from the group consisting of mechlorothamine, cyclophosphamide, ifosfamide, melphalan, chlorambucil, ethyleneimines, methylmelamines, procarbazine, dacarbazine, temozolomide, busulfan, carmustine, lomustine, methotrexate, fluorouracil, capecitabine, cytarabine, gemcitabine, cytosine arabinoside, mecaptopurine, fludarabine, cladribine, thioguanine, azathioprine, vinblastine, vincristine, paclitaxel, docetaxel, colchicine, actinomycin D, daunorubicin, bleomycin,L-asparaginase, cisplatin, carboplatin, oxaliplatin, prednisone, dexamethasone, amino glutethimide, formestane, anastrozole, hydroxyprogesterone caproate, medroxyprogesterone, tamoxifen, amsacrine, mitoxantrone, topotecan, irinotecan, camptothecin, afatinib, axitinib, bosutinib, bortezomib, carfilzomib, cabozantinib, cediranib, crizotinib, dasatinib, dabrafenib, evorolimus, ibrutinib, LDK378, LGX818, MEK162, regorafenib, ruxolitinib, selumetinib, sorafenib, trametinib, vemurafenib, erlotinib, gefitinib, imatinib, lapatinib, lestaurtinib, nilotinib, palbociclib, pazopanib, pomatinib, semaxanib, sirolimus, sunitinib, temsirolimus, vatalanib, vandetanib, anti Her2 antibodies, interferon-α , interferon-γ, interleukin 2, GM CSF, anti CTLA 4 antibodies, rituximab, anti CD33 antibodies, MGCD0103, vorinostat, 17-AAG, thalidomide, lenalidomide, rapamycin, CCI-779, doxorubicine, gemcitabine, melphalan, NPI052, gemtuzumab, alemtuzumab, cetuximab, ibritumomab tiuxaetan, tositumomab, iodine-131 tositumomab, trastuzumab, ado-trastuzumab emtansine, obinutuzumab, bevacizumab, rituximab, and anti-TRAIL death receptor antibodies.

16. A compound according to any of claims 1-9, for use in treating cancer wherein the compound is administered in combination with a therapeutically effective amount of one or more immuno-oncology agents.

17. A compound of any of claims 1-9, for use in treating cancer wherein the compound is administered in conjunction with an anti-cancer agent which is an antibody or an antigen-

binding portion thereof that binds specifically to a Programmed Death-1 (PD-1) receptor and inhibits PD-1 activity.

18. The compound for use according to claim 17, wherein the anti-PD-1 antibody is nivolumab.