

BENZIMIDAZOLONE DERIVATIVES AS BROMODOMAIN INHIBITORS

[0001] This application claims the benefits of U.S. Provisional Application 61/805,995, filed on March 28, 2013, and U.S. Provisional Application 61/860,230, filed on July 30, 2013, both of which are incorporated herein by reference in their entireties.

FIELD

[0002] This application relates to chemical compounds which may inhibit or otherwise modulate the activity of a bromodomain-containing protein, including bromodomain-containing protein 4 (BRD4), and to compositions and formulations containing such compounds, and methods of using and making such compounds.

BACKGROUND

[0003] The bromodomain and extraterminal (BET) family of proteins (BET proteins) are readers of the epigenetic code that couple acetylation of lysine residues on histones to changes in chromatin structure and gene expression. The BET family includes BRD2, BRD3, BRD4, and BRDT, all of which are widely expressed across diverse tissues, with the exception of the BRDT, whose expression is restricted to the testes. See Wu, S.Y. & Chiang, C.M., *J. Biol. Chem.*, 282: 13141-13145 (2007). Each BET family member contains tandem bromodomains in the N-terminal regions that specifically bind acetylated lysine residues in histones H3 and H4. Id. Once bound to histones, BET proteins recruit protein complexes that modulate gene transcription either directly, such as transcriptional activators or repressors, or indirectly such as chromatin remodeling complexes. BRD4 is the most well studied member of the BET family and is known to preferentially recognize tetra-acetylated histone H4 epigenetic marks. See Filippakopoulos, P., et al., *Cell*, 149: 214-231 (2012). BRD4 recruits the p-TEFb complex to nucleosomes, which in turn phosphorylates the C-terminal tail of RNA polymerase II and increases the transcriptional elongation of neighboring genes. See Yang, Z., et al., *Mol. Cell Biol.*, 28: 967-976 (2008); Urano, E., et al., *FEBS Lett.*, 582: 4053-4058 (2008).

[0004] The epigenetic code, including histone acetylation, is highly perturbed in many pathological disease states, resulting in the aberrant expression of genes that control cell fate, cell differentiation, cell survival, and inflammatory processes. See, e.g., Cohen, I., et al., *Genes Cancer*, 2: 631-647 (2011); Brooks, W.H., et al., *J. Autoimmun.*, 34: J207-219 (2010);

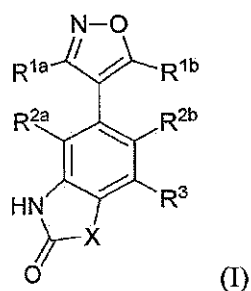
5 Wierda, R.J., et al., *J. Cell Mol. Med.*, 14: 1225-1240 (2010); Shirodkar, A.V. & Marsden, P.A., *Curr. Opin. Cardiol.*, 26: 209-215 (2011); Villeneuve, L.M., et al., *Clin. Exp. Pharmacol. Physiol.*, 38: 401-409 (2011). BET proteins including BRD4 have been identified as important mediators of altered gene expression profiles found in numerous diseases including cancer, diabetes, obesity, atherosclerosis, cardiovascular and renal disorders, and

10 viral infection. See Muller, S., et al., *Expert Rev. Mol. Med.*, 13: e29 (2011); Zhou, M., et al., *J. Virol.*, 83: 1036-1044 (2009); Chung, C.W., et al., *J. Med. Chem.*, 54: 3827-3838 (2011). For example, MYC has been implicated in the majority of human cancers and BET proteins have been identified as regulatory factors of c-Myc; inhibition of BET, including BRD4, has been shown to downregulate MYC transcription. See Delmore, J.E., et al. *Cell*,

15 146, 904-17 (2011); Lovén, J. et al., *Cell*, 153, 320-34 (2013). Inhibitors and modulators of BET proteins, including BRD4, are therefore needed.

SUMMARY

[0005] One aspect provides for a compound of Formula (I)



20

wherein

R^{1a} and R^{1b} are each independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ hydroxyalkyl, C₃-C₆ cycloalkyl, or CH₂-C₃-C₆ cycloalkyl;

R^{2a} and R^{2b} are each independently H or halogen;

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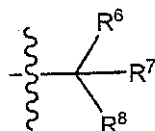
R³ is

C₅-C₁₀ aryl, C₅-C₁₀ heteroaryl, or C₅-C₁₀ heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups; or

-S(O)₂NHR⁴,

wherein R⁴ is C₁-C₆ alkyl or C₃-C₇ cycloalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups; or

a moiety of the formula



wherein

R⁶ is H, OH, or halogen; and R⁷ and R⁸ are each independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, or C₅-C₁₂ heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups; or

R⁶ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, phenyl, naphthyl, or C₃-C₁₂ heteroaryl; and R⁷ and R⁸ together form a C₁-C₆ alkylidene group having a double bond with the carbon to which each of R⁶, R⁷, and R⁸ are bound wherein each of the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, phenyl, naphthyl, or C₃-C₁₂ heteroaryl groups is optionally substituted with from 1 to 5 R²⁰ groups;

X is N-Q, or O;

Q is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, benzyl or substituted benzyl;

each R²⁰ is independently C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, halogen, oxo, -OR^a, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -OC(O)NR^aR^b, -NR^aR^b, -NR^aC(O)R^b, -NR^aC(O)OR^b, -S(O)_{0.2}R^a, -S(O)₂NR^aR^b, -NR^aS(O)₂R^b, -N₃, -CN, or -NO₂, wherein each C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl is optionally substituted with from one to five halogen, oxo, -OR^a, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -OC(O)NR^aR^b, -NR^aR^b, -NR^aC(O)R^b, -NR^aC(O)OR^b, -S(O)_{0.2}R^a, -S(O)₂NR^aR^b, -NR^aS(O)₂R^b, -N₃, -CN, or -NO₂;

each R^a and R^b is independently H; or C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, each of which is optionally substituted with from one to five R²¹; or R^a and R^b together with the atoms to which they are attached form a heterocycle, and;

each R²¹ is independently C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, or halogen;

or a pharmaceutically acceptable salt thereof.

[0006] Another aspect provides for a compound selected from the group consisting the title compounds listed in Examples 1 to 201.

5 [0007] Another aspect provides for a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

[0008] Another aspect provides for a use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in therapy. Such aspects include use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for the treatment of a subject
10 having a disease or condition responsive to the inhibition of a bromodomain-containing protein; and use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of a human having a disease or condition responsive to the inhibition of a bromodomain-containing protein. Another aspect provides for a method of treating a subject having a disease or condition responsive to the
15 inhibition of a bromodomain-containing protein, comprising administering a therapeutically effective amount of a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In some aspects, the bromodomain-containing protein is BRD4. In some aspects, the disease or condition is an autoimmune disease, an inflammatory disease, a neurodegenerative disease, a cancer, a cardiovascular disorder, a renal disorder, a viral infection, or obesity. In certain
20 embodiments, the disease or condition is chosen from rheumatoid arthritis, osteoarthritis, atherosclerosis, psoriasis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, asthma, chronic obstructive airways disease, pneumonitis, dermatitis, alopecia, nephritis, vasculitis, atherosclerosis, Alzheimer's disease, hepatitis, primary biliary cirrhosis, sclerosing cholangitis, diabetes (including type I diabetes), acute rejection of
25 transplanted organs, lymphomas, multiple myelomas, leukemias, neoplasms and solid tumors. In some aspects the disease or condition is a solid tumor of the colon, rectum, prostate, lung, pancreas, liver, kidney, cervix, stomach, ovaries, breast, skin, brain, meninges, or central nervous system (including a neuroblastoma or a glioblastoma). In some aspects, the disease or condition is a lymphoma. In some aspects, the disease or condition is a B-cell lymphoma.
30 In some aspects, the disease or condition is Burkitt's lymphoma. In some aspects, the disease or condition is diffuse large B-cell lymphoma. In some aspects, the disease or condition is multiple myeloma. In some aspects the disease or condition is a carcinoma. In some aspects

the disease or condition is NUT midline carcinoma. In some aspects the subject is a human.

[0009] Another aspect provides for a method of downregulating or decreasing MYC transcription in a subject, comprising administering to the subject a compound of Formula (I). Another aspect provides for a method of treating a disease or condition in a subject in which
5 activation of MYC is implicated, comprising administering to the subject a compound of Formula (I).

[0010] In some aspects, the compound is administered intravenously, intramuscularly, parenterally, nasally, or orally. In one aspect, the compound is administered orally.

[0011] Also provided is a method of inhibiting a bromodomain in a subject, comprising
10 providing to the subject a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically or a pharmaceutically acceptable salt thereof. Also provided is a method of inhibiting a bromodomain in a cell, comprising providing to the cell a compound of Formula (I). It is understood that providing to the cell may be accomplished by administering the compound to the subject. Also provided is a method of inhibiting a
15 bromodomain, comprising contacting the bromodomain with a compound of Formula (I), or a pharmaceutically acceptable salt thereof.

[0012] Also provided is the use of a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of a disease or condition responsive to bromodomain inhibition.

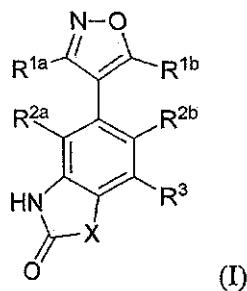
[0013] Also provided are kits that include a compound of Formula (I), or a pharmaceutically acceptable salt thereof. In one aspect, the kit further includes instructions for use. In one aspect, a kit includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and instructions for use of the compounds in the treatment of the diseases or conditions described above.

[0014] Also provided are articles of manufacture that include a compound of Formula (I), or
25 a pharmaceutically acceptable salt thereof. In one embodiment, the container may be a vial, jar, ampoule, preloaded syringe, or an intravenous bag.

DETAILED DESCRIPTION

[0015] Described herein are compounds of Formula (I), which include compounds of Formulae (Ia) and (Ib), compositions and formulations containing such compounds, and methods of using and making such compounds.

5 [0016] One aspect of the current disclosure relates to compounds of Formula (I)



wherein

R^{1a} and R^{1b} are each independently C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_1 - C_6 haloalkyl, C_1 - C_6 haloalkoxy, C_1 - C_6 hydroxyalkyl, C_3 - C_6 cycloalkyl, or CH_2 - C_3 - C_6 cycloalkyl;

10 R^{2a} and R^{2b} are each independently H or halogen;

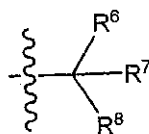
R^3 is

C_5 - C_{10} aryl, C_5 - C_{10} heteroaryl, or C_5 - C_{10} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; or

- $S(O)_2NHR^4$,

15 wherein R^4 is C_1 - C_6 alkyl or C_3 - C_7 cycloalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; or

a moiety of the formula



20 wherein

R^6 is H, OH, or halogen; and R^7 and R^8 are each independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl, or C_5 - C_{12} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; or

25 R^6 is H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, phenyl, naphthyl, or C_3 - C_{12} heteroaryl; and R^7 and R^8 together form a C_1 - C_6

alkylidene group having a double bond with the carbon to which each of R^6 , R^7 , and R^8 are bound wherein each of the C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, $-C_3$ - C_6 cycloalkyl, phenyl, naphthyl, or C_3 - C_{12} heteroaryl groups is optionally substituted with from 1 to 5 R^{20} groups;

5 X is N-Q, or O;

Q is H, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, benzyl or substituted benzyl;

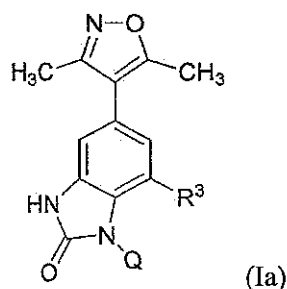
each R^{20} is independently C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_3 - C_6 heterocyclic, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl, halogen, oxo, $-OR^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-OC(O)NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-S(O)_{0-2}R^a$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2R^b$, $-N_3$, $-CN$, or $-NO_2$, wherein each C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_3 - C_6 heterocyclic, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl is optionally substituted with from one to five halogen, oxo, $-OR^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-OC(O)NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-S(O)_{0-2}R^a$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2R^b$, $-N_3$, $-CN$, or $-NO_2$;

15 each R^a and R^b is independently H; or C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_3 - C_6 heterocyclic, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl, each of which is optionally substituted with from one to five R^{21} ; or R^a and R^b together with the atoms to which they are attached form a heterocycle, and;

each R^{21} is independently C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_3 - C_6 heterocyclic, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl, or halogen;

20 or a pharmaceutically acceptable salt thereof.

[0017] One subset of compounds of Formula (I) relates to compounds of Formula (Ia)



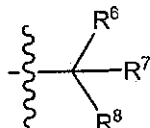
wherein

25 R^3 is C_5 - C_{10} aryl, C_5 - C_{10} heteroaryl, or C_5 - C_{10} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; or

-S(O)₂NHR⁴,

wherein R⁴ is C₁-C₆ alkyl or C₃-C₇ cycloalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups; or

a moiety of the formula



wherein

R⁶ is H, OH, or halogen; and R⁷ and R⁸ are each independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, or C₅-C₁₂ heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups; or

R⁶ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, phenyl, naphthyl, or C₃-C₁₂ heteroaryl; and R⁷ and R⁸ together form a C₁-C₆ alkylidene group having a double bond with the carbon to which each of R⁶, R⁷, and R⁸ are bound wherein each of the C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, phenyl, naphthyl, or C₃-C₁₂ heteroaryl groups is optionally substituted with from 1 to 5 R²⁰ groups;

Q is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, benzyl or substituted benzyl;

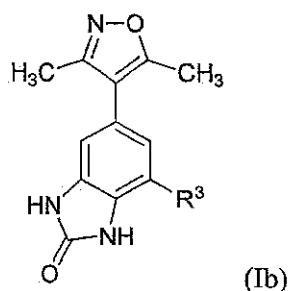
each R²⁰ is independently C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, halogen, oxo, -OR^a, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -OC(O)NR^aR^b, -NR^aR^b, -NR^aC(O)R^b, -NR^aC(O)OR^b, -S(O)₀₋₂R^a, -S(O)₂NR^aR^b, -NR^aS(O)₂R^b, -N₃, -CN, or -NO₂, wherein each C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl is optionally substituted with from one to five halogen, oxo, -OR^a, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -OC(O)NR^aR^b, -NR^aR^b, -NR^aC(O)R^b, -NR^aC(O)OR^b, -S(O)₀₋₂R^a, -S(O)₂NR^aR^b, -NR^aS(O)₂R^b, -N₃, -CN, or -NO₂;

each R^a and R^b is independently H; or C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, each of which is optionally substituted with from one to five R²¹; or R^a and R^b together with the atoms to which they are attached form a heterocycle, and;

each R²¹ is independently C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, or halogen;

or a pharmaceutically acceptable salt thereof.

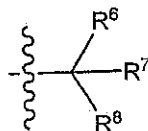
[0018] Another subset of compounds of Formula (I) relates to compounds of Formula (Ib)



wherein

R^3 is

- 5 C_5 - C_{10} aryl, C_5 - C_{10} heteroaryl, or C_5 - C_{10} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; or
 $-S(O)_2NHR^4$,
 wherein R^4 is C_1 - C_6 alkyl or C_3 - C_7 cycloalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; or
 10 a moiety of the formula



wherein

- 15 R^6 is H, OH, or halogen; and R^7 and R^8 are each independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl, or C_5 - C_{12} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; or
 R^6 is H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, phenyl, naphthyl, or C_3 - C_{12} heteroaryl; and R^7 and R^8 together form a C_1 - C_6
 20 alkylidene group having a double bond with the carbon to which each of R^6 , R^7 , and R^8 are bound wherein each of the C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, phenyl, naphthyl, or C_3 - C_{12} heteroaryl groups is optionally substituted with from 1 to 5 R^{20} groups;
 each R^{20} is independently C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_3 - C_6
 25 heterocyclic, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl, halogen, oxo, $-OR^a$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)NR^aR^b$, $-OC(O)NR^aR^b$, $-NR^aR^b$, $-NR^aC(O)R^b$, $-NR^aC(O)OR^b$, $-S(O)_{0-2}R^a$, $-S(O)_2NR^aR^b$, $-NR^aS(O)_2R^b$, $-N_3$, $-CN$, or $-NO_2$, wherein each C_1 - C_6

alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl is optionally substituted with from one to five halogen, oxo, -OR^a, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -OC(O)NR^aR^b, -NR^aR^b, -NR^aC(O)R^b, -NR^aC(O)OR^b, -S(O)_{0.2}R^a, -S(O)₂NR^aR^b, -NR^aS(O)₂R^b, -N₃, -CN, or -NO₂;

5 each R^a and R^b is independently H; or C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, each of which is optionally substituted with from one to five R²¹; or R^a and R^b together with the atoms to which they are attached form a heterocycle, and;

each R²¹ is independently C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, or halogen;

10 or a pharmaceutically acceptable salt thereof.

[0019] In some compounds of Formula (I), R^{1a} and R^{1b} are each independently C₁-C₆ alkyl. In some compounds of Formula (I), R^{1a} and R^{1b} are each independently methyl, ethyl, or propyl. In some compounds of Formula (I), R^{1a} and R^{1b} are different. In some compounds of

15 Formula (I), R^{1a} and R^{1b} are the same. In some compounds of Formula (I), R^{1a} and R^{1b} are both methyl.

[0020] In some compounds of Formula (I), R^{2a} and R^{2b} are both H. In some compounds of Formula (I), R^{2a} and R^{2b} are both halo. In some compounds of Formula (I), one of R^{2a} and R^{2b} is H and the other is halo. In some compounds of Formula (I), the halo is -F or -Cl.

20 [0021] In some compound of Formula (I), X is N-Q.

[0022] In some compounds of Formula (I) or (Ia), Q is H, C₁-C₃ alkyl, or C₁-C₃ haloalkyl.

[0023] In some compounds of Formula (I), (Ia) or (Ib), R³ is C₅-C₁₀ aryl, C₅-C₁₀ heteroaryl, or C₅-C₁₀ heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups.

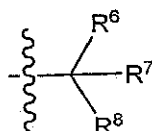
[0024] In some compounds of Formula (I), (Ia) or (Ib), R³ is phenyl, oxetanyl, tetrahydrofuranyl, furanyl, tetrahydrothiophenyl, thiophenyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, dioxolanayl, oxazolyl, thiazolyl, imidazolyl, imidazoliny, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyranyl, pyridinyl, piperidinyl, dioxanyl, morpholinyl, thiomorpholinyl, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, triazinyl, indoliziny, indolyl, isoindolyl,

25 indoliny, chromenyl, benzofuranyl, benzothiophenyl, dihydrobenzothiophenyl, indazolyl,

30

benzimidazolyl, benzothiazolyl, benzoxazolyl, imidazo[1,2-a]pyridinyl, purinyl, quinolinyl, quinoliziny, isoquinolinyl, cinnolinyl, phthalazinyl, quinazolinyl, quinoxalinyl, indenyl, naphthalenyl, or azulenyl, each of which is optionally substituted with from 1 to 5 R^{20} groups.

[0025] In some compounds of Formula (I), (Ia) or (Ib), R^3 is a moiety of the formula

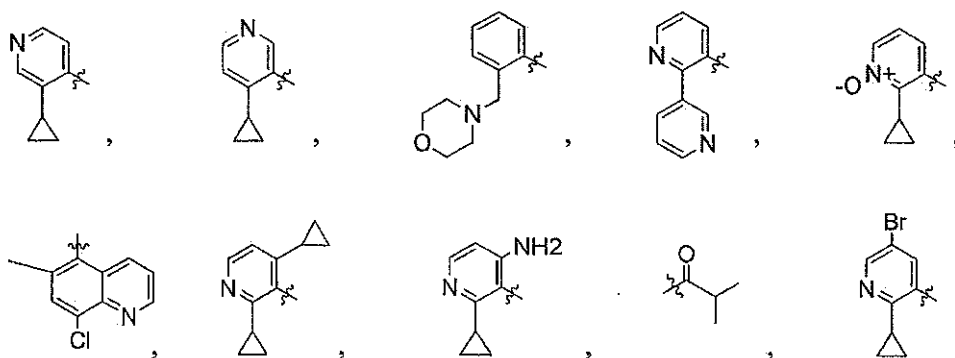


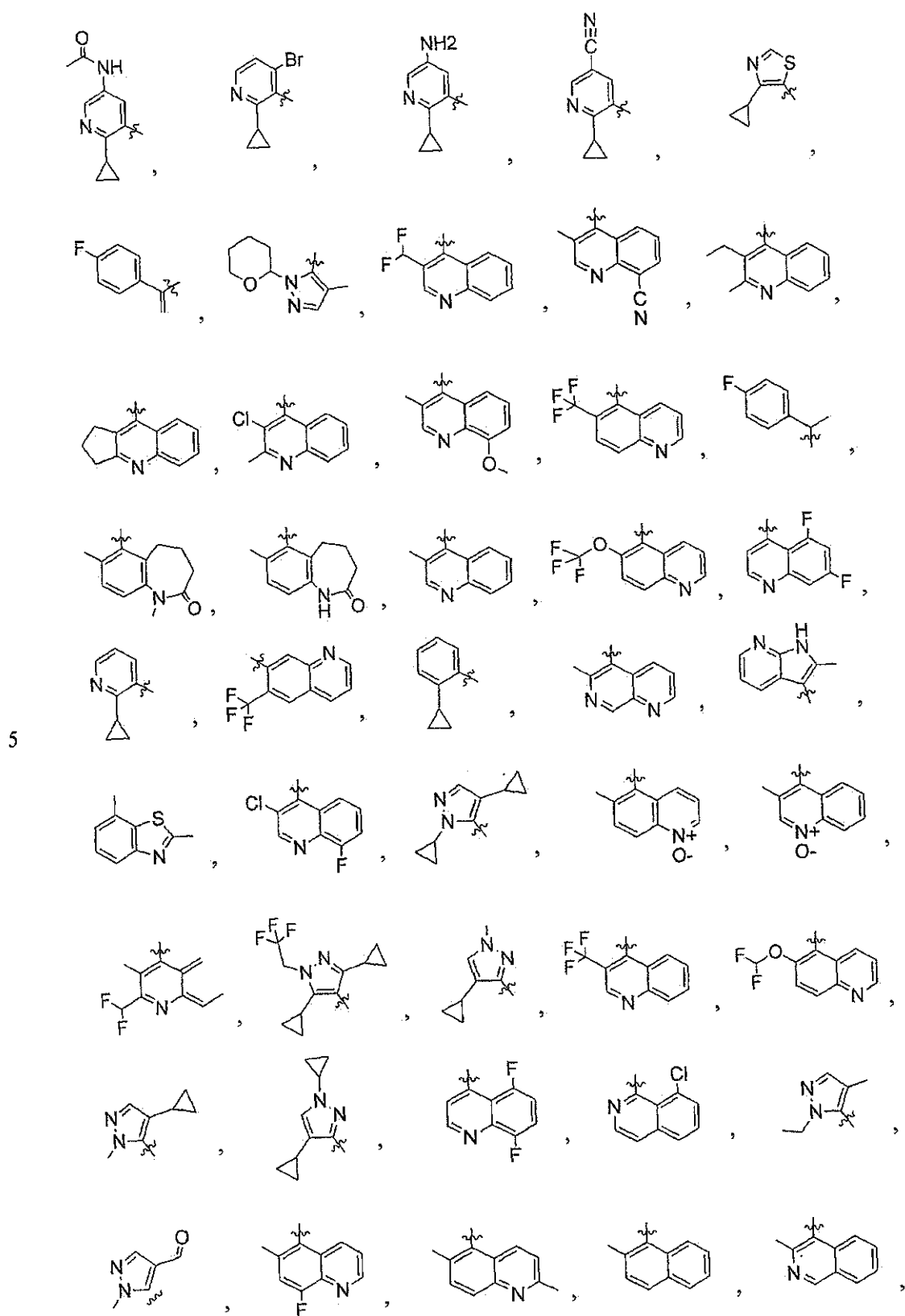
wherein R^6 is H, OH, or halogen; and R^7 and R^8 are each independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl, or C_5 - C_{12} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups.

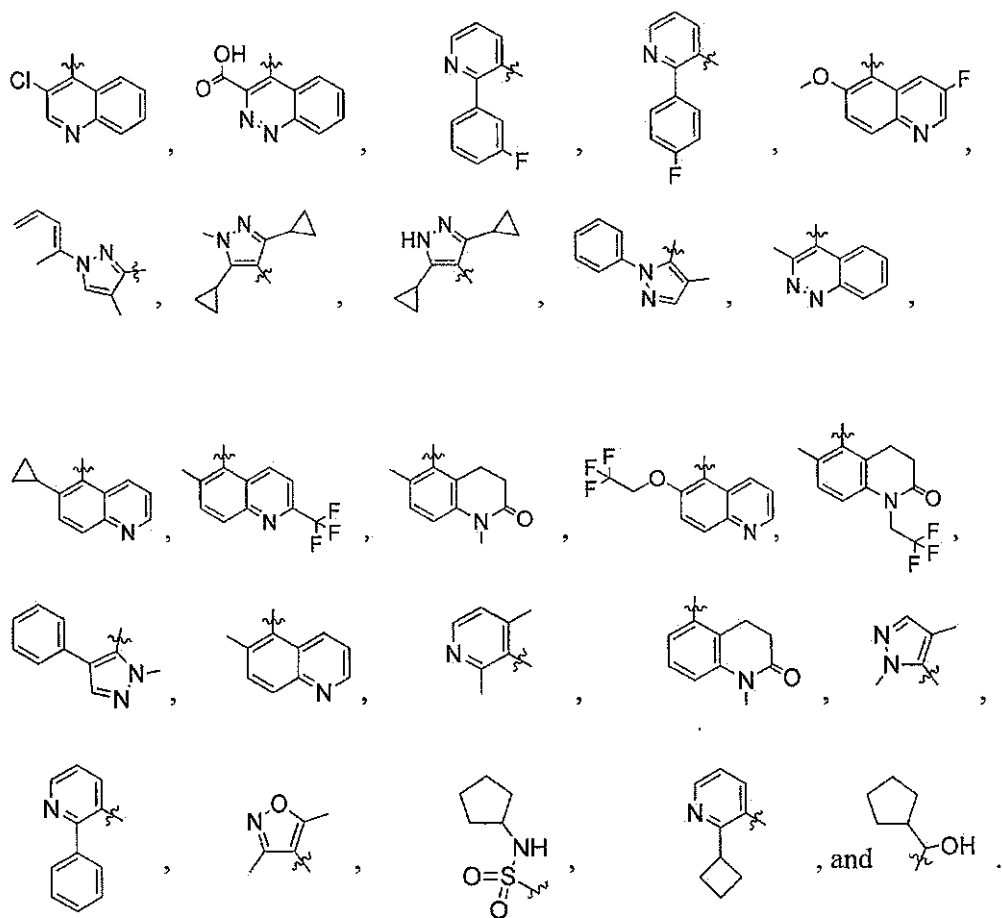
In some compounds, R^6 is OH. In some compounds, R^7 and R^8 are each independently C_1 - C_6

alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl, or C_5 - C_{12} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups. In some compounds of Formula (I), (Ia) or (Ib), R^7 and R^8 are each independently C_1 - C_6 alkyl, C_6 aryl or C_6 heteroaryl, each of which is optionally substituted with from 1 to 5 R^{20} groups. In some compounds, R^7 and R^8 are each independently C_6 aryl or C_6 heteroaryl (e.g. a pyridyl), each of which is optionally substituted with from 1 to 5 R^{20} groups. In some compounds of Formula (I), (Ia) or (Ib), R^7 and R^8 are each independently C_1 - C_6 alkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups.

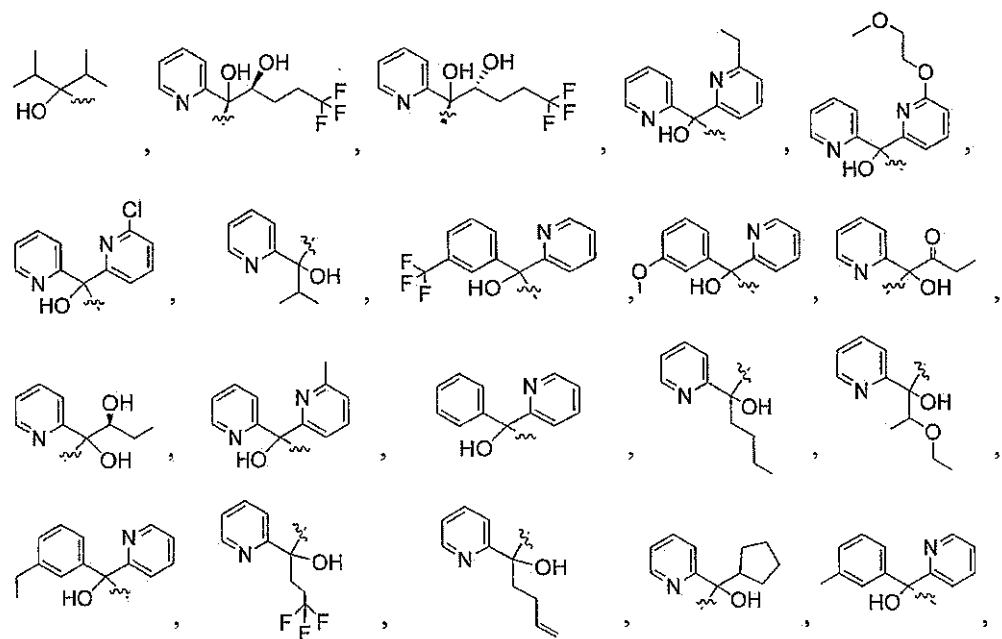
[0026] Other non-limiting examples of R^3 include the following:

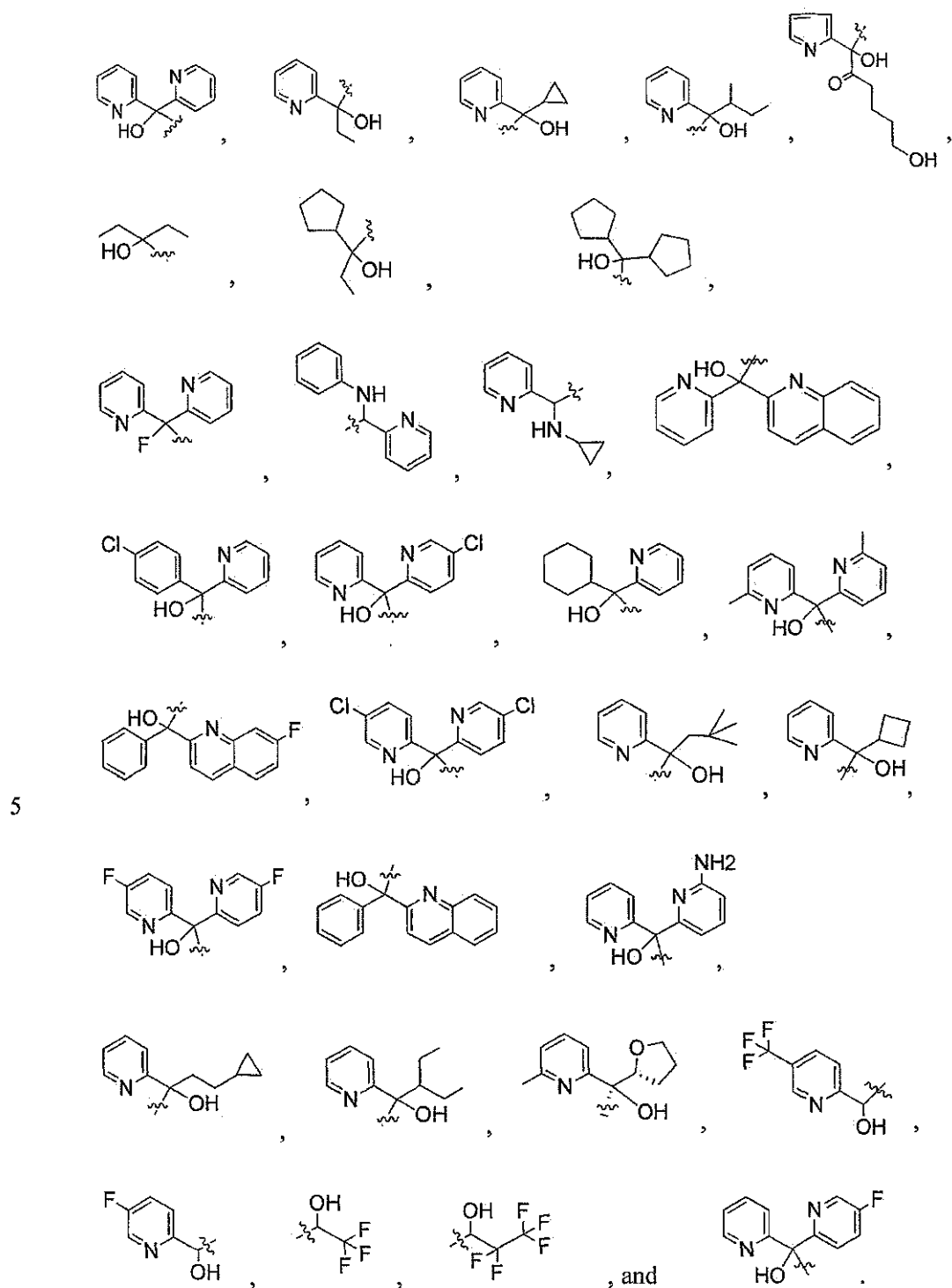




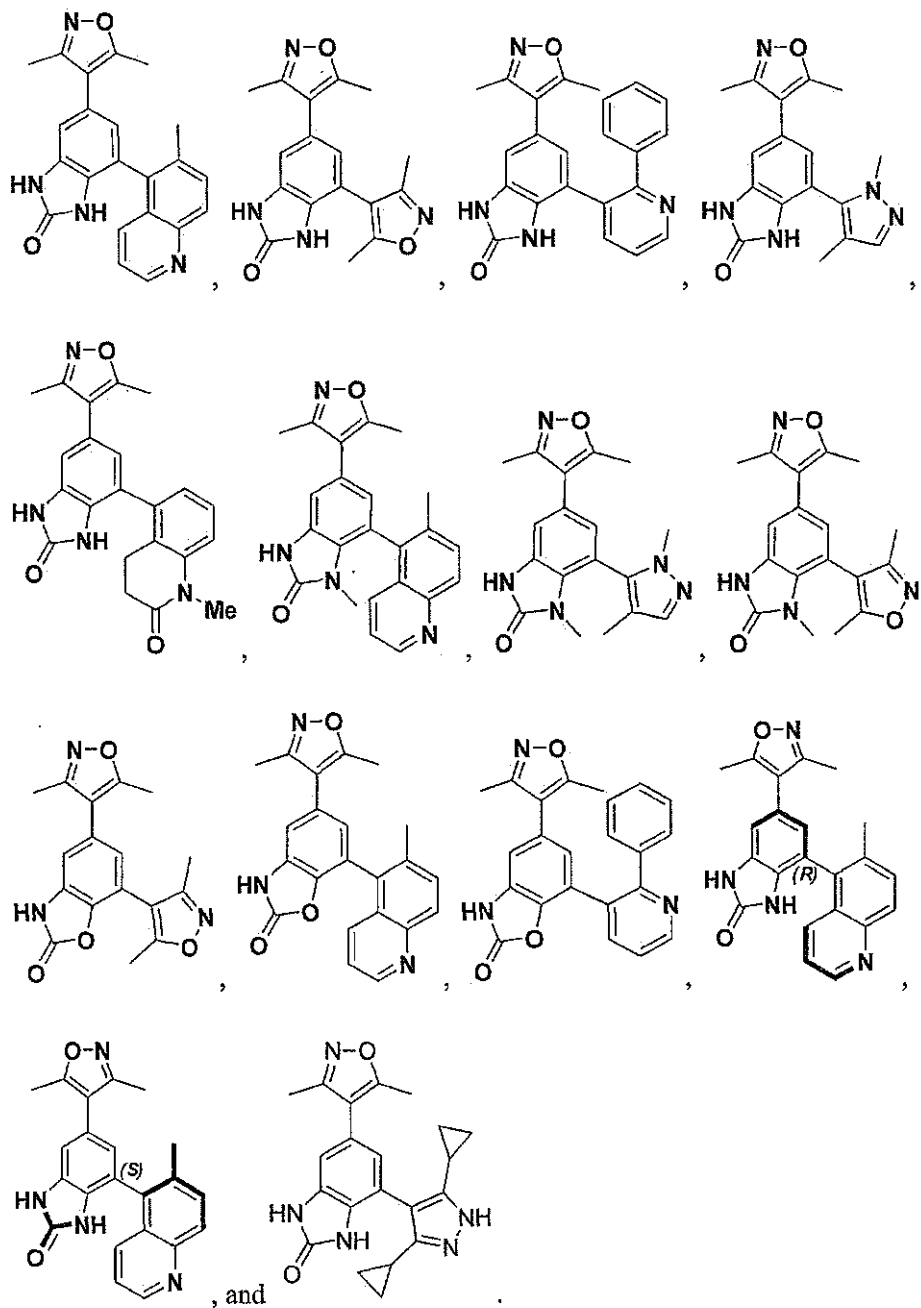


[0027] Additional non-limiting examples of R³ include the following:

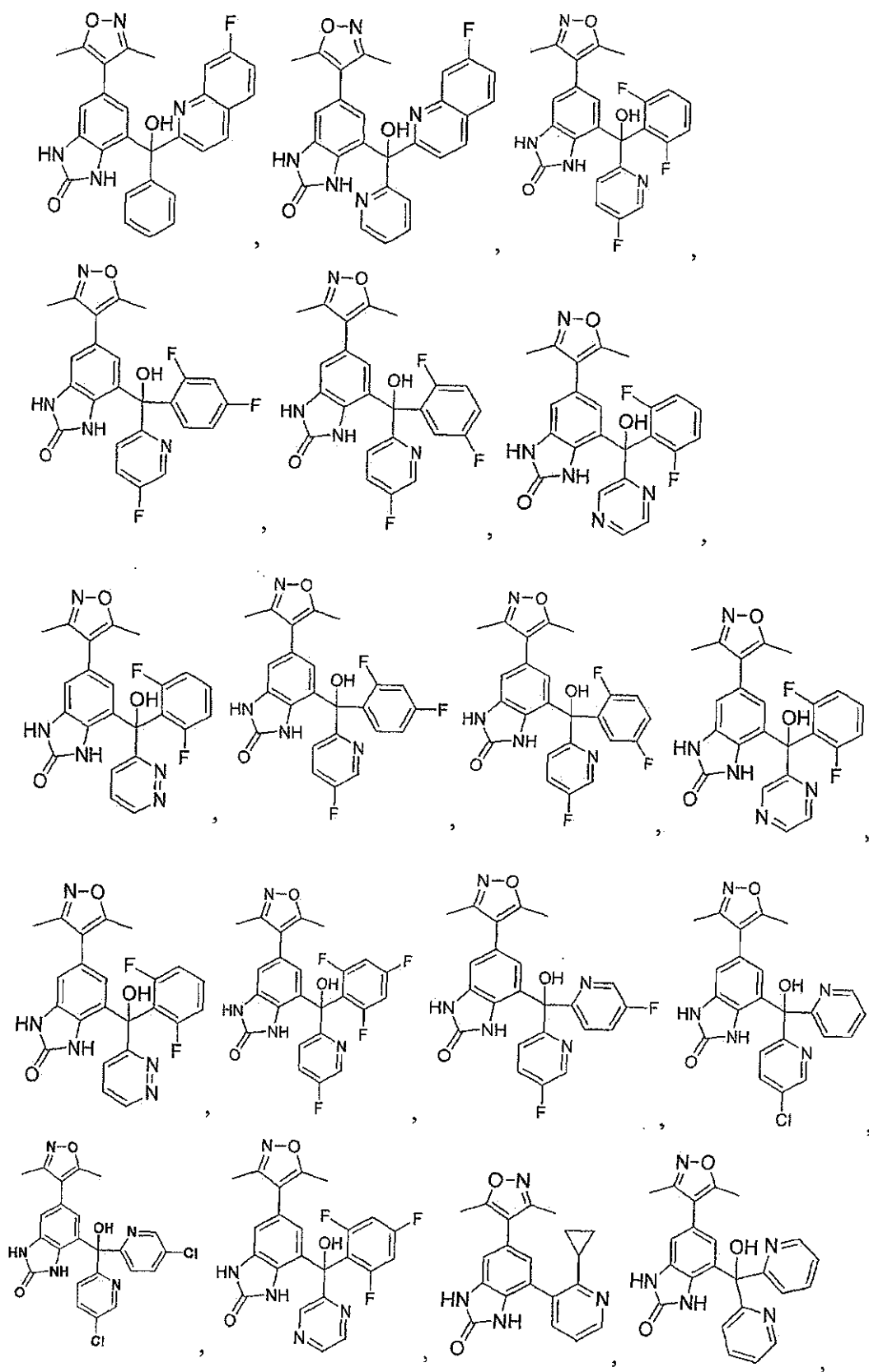


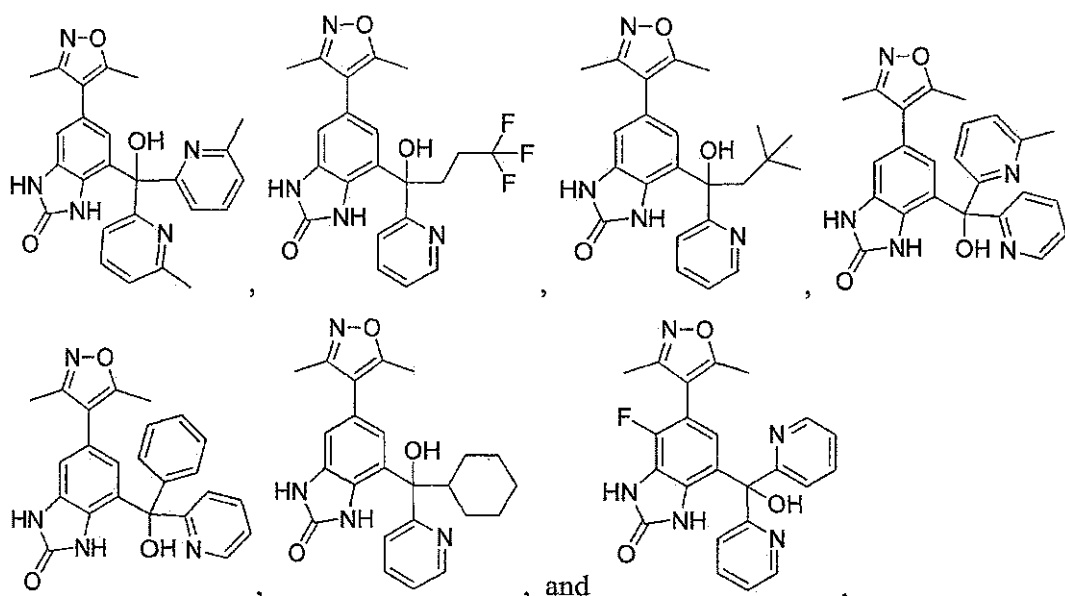


[0028] In another aspect, the compound of Formula (I) may be any of the following
 10 compounds:



- 5 [0029] In another aspect, the compound of Formula (I) may be any of the following compounds:





[0030] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art. It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural referents unless the context clearly dictates otherwise. Thus, e.g., reference to "the compound" includes a plurality of such compounds and reference to "the assay" includes reference to one or more assays and equivalents thereof known to those skilled in the art, and so forth.

[0031] A dash at the front or end of a chemical group is a matter of convenience; chemical groups may be depicted with or without one or more dashes without losing their ordinary meaning. A wavy line drawn through a line in a structure indicates a point of attachment of a group. A dashed line indicates an optional bond. Unless chemically or structurally required, no directionality is indicated or implied by the order in which a chemical group is written.

For instance, the group $-\text{SO}_2\text{CH}_2-$ is equivalent to $-\text{CH}_2\text{SO}_2-$ and both may be connected in either direction. The prefix C_{u-v} indicates that the following group has from u to v carbon atoms, one or more of which, in certain groups (e.g. heteroalkyl, heteroaryl, heteroarylalkyl, etc.), may be replaced with one or more heteroatoms or heteroatomic groups. For example, C_{1-6} alkyl indicates that the alkyl group has from 1 to 6 carbon atoms.

[0032] Also, certain commonly used alternative chemical names may or may not be used. For example, a divalent group such as a divalent "alkyl" group, a divalent "aryl" group, etc., may also be referred to as an "alkylene" group or an "alkylenyl" group, an "arylene" group or

an “arylenyl” group, respectively.

[0033] “Alkyl” refers to any group derived from a linear or branched saturated hydrocarbon.

Alkyl groups include, but are not limited to, methyl, ethyl, propyls such as propan-1-yl, propan-2-yl (iso-propyl), butyls such as butan-1-yl, butan-2-yl (sec-butyl), 2-methyl-propan-1-yl (iso-butyl), 2-methyl-propan-2-yl (t-butyl), pentyls, hexyls, octyls, decyls, and the like.

Unless otherwise specified, an alkyl group has from 1 to about 10 carbon atoms, for example from 1 to 10 carbon atoms, for example from 1 to 6 carbon atoms, for example from 1 to 4 carbon atoms.

[0034] “Alkenyl” refers to any group derived from a straight or branched hydrocarbon with at least one carbon-carbon double bond. Alkenyl groups include, but are not limited to, ethenyl (vinyl), propenyl (allyl), 1-butenyl, 1,3-butadienyl, and the like. Unless otherwise specified, an alkenyl group has from 2 to about 10 carbon atoms, for example from 2 to 10 carbon atoms, for example from 2 to 6 carbon atoms, for example from 2 to 4 carbon atoms.

[0035] “Alkynyl” refers to any group derived from a straight or branched hydrocarbon with at least one carbon-carbon triple bond and includes those groups having one triple bond and one double bond. Examples of alkynyl groups include, but are not limited to, ethynyl ($\text{-C}\equiv\text{CH}$), propargyl ($\text{-CH}_2\text{C}\equiv\text{CH}$), (*E*)-pent-3-en-1-ynyl, and the like. Unless otherwise specified, an alkynyl group has from 2 to about 10 carbon atoms, for example from 2 to 10 carbon atoms, for example from 2 to 6 carbon atoms, for example from 2 to 4 carbon atoms.

[0036] “Aryl” refers to any group derived from one or more aromatic rings, that is, a single aromatic ring, a bicyclic or a multicyclic ring system. Aryl groups include, but are not limited to, those groups derived from acenaphthylene, anthracene, azulene, benzene, chrysene, a cyclopentadienyl anion, naphthalene, fluoranthene, fluorene, indane, perylene, phenalene, phenanthrene, pyrene and the like.

[0037] “Arylalkyl” (also “aralkyl”) refers to any combination of one or more aryl groups and one or more alkyl groups. Arylalkyl groups include, but are not limited to, those groups derived from benzyl, tolyl, dimethylphenyl, 2-phenylethan-1-yl, 2-naphthylmethyl, phenylmethylbenzyl, 1,2,3,4-tetrahydronaphthyl, and the like. An arylalkyl group comprises from 6 to about 30 carbon atoms, for example the alkyl group can comprise from 1 to about 10 carbon atoms and the aryl group can comprise from 5 to about 20 carbon atoms.

[0038] "Cycloalkyl" refers to a cyclic alkyl group. A cycloalkyl group can have one or more cyclic rings and includes fused and bridged groups. Examples include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, adamantyl, methylcyclopropyl (cyclopropylmethyl), ethylcyclopropyl, and the like.

5 [0039] "Halo" and "halogen" refer to fluoro, chloro, bromo and iodo.

[0040] "Haloalkyl" refers to an alkyl wherein one or more hydrogen atoms are each replaced by a halogen. Examples include, but are not limited to, $-\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{F}$, $-\text{CH}_2\text{Br}$, $-\text{CFClBr}$, $-\text{CH}_2\text{CH}_2\text{Cl}$, $-\text{CH}_2\text{CH}_2\text{F}$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CH}_2\text{CCl}_3$, and the like, as well as alkyl groups such as perfluoroalkyl in which all hydrogen atoms are replaced by fluorine atoms.

10 [0041] "Heteroalkyl" refers to an alkyl in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatom or heteroatomic group. Heteroatoms include, but are not limited to, N, P, O, S, etc. Heteroatomic groups include, but are not limited to, $-\text{NR}-$, $-\text{O}-$, $-\text{S}-$, $-\text{PH}-$, $-\text{P}(\text{O})_2-$, $-\text{S}(\text{O})-$, $-\text{S}(\text{O})_2-$, and the like, where R is H, alkyl, aryl, cycloalkyl, heteroalkyl, heteroaryl or
 15 cycloheteroalkyl. The term "heteroalkyl" includes heterocycloalkyl (a cyclic heteroalkyl group), alkyl-heterocycloalkyl (a linear or branched C1-C6 alkyl group attached to a cyclic heteroalkyl group), and the like. Heteroalkyl groups include, but are not limited to, $-\text{OCH}_3$, $-\text{CH}_2\text{OCH}_3$, $-\text{SCH}_3$, $-\text{CH}_2\text{SCH}_3$, $-\text{NRCH}_3$, $-\text{CH}_2\text{NRCH}_3$, and the like, where R is hydrogen, alkyl, aryl, arylalkyl, heteroalkyl, or heteroaryl, each of which may be optionally substituted.
 20 A heteroalkyl group comprises from 1 to about 10 carbon and hetero atoms, e.g., from 1 to 6 carbon and hetero atoms.

[0042] "Heteroaryl" refers to an aryl group in which one or more of the carbon atoms (and any associated hydrogen atoms) are each independently replaced with the same or different heteroatom or heteroatomic group, as defined above. Heteroaryl groups include, but are not
 25 limited to, groups derived from acridine, benzoimidazole, benzothiophene, benzofuran, benzoxazole, benzothiazole, carbazole, carboline, cinnoline, furan, imidazole, imidazopyridine, indazole, indole, indoline, indolizine, isobenzofuran, isochromene, isoindole, isoindoline, isoquinoline, isothiazole, isoxazole, naphthyridine, oxadiazole, oxazole, perimidine, phenanthridine, phenanthroline, phenazine, phthalazine, pteridine,
 30 purine, pyran, pyrazine, pyrazole, pyridazine, pyridine, pyrimidine, pyrrole, pyrrolizine, quinazoline, quinoline, quinolizine, quinoxaline, tetrazole, thiadiazole, thiazole, thiophene,

triazole, xanthene, and the like.

[0043] "Heteroarylalkyl" refers to an arylalkyl group in which one or more carbon atoms (and any associated hydrogen atoms) are independently replaced with the same or different heteroatoms or heteroatomic groups, as defined above. Heteroarylalkyl groups include, but are not limited to, groups derived from heteroaryl groups with alkyl substituents (e.g. methylpyridines, ethylthiophenes, methylthiazoles, dimethylisoxazoles, etc.), hydrogenated heteroaryl groups (dihydroquinolines, e.g. 3,4-dihydroquinoline, dihydroisoquinolines, e.g. 1,2-dihydroisoquinoline, dihydroimidazole, tetrahydroimidazole, etc.), indoline, isoindoline, isoindolones (e.g. isoindolin-1-one), isatin, dihydrophthalazine, quinolinone, spiro[cyclopropane-1,1'-isoindolin]-3'-one, and the like.

[0044] "Heterocycle," "heterocyclic," and "heterocyclyl" refer to a single saturated or partially unsaturated non-aromatic ring or a non-aromatic multiple-ring system with at least one heteroatom or heteroatomic group, as defined above. Heterocycles include, but are not limited to, groups derived from azetidine, aziridine, imidazolidine, morpholine, oxirane (epoxide), oxetane, piperazine, piperidine, pyrazolidine, piperidine, pyrrolidine, pyrrolidinone, tetrahydrofuran, tetrahydrothiophene, dihydropyridine, tetrahydropyridine, quinuclidine, N-bromopyrrolidine, N-chloropiperidine, and the like.

[0045] The term "pharmaceutically acceptable" with respect to a substance refers to that substance which is generally regarded as safe and suitable for use without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio.

[0046] "Pharmaceutically acceptable salt" refers to a salt of a compound that is pharmaceutically acceptable and that possesses (or can be converted to a form that possesses) the desired pharmacological activity of the parent compound. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, benzenesulfonic acid, benzoic acid, camphorsulfonic acid, citric acid, ethanesulfonic acid, fumaric acid, glucoheptonic acid, gluconic acid, lactic acid, maleic acid, malonic acid, mandelic acid, methanesulfonic acid, 2-naphthalenesulfonic acid, oleic acid, palmitic acid, propionic acid, stearic acid, succinic acid, tartaric acid, p-toluenesulfonic acid, trimethylacetic acid, and the like, and salts formed when an acidic proton present in the parent compound is replaced by either a metal ion, e.g., an alkali metal ion, an alkaline earth

ion, or an aluminum ion; or coordinates with an organic base such as diethanolamine, triethanolamine, N-methylglucamine and the like. Also included in this definition are ammonium and substituted or quaternized ammonium salts. Representative non-limiting lists of pharmaceutically acceptable salts can be found in S.M. Berge et al., J. Pharma Sci., 66(1), 1-19 (1977), and Remington: The Science and Practice of Pharmacy, R. Hendrickson, ed., 21st edition, Lippincott, Williams & Wilkins, Philadelphia, PA, (2005), at p. 732, Table 38-5, both of which are hereby incorporated by reference herein.

[0047] "Subject" and "subjects" refers to humans, domestic animals (e.g., dogs and cats), farm animals (e.g., cattle, horses, sheep, goats and pigs), laboratory animals (e.g., mice, rats, hamsters, guinea pigs, pigs, rabbits, dogs, and monkeys), and the like.

[0048] "Treating" and "treatment" of a disease include the following:

- (1) preventing or reducing the risk of developing the disease, i.e., causing the clinical symptoms of the disease not to develop in a subject that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,
- (2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms, or
- (3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

[0049] "Effective amount" refers to an amount that may be effective to elicit the desired biological, clinical, or medical response, including the amount of a compound that, when administered to a subject for treating a disease, is sufficient to effect such treatment. The effective amount will vary depending on the compound, the disease and its severity and the age, weight, etc., of the subject to be treated. The effective amount can include a range of amounts.

[0050] It is understood that combinations of chemical groups may be used and will be recognized by persons of ordinary skill in the art. For instance, the group "hydroxyalkyl" would refer to a hydroxyl group attached to an alkyl group. A great number of such combinations may be readily envisaged.

[0051] Provided are also compounds in which from 1 to n hydrogen atoms attached to a carbon atom may be replaced by a deuterium atom or D, in which n is the number of

hydrogen atoms in the molecule. As known in the art, the deuterium atom is a non-radioactive isotope of the hydrogen atom. Such compounds exhibit may increase resistance to metabolism, and thus may be useful for increasing the half-life of the compounds when administered to a mammal. See, e.g., Foster, "Deuterium Isotope Effects in Studies of Drug
5 Metabolism," Trends Pharmacol. Sci., 5(12):524-527 (1984). Such compounds are synthesized by means well known in the art, for example by employing starting materials in which one or more hydrogen atoms have been replaced by deuterium.

[0052] Compounds of a given formula described herein encompasses the compound disclosed and all pharmaceutically acceptable salts, stereoisomers, tautomers, solvates, and
10 deuterated forms thereof, unless otherwise specified.

[0053] The pharmaceutical compositions of compounds of Formula (I) (including compounds of Formulae (Ia) and (Ib)) may be administered in either single or multiple doses by any of the accepted modes of administration of agents having similar utilities, for example as described in those patents and patent applications incorporated by reference, including
15 rectal, buccal, intranasal and transdermal routes, by intra-arterial injection, intravenously, intraperitoneally, parenterally, intramuscularly, subcutaneously, orally, topically, as an inhalant, or via an impregnated or coated device such as a stent, for example, or an artery-inserted cylindrical polymer.

[0054] In one aspect, the compounds described herein may be administered orally. Oral
20 administration may be via, for example, capsule or enteric coated tablets. In making the pharmaceutical compositions that include at least one compound of Formula (I), or a pharmaceutically acceptable salt, ester, prodrug, or solvate thereof, the active ingredient is usually diluted by an excipient and/or enclosed within such a carrier that can be in the form of a capsule, sachet, paper or other container. When the excipient serves as a diluent, it can
25 be in the form of a solid, semi-solid, or liquid material (as above), which acts as a vehicle, carrier or medium for the active ingredient. Thus, the compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), ointments containing, for example, up to 10% by weight of the active compound, soft and hard gelatin capsules, sterile injectable
30 solutions, and sterile packaged powders.

[0055] Some examples of suitable excipients include lactose, dextrose, sucrose, sorbitol,

mannitol, starches, gum acacia, calcium phosphate, alginates, tragacanth, gelatin, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, sterile water, syrup, and methyl cellulose. The formulations can additionally include: lubricating agents such as talc, magnesium stearate, and mineral oil; wetting agents; emulsifying and suspending agents; 5 preserving agents such as methyl and propylhydroxy-benzoates; sweetening agents; and flavoring agents.

[0056] The compositions that include at least one compound of Formula (I), or a pharmaceutically acceptable salt, ester, prodrug, or solvate thereof, can be formulated so as to provide quick, sustained or delayed release of the active ingredient after administration to the 10 subject by employing procedures known in the art. Controlled release drug delivery systems for oral administration include osmotic pump systems and dissolutional systems containing polymer-coated reservoirs or drug-polymer matrix formulations. Examples of controlled release systems are given in U.S. Patent Nos. 3,845,770; 4,326,525; 4,902,514; and 5,616,345. Another formulation for use in the methods of the present invention employs 15 transdermal delivery devices ("patches"). Such transdermal patches may be used to provide continuous or discontinuous infusion of the compounds of the present invention in controlled amounts. The construction and use of transdermal patches for the delivery of pharmaceutical agents is well known in the art. See, e.g., U.S. Patent Nos. 5,023,252, 4,992,445 and 5,001,139. Such patches may be constructed for continuous, pulsatile, or on demand delivery 20 of pharmaceutical agents.

[0057] The compositions may, in some embodiments, be formulated in a unit dosage form. 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 25 suitable pharmaceutical excipient (e.g., a tablet, capsule, ampoule). The compounds are generally administered in a pharmaceutically effective amount. In some embodiments, for oral administration, each dosage unit contains from about 10 mg to about 1000 mg of a compound described herein, for example from about 50 mg to about 500 mg, for example about 50 mg, about 75 mg, about 100 mg, about 150 mg, about 200 mg, about 250 mg, or 30 about 300 mg. In other embodiments, for parenteral administration, each dosage unit contains from 0.1 to 700 mg of a compound described herein. It will be understood, however, that the amount of the compound actually administered usually will be

determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered and its relative activity, the age, weight, and response of the individual subject, and the severity of the subject's symptoms.

5 [0058] In certain embodiments, dosage levels may be from 0.1 mg to 100 mg per kilogram of body weight per day, for example from about 1 mg to about 50 mg per kilogram, for example from about 5 mg to about 30 mg per kilogram. Such dosage levels may, in certain instances, be useful in the treatment of the above-indicated conditions. In other embodiments, dosage levels may be from about 10 mg to about 2000 mg per subject per day. The amount of active
10 ingredient that may be combined with the vehicle to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms may contain from 1 mg to 500 mg of an active ingredient.

[0059] Frequency of dosage may also vary depending on the compound used and the particular disease or condition treated. In some embodiments, for example, for the treatment
15 of an autoimmune and/or inflammatory disease, a dosage regimen of 4 times daily or less is used. In some embodiments, a dosage regimen of 1 or 2 times daily is used. It will be understood, however, that the specific dose level for any particular subject will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of
20 excretion, drug combination and the severity of the particular disease in the subject undergoing therapy.

[0060] For preparing solid compositions such as tablets, the principal active ingredient may be mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound of Formula (I), or a pharmaceutically
25 acceptable salt, ester, prodrug, or solvate thereof. When referring to these preformulation compositions as homogeneous, the active ingredient may be dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules.

[0061] The tablets or pills of the compounds described herein may be coated or otherwise
30 compounded to provide a dosage form affording the advantage of prolonged action, or to protect from the acid conditions of the stomach. 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 that 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.

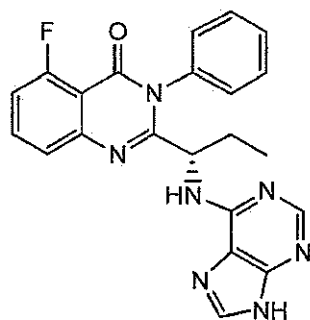
[0062] Kits that include a compound of Formula (I), or a pharmaceutically acceptable salt, thereof, and suitable packaging are provided. In one embodiment, a kit further includes instructions for use. In one aspect, a kit includes a compound of Formula (I), or a pharmaceutically acceptable salt thereof, and instructions for use of the compounds in the treatment of the diseases or conditions described herein.

[0063] Articles of manufacture that include a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in a suitable container are provided. The container may be a vial, jar, ampoule, preloaded syringe, and intravenous bag.

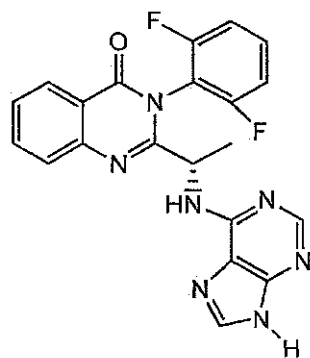
[0064] Compounds of Formula (I) may be combined with one or more additional anti-cancer or anti-inflammatory agents, including any of the following. Various kinase inhibitors are being used and are being developed to treat various cancers. For example, the activation of the phosphatidylinositol 3-kinase (PI3K) pathway is observed in human cancer, and agents inhibiting PI3K are being investigated or developed as potential anti-cancer drugs and for the use in anti-cancer therapies. Additional kinase inhibitors include inhibitors of spleen tyrosine kinase (Syk) and Janus kinase (JAK). Other agents inhibiting related pathways are also of interest as anti-cancer or anti-inflammatory agents, including agents inhibiting the Ras/Raf/MEK/ERK pathway and the PI3K/PTEN/Akt/mTOR pathway. As described herein, such inhibitors include agents that inhibit all subclasses of a target (e.g. PI3K alpha, beta, delta and gamma), agents that inhibit primarily one subclass, and agents that inhibit a subset of all subclasses. Compounds of Formula (I) may also be combined with one or more additional anti-cancer or anti-inflammatory agents including inhibitors or antagonists of lysyl oxidase-like 2 (LOXL2), and inhibitors or antagonists of adenosine A2B receptor.

[0065] In various aspects, compounds of Formula (I) may be combined with one or more kinase inhibitors. Examples of kinase inhibitors include PI3K inhibitors, Syk inhibitors and JAK inhibitors.

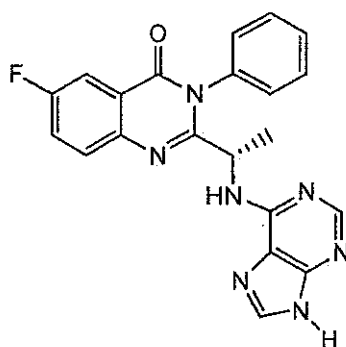
[0066] Examples of PI3K inhibitors include Compound A, Compound B, and Compound C:



(Compound A)



(Compound B)



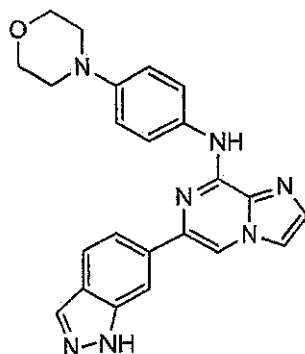
(Compound C).

[0067] Additional examples of PI3K inhibitors include XL147, BKM120, GDC-0941, BAY80-6946, PX-866, CH5132799, XL756, BEZ235, and GDC-0980.

10 [0068] Inhibitors of mTOR include OSI-027, AZD2014, and CC-223.

[0069] Inhibitors of AKT include MK-2206, GDC-0068 and GSK795.

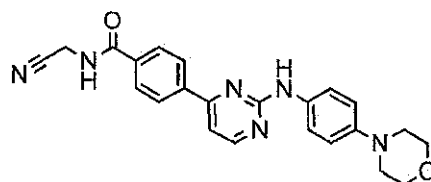
[0070] Examples of Syk inhibitors include compound D:



(Compound D).

[0071] Additional Syk inhibitors include R788 (fostamatinib), R-406 (tamatinitib), and
5 PRT062607.

[0072] Examples of JAK inhibitors include Compound E:



(Compound E).

[0073] Additional JAK inhibitors include Ruxolitinib, Tofacitinib, Baricitinib, CYT387,
10 Lestaurtinib, Pacritinib, and TG101348.

[0074] In other aspects, compounds of Formula (I) may be combined with one or more inhibitors or modulators (e.g. antagonists) of LOXL2, adenosine A2B receptor, MMP-9, ASK1, BTK, mTOR, HDAC, and MEK.

[0075] In other aspects, compounds of Formula (I) may be combined with one or more
15 components of CHOP therapy (cyclophosphamide, Adriamycin, Vincristine, Prednisolone).

[0076] In other aspects, compounds of Formula (I) may be combined with one or more of ribavirin and interferon.

[0077] In other aspects, compounds of Formula (I) may be combined with one or more agents that activate or reactivate latent human immunodeficiency virus (HIV). For example,

compounds of Formula (I) may be combined with a histone deacetylase (HDAC) inhibitor (listed above) or a protein kinase C (PKC) activator. For example, compounds of Formula (I) may be combined with romidepsin or panobinostat.

5

EXAMPLES

[0078] General Methods. Synthesis of certain compounds, and intermediates used to prepare compounds, is detailed in the following sections. Compound numbers are listed for convenience.

10 [0079] All operations involving moisture and/or oxygen sensitive materials were conducted under an atmosphere of dry nitrogen in pre-dried glassware. Unless noted otherwise, materials were obtained from commercially available sources and used without further purification.

[0080] Flash chromatography was performed on an Isco Combiflash Companion using RediSep Rf silica gel cartridges by Teledyne Isco. Thin layer chromatography was
15 performed using precoated plates purchased from E. Merck (silica gel 60 PF254, 0.25 mm) and spots were visualized with long-wave ultraviolet light followed by an appropriate staining reagent.

[0081] Nuclear magnetic resonance ("NMR") spectra were recorded on a Varian 400 MHz resonance spectrometer. ¹H NMR chemical shifts are given in parts per million (δ)
20 downfield from tetramethylsilane ("TMS") using TMS or the residual solvent signal (CHCl₃ = δ 7.24, DMSO = δ 2.50) as internal standard. ¹H NMR information is tabulated in the following format: multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant(s) (J) in Hertz, number of protons. The prefix app is occasionally applied in cases where the true signal multiplicity was unresolved and br indicates the signal in
25 question was broadened.

[0082] The compounds were named using ChemBioDraw Ultra Version 12.0.

[0083] LCMS analysis was performed using a PE SCIEX API 2000 spectrometer with a Phenomenex Luna 5 micron C18 column.

[0084] Preparatory HPLC was performed on a Gilson HPLC 215 liquid handler with a

Phenomenex column (Gemini 10 μ m, C18, 110A) and a UV/VIS 156 detector.

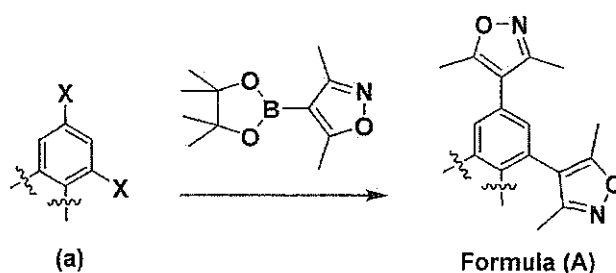
[0085] When production of starting materials is not particularly described, the compounds are known or may be prepared analogously to methods known in the art or as disclosed in the Examples. One of skill in the art will appreciate that synthetic methodologies described
 5 herein are only representative of methods for preparation of the compounds described herein, and that other known methods and variants of methods described herein may be used. The methods or features described in various Examples may be combined or adapted in various ways to provide additional ways of making the compounds described herein.

[0086] Methods for obtaining the novel compounds described herein will be apparent to
 10 those of ordinary skill in the art, procedures described in, for example, the reaction schemes and examples below, and in the references cited herein.

EXAMPLES

[0087] Methods for obtaining the novel compounds described herein will be apparent to
 15 those of ordinary skill in the art, with suitable procedures being described, for example, in the reaction schemes and examples below, and in the references cited herein.

Scheme 1



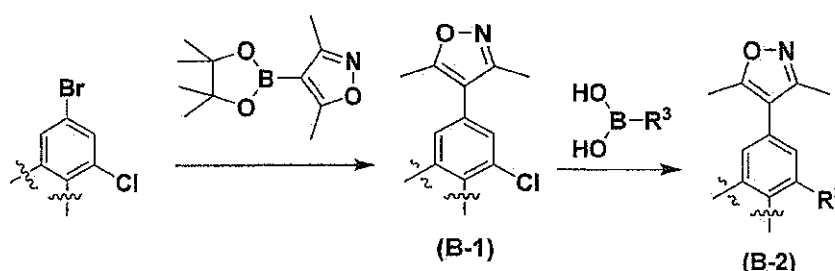
[0088] The compound of Formula (1-a) can be prepared by Suzuki coupling of a compound
 20 of commercially available compound of Formula (a) to commercially available isoxazole boronic acid ester shown above in the presence of a base. Substituents X in compound (a) may be any appropriate leaving group (e.g., Cl, Br, I, OTf). Suitable catalysts may include palladium catalysts, such as (1,3-bis(2,6-diisopropylphenyl)imidazolidene)(3-chloropyridyl)
 25 palladium(II) dichloride (Peppsi-iPr). Suitable bases may include, for example, cesium

carbonate or 1,8-diazobicycloundec-7-ene. Suitable solvents may include a combination of organic solvents and water, including, for example, 1,4-dioxane, THF, dimethoxyethane or dimethylformamide and water. The reaction is carried out in an appropriate solvent under nitrogen, at an elevated temperature of about 70°C to 150°C, for about 30 seconds to 5 hours.

- 5 When the reaction is substantially complete, the reaction is allowed to cool to room temperature. The reaction mixture can be partitioned between an aqueous phase and an organic phase. The aqueous phase is discarded, and the organic phase concentrated under reduced pressure, and the residue is purified by reverse phase high-performance liquid chromatography, eluting with an appropriate solvent mixture such as acetonitrile and water,
10 to isolate compounds of Formula (A).

[0089] Another exemplary method of preparing compounds of Formula (B) is shown in Reaction Scheme No. 2.

Scheme 2

Step 1 – Preparation of Formula (B-1)

[0090] The compound of Formula (B-1) can be prepared by Suzuki coupling of a compound of commercially available compound chloro-bromo substituted aromatic heterocycle which may bear an additional heteroaryl ring as shown above as two variable attachment bonds to commercially available isoxazole boronic acid ester shown above in the presence of a base. Suitable catalysts may include palladium catalysts, such as [1,1'-Bis(diphenylphosphino)ferrocene] dichloropalladium(II). Suitable bases may include, for example, cesium carbonate or 1,8-diazobicycloundec-7-ene. Suitable solvents may include a combination of organic solvents and water, including, for example, 1,4-dioxane, THF, dimethoxyethane or dimethylformamide and water. The reaction is carried out in an appropriate solvent under nitrogen, at an elevated temperature of about 70°C to 150°C, for about 30 seconds to 5 hours. When the reaction is substantially complete, the reaction is allowed to cool to room temperature. The reaction mixture can be partitioned between an aqueous phase and an organic phase. The aqueous phase is discarded, and the organic phase concentrated under reduced pressure, and the residue is purified by reverse phase high-performance liquid chromatography, eluting with an appropriate solvent mixture such as acetonitrile and water, to isolate compounds of Formula (B-1). The compound of Formula (B-1) may also be purified by other conventional means, such as silica gel chromatography.

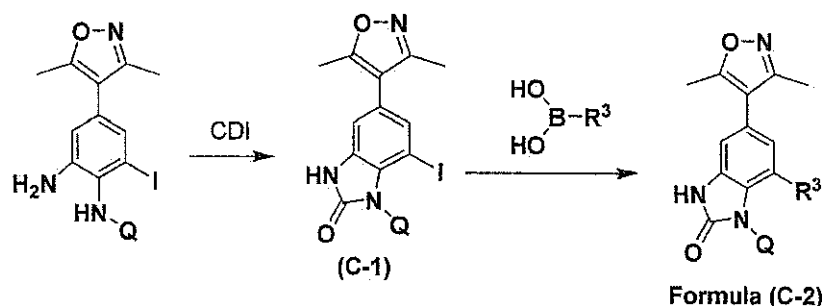
Step 2 – Preparation of Formula (B-2)

[0091] The compound of Formula (B-2) can be prepared by Suzuki coupling of a compound of Formula (B-1) to commercially available boronic acid derivatives bearing substituent R³ as defined in the specification for compounds of Formula (I). Suitable catalysts may include palladium catalysts, such as (1,3-bis(2,6-diisopropylphenyl)imidazolidene)(3-chloropyridyl)

palladium(II) dichloride (Peppsi-iPr). Suitable bases may include, for example, cesium carbonate or 1,8-diazobicycloundec-7-ene. Suitable solvents may include a combination of organic solvents and water, including, for example, 1,4-dioxane, THF, dimethoxyethane or dimethylformamide and water. The reaction is carried out in an appropriate solvent under nitrogen, at an elevated temperature of about 70°C to 150°C, for about 30 seconds to 5 hours. When the reaction is substantially complete, the reaction is allowed to cool to room temperature. The reaction mixture can be partitioned between an aqueous phase and an organic phase. The aqueous phase is discarded, and the organic phase concentrated under reduced pressure, and the residue is purified by reverse phase high-performance liquid chromatography, eluting with an appropriate solvent mixture such as acetonitrile and water, to isolate compounds of Formula (B-2).

[0092] Another exemplary method of preparing compounds of Formula (C-2) is shown in Reaction Scheme No. 3.

Scheme 3



Step 1 – Preparation of Formula (C-1)

[0093] An appropriate carbonyl-delivering reagent is reacted with the compound of Formula (C-1) (with substituent Q as either H or methyl) in an appropriate solvent, and allowed to react for a period of time such as 1-5 hours at an elevated temperature of 80-150 °C.

Appropriate solvents include organic solvents such as tetrahydrofuran. When the reaction is substantially complete, the compound of (C-1) is isolated by removal of solvent under vacuum and purification by conventional means, such as recrystallization or trituration in an appropriate solvent mixture, such as hexanes and ethyl acetate.

Step 2 – Preparation of Formula (C-2)

[0094] The compound of Formula (C-2) can be prepared by Suzuki coupling of a compound

of Formula (C-1) to boronic acid shown above in the presence of a base. As shown above, boronic acid is substituted with carbon-linked phenyl, naphthyl, or heteroaryl R³ group as defined in the specification for compounds of Formula (I). It should be understood that boronate esters, or other appropriate boron complexes (i.e. -BF₃K salts, etc.) may also be used in place of a boronic acid. Suitable catalysts may include palladium catalysts, such as (1,3-bis(2,6-diisopropylphenyl)imidazolidene)(3-chloropyridyl) palladium(II) dichloride (Peppsi-iPr). Suitable bases may include, for example, cesium carbonate or 1,8-diazobicycloundec-7-ene. Suitable solvents may include a combination of organic solvents and water, including, for example, 1,4-dioxane, THF, dimethoxyethane or dimethylformamide and water. The reaction is carried out in an appropriate solvent under nitrogen, at an elevated temperature of about 70°C to 150°C, for about 30 seconds to 5 hours. When the reaction is substantially complete, the reaction is allowed to cool to room temperature.

[0095] The reaction mixture can be partitioned between an aqueous phase and an organic phase. The aqueous phase is discarded, and the organic phase concentrated under reduced pressure, and the residue is purified by reverse phase high-performance liquid chromatography, eluting with an appropriate solvent mixture such as acetonitrile and water, to isolate compounds of Formula (C-2). Alternatively, the compound of Formula (C-2) may be purified by other conventional means, such as silica gel chromatography or recrystallization.

[0096] When the reactions described herein are substantially complete, the reaction may be allowed to cool to room temperature. The reaction mixture can then be concentrated and purified by any suitable method, including for example, chromatography on silica gel or preparative HPLC to obtain the compound of Formulas (I), (Ia), and (Ib), including each of the compounds in the examples provided below.

Step 3: Preparation of Formula (C1-C5)

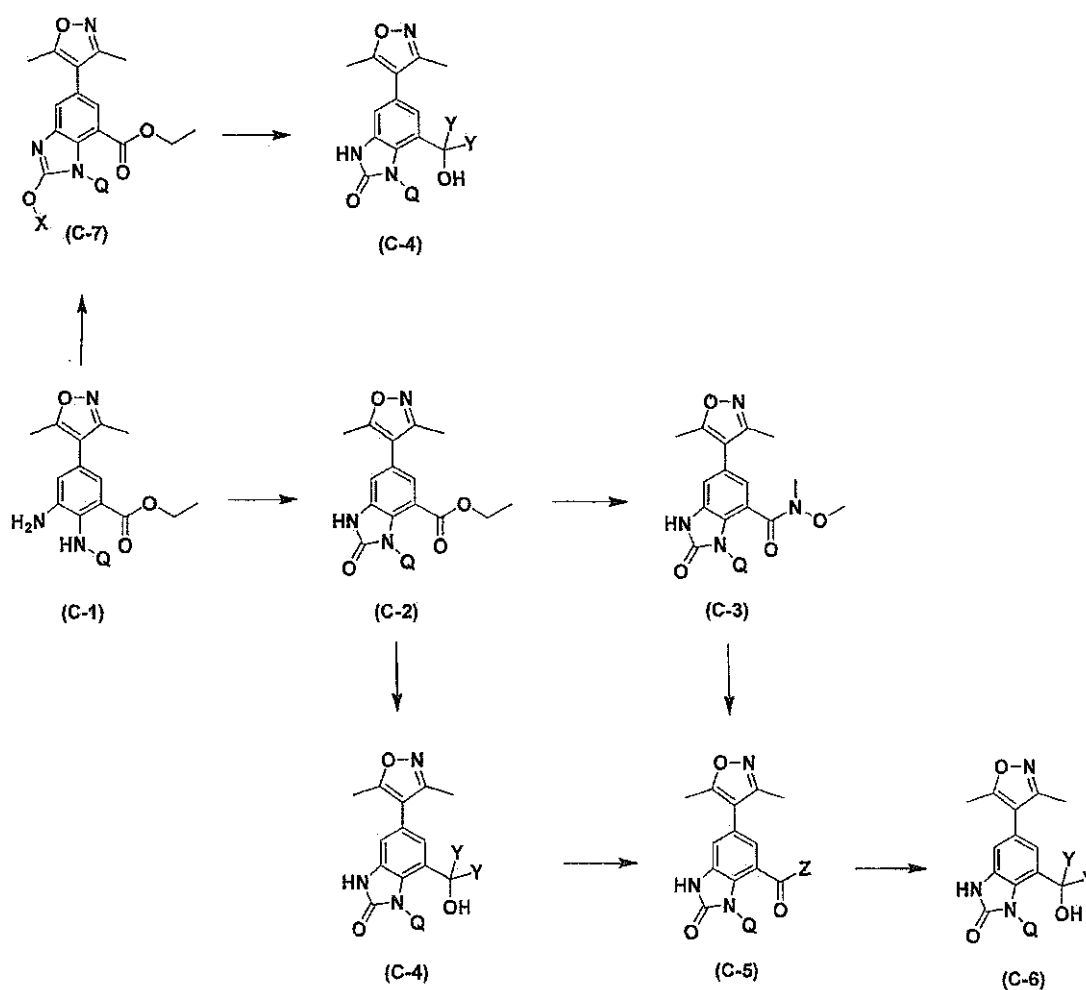
[0097] The compound of Formula (C-4, C-5 and C-6) can be prepared as follows: Reacting (C-1) with an appropriate carbonyl source as described previously affords (C-2). (C-2) is then reacted with metalated alkyl or aryl reagents (e.g. but not limited to Li or Mg) to symmetrical carbinols (C-4), or converted to *Weinreb* amide (C-3) followed by reaction with metalated alkyl and aryl reagents to afford ketone (C-5). Ketone (C-5) can then be reacted

again with metalated alkyl and aryl reagents to afford asymmetric carbinol (C-6).

[0098] Alternatively, compounds above can be prepared by converting (C-1) to the corresponding 2-alkoxy-benzimidazole (C-7), which is then further converted to (C-4) including (C-6) using methods above.

5

Scheme 3



[0099] The following examples are included to demonstrate certain preferred embodiments.

It should be appreciated by those of skill in the art that the techniques disclosed in the examples which follow represent techniques discovered by the inventor to function well in the practice of the invention, and thus can be considered to constitute certain preferred modes for its practice. However, those of skill in the art should, in light of the present disclosure, appreciate that many changes can be made in the specific embodiments which are disclosed,

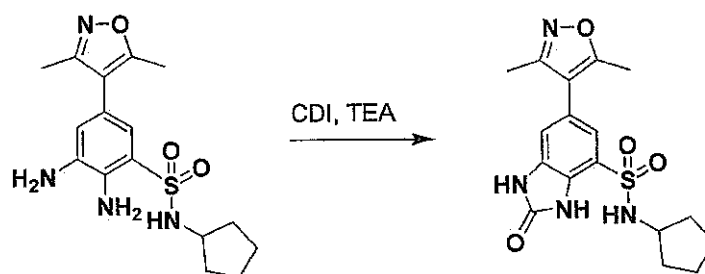
and still obtain a like or similar results without department from the spirit and the scope of the invention.

[00100] The following abbreviations are used in the Examples below:

	DME	1,2-dimethoxy ethane
5	DMF	dimethylformamide
	EtOAc	ethyl acetate
	Hepes	4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid
	mCPBA	meta chloroperbenzoic acid
	MeCN	acetonitrile
10	NBS	N-bromosuccinimide
	Peppsi-iPr (or PEPPSI iPr or PEPPSI TM -iPr)	(1,3-bis(2,6-diisopropylphenyl)imidazolidene)(3-chloropyridyl)palladium(II) dichloride
15	PdCl ₂ dppf	[1,1-Bis(diphenylphosphino)ferrocene]dichloropalladium (II)
	POCl ₃	phosphoryl chloride
	rf	retention factor
	TEA	triethylamine
	TFA	trifluoroacetic acid
20	THF	tetrahydrofuran

Example 1

N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-sulfonamide



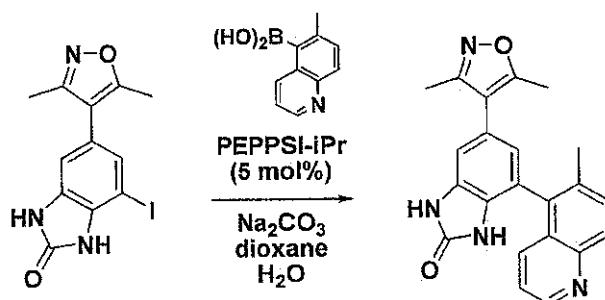
[00101] 2,3-Diamino-N-cyclopentyl-5-(3,5-dimethylisoxazol-4-yl)benzenesulfonamide (58 mg, 0.17 mmol) was dissolved in DMF (2 mL). To the solution was added CDI (360 mg, 4 mmol) and TEA (1 mL). The reaction was heated at 150 °C in microwave for 10h. The solvent was evaporated and the residue was purified by preparative HPLC (0-100% CH₃CN/H₂O) to afford N-cyclopentyl-6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-sulfonamide.

[00102] C₁₇H₂₀N₄O₄S. 377.0 (M+1). ¹H NMR (400MHz, CD₃OD) δ 7.34 (s, 1H), 7.18 (s, 1H), 3.63-3.58 (m, 1H), 2.41 (s, 3H), 2.25 (s, 3H), 1.70-1.60 (m, 4 H), 1.49-1.31 (m, 4H).

10

Example 2

6-(3,5-dimethylisoxazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one



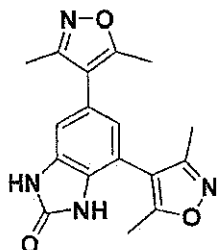
[00103] 6-(3,5-Dimethylisoxazol-4-yl)-4-iodo-1H-benzo[d]imidazol-2(3H)-one (38.9 mg, 0.11 mmol) was treated with 6-methylquinolin-5-ylboronic acid (30.9 mg, 0.165 mmol, 1.5 equiv.), 2M-Na₂CO₃ (aq) (1 mL) in the presence of PEPPSI iPr (3.7 mg, 0.0055 mmol, 0.05 equiv) in 1,4-dioxane (3 mL) at 150°C for 20 min in microwave reactor (Biotage, Optimizer). To the reaction mixture were added water (30 mL) and EtOAc (70 mL). The whole was filtered through Celite (3 g) and then organic layer was separated from the filtrate.

The organic layer was washed with brine (30 mL) and dried over Na₂SO₄. The solvent was removed under a reduced pressure to give a crude product. The crude product was purified by a preparative HPLC (5-95% acetonitrile: water with 0.05% trifluoroacetic acid, on a Phenomenex Luna C18 column) and a silica gel chromatography (MeOH:CH₂Cl₂ = 3:97~10:90) to give 6-(3,5-dimethylisoxazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one.

[00104] 6-(3,5-dimethylisoxazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one: C₂₂H₁₈N₄O₂. MS. m/z 371.1 (M+1). ¹H NMR (MeOH-*d*₄) δ 9.15 (d, *J* = 5.3 Hz, 1H), 8.58 (t, *J* = 8.7 Hz, 1H), 8.58 (d, *J* = 9.0 Hz, 1H), 8.22 (d, *J* = 9.0 Hz, 1H), 7.95 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.20 (d, *J* = 1.5 Hz, 1H), 6.95 (d, *J* = 1.5 Hz, 1H), 2.46 (s, 3H), 2.45 (s, 3H), 2.30 (s, 3H).

Example 3

4,6-bis(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



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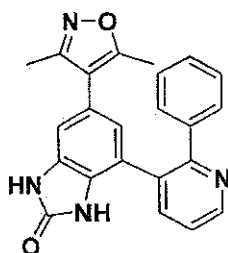
[00105] 4,6-bis(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one was synthesized using 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole and Cs₂CO₃ in a similar fashion as 6-(3,5-dimethylisoxazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one (Example 2).

[00106] C₁₇H₁₆N₄O₃. MS. 325.1 (M+1). ¹H NMR (MeOH-*d*₄) δ 7.04 (d, *J* = 1.5 Hz, 1H), 6.87 (dd, *J* = 1.5 Hz, 1H), 2.43 (s, 3H), 2.35 (s, 3H), 2.27 (s, 3H), 2.20 (s, 3H).

20

Example 4

6-(3,5-dimethylisoxazol-4-yl)-4-(2-phenylpyridin-3-yl)-1H-benzo[d]imidazol-2(3H)-one

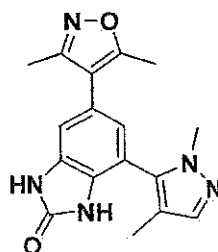


- 5 [00107] 6-(3,5-dimethylisoxazol-4-yl)-4-(2-phenylpyridin-3-yl)-1H-benzo[d]imidazol-2(3H)-one was synthesized using 2-phenylpyridin-3-ylboronic acid and Cs_2CO_3 in a similar fashion as 6-(3,5-dimethylisoxazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one (Example 2).

$\text{C}_{23}\text{H}_{18}\text{N}_4\text{O}_2$. MS. 383.1 (M+1). ^1H NMR ($\text{MeOH}-d_4$) δ 8.89 (dd, $J = 5.7, 1.5$ Hz, 1H), 8.60 (dd, $J = 7.9, 1.5$ Hz, 1H), 8.04 (dd, $J = 7.9, 5.7$ Hz, 1H), 7.51 – 7.39 (m, 5H), 6.98 (d, $J = 1.5$ Hz, 1H), 6.75 (d, $J = 1.5$ Hz, 1H), 2.19 (s, 3H), 2.03 (s, 3H).

Example 5

4-(3,5-dimethyl-1H-pyrazol-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



[00108] 4-(1,4-dimethyl-1H-pyrazol-5-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one was synthesized using 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole and Cs_2CO_3 in a similar fashion as 6-(3,5-dimethylisoxazol-

4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one (Example 2).

[00109] $C_{17}H_{17}N_5O_2$. MS. 324.1 (M+1). ^1H NMR (MeOH- d_4) δ 7.51 (s, 1H), 7.11 (d, J = 1.5 Hz, 1H), 6.92 (d, J = 1.5 Hz, 1H), 3.74 (s, 3H), 2.43 (s, 3H), 2.28 (s, 3H), 2.00 (s, 3H).

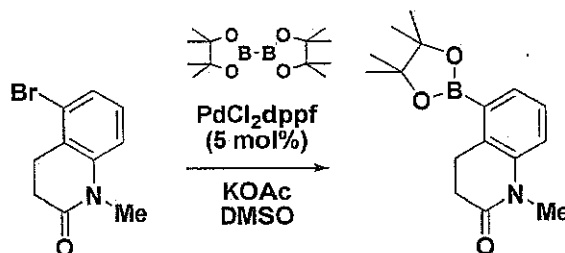
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Example 6

5-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-1-methyl-3,4-dihydroquinolin-2(1H)-one

Step 1: Preparation of 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinolin-2(1H)-one

10

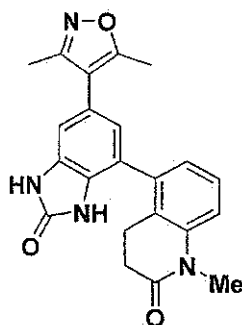


[00110] 5-bromo-1-methyl-3,4-dihydroquinolin-2(1H)-one (171.4 mg, 0.714 mmol) was treated with 4,4,4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (272.0 mg, 1.071 mmol, 1.5 equiv.), KOAc (210.2 mg, 2.142 mmol, 3.0 equiv) in the presence of PdCl₂dppf (26.1 mg, 0.0357 mmol, 0.05 equiv) in DMSO (4 mL) at 100°C for 20 min in a microwave reactor. To the reaction mixture was added water (30 mL) and EtOAc (70 mL). The mixture was filtered through Celite (3 g) and then organic layer was separated from the filtrate. The organic layer was washed with brine (30 mL) and dried over Na₂SO₄. The solvent was removed under a reduced pressure to give a crude product. The crude product was purified by a preparative HPLC (5-95% acetonitrile: water with 0.05% trifluoroacetic acid, on a Phenomenex Luna C18 column) and a silica gel chromatography (MeOH:CH₂Cl₂ = 3:97~10:90) to give 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinolin-2(1H)-one (117.2 mg). $C_{16}H_{22}BNO_3$. MS. m/z 389.1 (M+1).

15

20

Step 2: Preparation of 5-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-1-methyl-3,4-dihydroquinolin-2(1H)-one



[00111] 5-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-1-methyl-3,4-dihydroquinolin-2(1H)-one was synthesized using 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,4-dihydroquinolin-2(1H)-one and Cs_2CO_3 in a similar fashion as 6-(3,5-dimethylisoxazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one (Example 2).

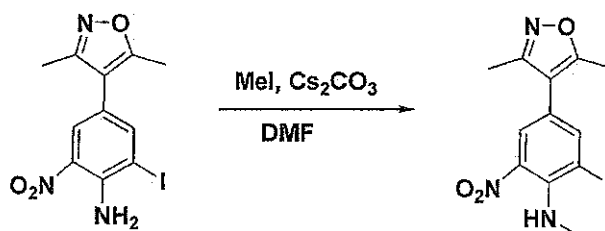
[00112] 5-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-1-methyl-3,4-dihydroquinolin-2(1H)-one: $\text{C}_{22}\text{H}_{20}\text{N}_4\text{O}_3$. MS. m/z 389.1 ($M+1$). ^1H NMR ($\text{MeOH}-d_4$) δ 7.41 (t, $J = 8.0$ Hz, 1H), 7.24 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.11 (dd, $J = 8.0, 1.1$ Hz, 1H), 7.02 (d, $J = 1.5$ Hz, 1H), 6.84 (d, $J = 1.5$ Hz, 1H), 3.42 (s, 3H), 2.88 – 2.64 (m, 2H), 2.64 – 2.46 (m, 2H), 2.42 (s, 3H), 2.27 (s, 3H).

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Example 7

5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one

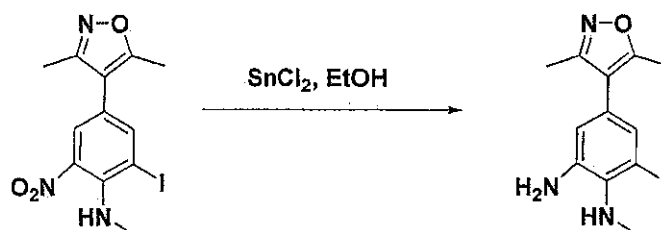
Step 1: Preparation of 4-(3,5-dimethylisoxazol-4-yl)-2-iodo-N-methyl-6-nitroaniline



[00113] Into a flask containing 4-(3,5-dimethylisoxazol-4-yl)-2-iodo-6-nitroaniline (1000 mg, 2.78 mmol, 1 equiv) is added DMF (15 mL, 0.2 M) before adding cesium carbonate (1.4 gm, 4.17 mmol, 1.5 equiv.) and idomethane (260 μ L, 4.17 mmol, 1.5 equiv). After an hour, the reaction was quenched with water and the reaction was partitioned between
 5 water and ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. Purification was carried out by flash column chromatography to furnish 4-(3,5-dimethylisoxazol-4-yl)-2-iodo-N-methyl-6-nitroaniline (615 mg, 60 %).

[00114] LCMS (m/z +1) 373.85. ^1H NMR (400 MHz, cdcl_3) δ 7.81 (t, J = 3.0 Hz, 1H), 7.70 (d, J = 2.1 Hz, 1H), 2.97 (s, 3H), 2.40 (d, J = 16.8 Hz, 3 H), 2.26 (d, J = 14.2 Hz, 3H).

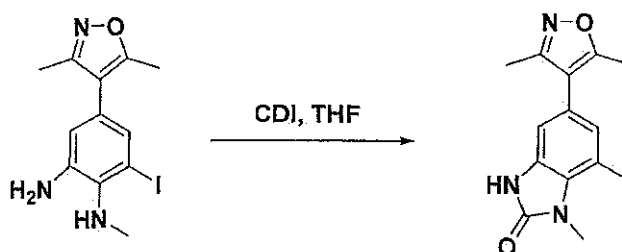
10 Step 2: Preparation of 4-(3,5-dimethylisoxazol-4-yl)-6-iodo-N1-methylbenzene-1,2-diamine



[00115] Into a microwave vial containing 4-(3,5-dimethylisoxazol-4-yl)-2-iodo-N-methyl-6-nitroaniline (610 mg, 1.64 mmol, 1 equiv) is added EtOH (12mL, 0.25M) and tin (II) chloride (622 mg, 3.28 mmol, 2 equiv). The reaction was heated for 30 min at 110°C. The
 15 reaction was then stirred in 2N NaOH solution for 20 minutes before being partitioned between water and ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. Purification was carried out by flash column chromatography to furnish 4-(3,5-dimethylisoxazol-4-yl)-6-iodo-N1-methylbenzene-1,2-diamine.

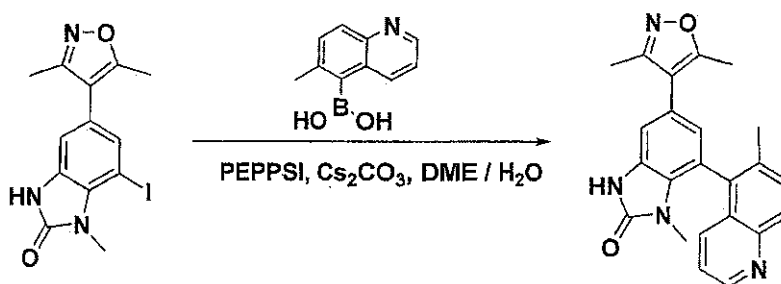
[00116] LCMS (m/z +1) 344.02.

Step 3: Preparation of 5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1-methyl-1H-benzo[d]imidazol-2(3H)-one



- [00117] Into a flask containing 4-(3,5-dimethylisoxazol-4-yl)-6-iodo-N1-methylbenzene-1,2-diamine (299 mg, 0.87mmol, 1 equiv) is added THF (8 mL, 0.1 M) and CDI (282 mg, 1.74 mmol, 2 equiv). The reaction was heated for 2 hr at 120°C. The reaction was then concentrated *in vacuo* and the solid triturated with diethyl ether before being air dried to furnish 5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1-methyl-1H-benzo[d]imidazol-2(3H)-one as a light yellow solid.
- 10 [00118] LCMS (m/z +1) 370.00.

Step 4: Preparation of 5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one



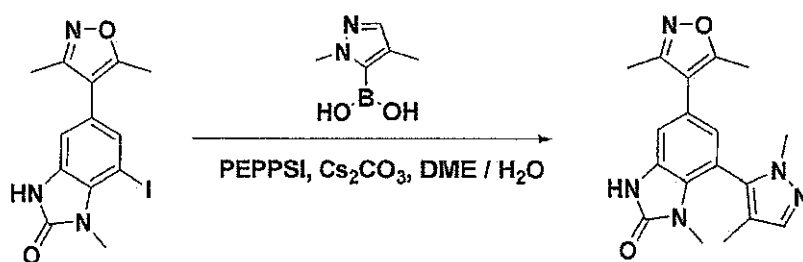
- 15 [00119] To a microwave vial containing 5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1-methyl-1H-benzo[d]imidazol-2(3H)-one (40 mg, 0.11 mmol, 1 equiv.) was added 3,5-6-methylquinolin-5-ylboronic acid (51 mg, 0.27 mmol, 2.5 equiv.), Cs₂CO₃ (141 mg, 0.43 mmol, 4 equiv.) and PEPPSI[™]-IPr catalyst (8 mg, 0.02 mmol, 0.1 equiv.) and dissolved in DME-H₂O (20 mL, 0.2 M, 2/1, v/v). The mixture was heated to 140°C. After 2 hr, the reaction
- 20 was complete. After cooling, the reaction was extracted with EtOAc and washed with water

and saturated NH_4Cl . After drying with MgSO_4 , it was filtered and concentrated to dryness. Purification was carried out by reverse phase HPLC to furnish 5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one.

[00120] LCMS ($m/z + 1$) 385.23. ^1H NMR (400 MHz, cd_3od) δ 8.82 (d, $J = 4.3$ Hz, 1H), 8.09 (d, $J = 8.7$ Hz, 1H), 7.82 (t, $J = 7.1$ Hz, 2H), 7.47 (dd, $J = 8.5, 4.3$ Hz, 1H), 7.17 (d, $J = 1.6$ Hz, 1H), 6.82 (d, $J = 1.6$ Hz, 1H), 2.53 (s, 3H), 2.42 (s, 3H), 2.33 (s, 3H), 2.27 (s, 3H).

Example 8

10 7-(1,4-dimethyl-1H-pyrazol-5-yl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one

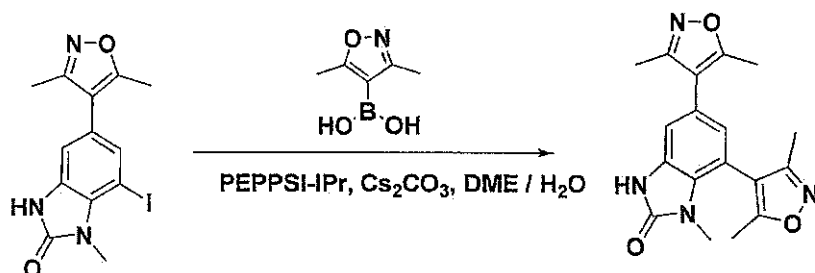


[00121] To a microwave vial containing 5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1-methyl-1H-benzo[d]imidazol-2(3H)-one (40 mg, 0.11 mmol, 1 equiv.) was added 1,4-dimethyl-1H-pyrazol-5-ylboronic acid (72 mg, 0.32 mmol, 3 equiv.), Cs_2CO_3 (141 mg, 0.43 mmol, 4 equiv.) and PEPPSITM-IPr catalyst (8 mg, 0.02 mmol, 0.1 equiv.) and dissolved in DME- H_2O (20 mL, 0.2 M, 2/1, v/v). The mixture was heated to 140°C . After 1 hr, the reaction was complete. After cooling, the reaction was extracted with EtOAc and washed with water and saturated NH_4Cl . After drying with MgSO_4 , it was filtered and concentrated to dryness. Purification was carried out by reverse phase HPLC to furnish 7-(1,4-dimethyl-1H-pyrazol-5-yl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one.

[00122] LCMS ($m/z + 1$) 338.19. ^1H NMR (400 MHz, cd_3od) δ 7.44 (s, 1H), 7.15 (d, $J = 1.6$ Hz, 1H), 6.88 (d, $J = 1.6$ Hz, 1H), 3.65 (s, 3H), .90 (s, 3H), 2.42 (s, 3H), 2.27 (s, 7H), 1.95 (s, 3H).

Example 9

7-(1,4-dimethyl-1H-pyrazol-5-yl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one



5

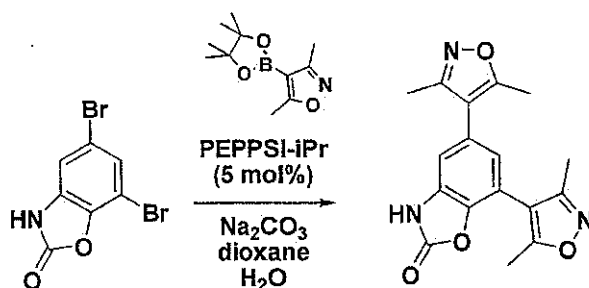
[00123] To a microwave vial containing 5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1-methyl-1H-benzo[d]imidazol-2(3H)-one (40 mg, 0.11 mmol, 1 equiv.) was added 3,5-Dimethylisoxazole-4-boronic acid pinacol ester (72 mg, 0.32 mmol, 3 equiv.), Cs₂CO₃ (141 mg, 0.43 mmol, 4 equiv.) and PEPPSI[™]-IPr catalyst (8 mg, 0.02 mmol, 0.1 equiv.) and dissolved in DME-H₂O (20 mL, 0.2 M, 2/1, v/v). The mixture was heated to 140°C. After 1 hr, the reaction was complete. After cooling, the reaction was extracted with EtOAc and washed with water and saturated NH₄Cl. After drying with MgSO₄, it was filtered and concentrated to dryness. Purification was carried out by reverse phase HPLC to furnish 7-(1,4-dimethyl-1H-pyrazol-5-yl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one.

15

[00124] LCMS (m/z +1) 339.15. ¹H NMR (400 MHz, cd₃od) δ 7.09 (d, *J* = 1.6 Hz, 1H), 6.81 (d, *J* = 1.6 Hz, 1H) 3.11 (d, *J* = 14.5 Hz, 3H), 2.41 (s, 3H), 2.35 – 2.23 (m, 6H), 2.15 (s, 3H).

Example 10

5,7-bis(3,5-dimethylisoxazol-4-yl)benzo[d]oxazol-2(3H)-one



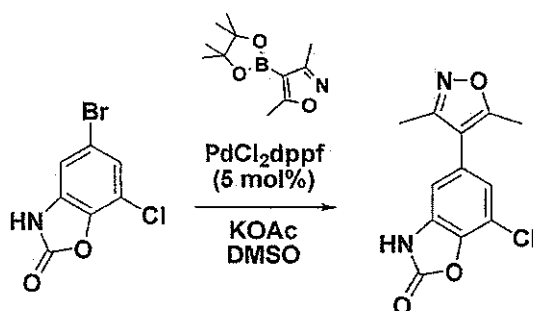
5 [00125] 5,7-Dibromobenzo[d]oxazol-2(3H)-one (100.0 mg, 0.341 mmol) was treated with 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (304.7 mg, 1.366 mmol, 4.0 equiv.), 2M-Na₂CO₃ (aq) (1 mL) in the presence of PEPPSI-iPr (11.6 mg, 0.017 mmol, 0.05 equiv) in 1,4-dioxane (3 mL) at 150°C for 10 min in microwave reactor. To the reaction mixture were added water (30 mL) and EtOAc (70 mL). The mixture was filtered
10 through Celite (3 g) and then organic layer was separated from the filtrate. The organic layer was washed with brine (30 mL) and dried over Na₂SO₄. The solvent was removed under a reduced pressure to give a crude product. The crude product was purified by a preparative HPLC (5-95% acetonitrile: water with 0.05% trifluoroacetic acid, on a Phenomenex Luna C18 column) and a silica gel column chromatography (MeOH:CH₂Cl₂ = 3:97~10:90) to give
15 5,7-bis(3,5-dimethylisoxazol-4-yl)benzo[d]oxazol-2(3H)-one.

[00126] C₁₇H₁₅N₃O₄. MS. m/z 326.0 (M+1). ¹H NMR (MeOH-*d*₄) δ 7.08 (s, 1H), 7.01 (s, 1H), 2.433 (s, 3H), 2.430 (s, 3H), 2.28 (s, 3H), 2.27 (s, 3H).

Example 11

5-(3,5-dimethylisoxazol-4-yl)-7-(6-methylquinolin-5-yl)benzo[d]oxazol-2(3H)-one

Step 1:

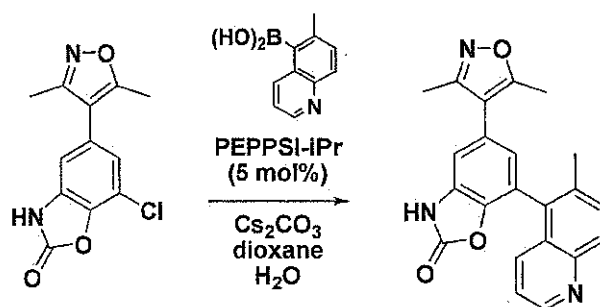


5

[00127] 5-Bromo-7-chlorobenzo[d]oxazol-2(3H)-one (100.0 mg, 0.4025 mmol) was treated with 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (89.8 mg, 0.4025 mmol, 1.0 equiv.), DBU (183.8 mg, 1.2075 mmol, 3.0 equiv.) in the presence of PdCl₂dppf (14.7 mg, 0.02015 mmol, 0.05 equiv) in DMSO (3 mL) and water (1 mL) at 120°C for 1 h in an oil bath. To the reaction mixture were added water (30 mL) and EtOAc (70 mL). The mixture was filtered through Celite (3 g) and then organic layer was separated from the filtrate. The organic layer was washed with brine (30 mL) and dried over Na₂SO₄. The solvent was removed under a reduced pressure to give a crude product. The crude product was purified by a preparative HPLC (5-95% acetonitrile: water with 0.05% trifluoroacetic acid, on a Phenomenex Luna C18 column) and a silica gel column chromatography (hexane:EtOAc = 1:1) to give 7-chloro-5-(3,5-dimethylisoxazol-4-yl)benzo[d]oxazol-2(3H)-one.

15

[00128] C₁₂H₉ClN₂O₃. MS. m/z 265.0 (M-1), 267.0 (M+1).

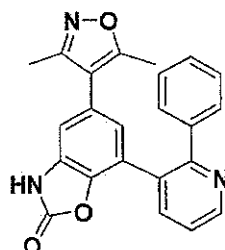
Step 2:

[00129] 7-Chloro-5-(3,5-dimethylisoxazol-4-yl)benzo[d]oxazol-2(3H)-one (20.8 mg, 0.0786 mmol) was treated with 6-methylquinolin-5-ylboronic acid (44.1 mg, 0.2358 mmol, 3.0 equiv.), Cs₂CO₃ (153.7 mg, 0.4716 mmol, 6.0 equiv.) in the presence of PEPPSI iPr (2.9 mg, 0.00393 mmol, 0.05 equiv) in 1,4-dioxane (3 mL) and water (1 mL) at 150°C for 1 h in a microwave reactor. To the reaction mixture were added water (30 mL) and EtOAc (70 mL). The mixture was filtered through Celite (3 g) and then organic layer was separated from the filtrate. The organic layer was washed with brine (30 mL) and dried over Na₂SO₄. The solvent was removed under a reduced pressure to give a crude product. The crude product was purified by a preparative HPLC (5-95% acetonitrile: water with 0.05% trifluoroacetic acid, on a Phenomenex Luna C18 column) to give 5-(3,5-dimethylisoxazol-4-yl)-7-(6-methylquinolin-5-yl)benzo[d]oxazol-2(3H)-one.

[00130] C₂₂H₁₇N₃O₃. MS. m/z 372.1 (M+1). ¹H NMR (MeOH-*d*₄) δ 9.16 (d, *J* = 5.3 Hz, 1H), 8.69 (d, *J* = 8.7 Hz, 1H), 8.28 (d, *J* = 8.9 Hz, 1H), 8.21 (d, *J* = 8.9 Hz, 1H), 7.97 (dd, *J* = 8.7, 5.3 Hz, 1H), 7.27 (d, *J* = 1.6 Hz, 1H), 7.07 (d, *J* = 1.6 Hz, 1H), 2.49 (s, 3H), 2.45 (s, 3H), 2.30 (s, 3H)

Example 12

5-**(3,5-dimethylisoxazol-4-yl)-7-(2-phenylpyridin-3-yl)benzo[d]oxazol-2(3H)-one**



The title compound was synthesized using 2-phenylpyridin-3-ylboronic acid in a similar fashion with 5-(3,5-dimethylisoxazol-4-yl)-7-(6-methylquinolin-5-yl)benzo[d]oxazol-2(3H)-one (Example 11).

[00131] $C_{23}H_{17}N_3O_3$. MS. 384.1 (M+1). ^1H NMR (MeOH- d_4) δ 8.02 (dd, $J = 5.4, 1.5$ Hz, 1H), 7.68 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.10 (dd, $J = 8.0, 5.4$ Hz, 1H), 6.67 - 6.55 (m, 5H), 6.21 (d, $J = 1.6$ Hz, 1H), 5.97 (d, $J = 1.6$ Hz, 1H), 1.35 (s, 3H), 1.19 (s, 3H).

10

Example 13 and

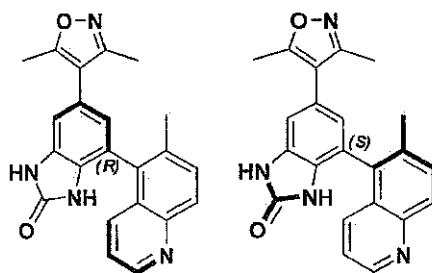
Example 14

(R)-6-(3,5-dimethylisoxazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one

15

and

(S)-6-(3,5-dimethylisoxazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one



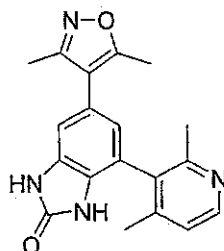
[00132] (R)-6-(3,5-Dimethylisoxazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one and (S)-6-(3,5-dimethylisoxazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one were obtained by resolving the racemate (Example 2) by
 5 supercritical fluid chromatography on a chiral column (25% MeOH with 0.1% v/v TFA on an SFC Chiralpak AD-H column.)

[00133] First eluting compound: (R)-6-(3,5-dimethylisoxazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one. $C_{22}H_{18}N_4O_2$. 371.1 (M+1). SFC
 10 retention time 3.525 min (Chiralpak AD-H 250mm x 10mm, 16 mL/min, 10 minute run time, 40 °C column oven, 10 MPa back-pressure limiter). ^1H NMR spectra identical to racemic compound.

[00134] Second eluting compound: (S)-6-(3,5-dimethylisoxazol-4-yl)-4-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one. $C_{22}H_{18}N_4O_2$. 371.1 (M+1). SFC
 15 retention time 4.992 min (Chiralpak AD-H 250mm x 10mm, 16 mL/min, 10 minute run time, 40 °C column oven, 10 MPa back-pressure limiter). ^1H NMR spectra identical to racemic compound.

Example 15

6-(3,5-dimethylisoxazol-4-yl)-4-(2,4-dimethylpyridin-3-yl)-1H-benzo[d]imidazol-2(3H)-one

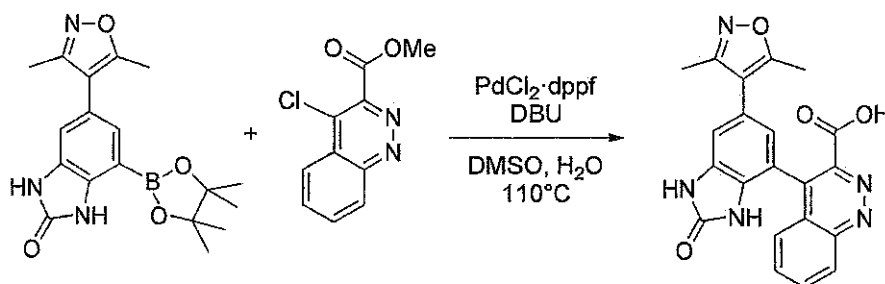


- 5 [00135] 6-(3,5-Dimethylisoxazol-4-yl)-4-(2,4-dimethylpyridin-3-yl)-1H-benzo[d]imidazol-2(3H)-one was synthesized using 2,4-dimethylpyridin-3-ylboronic acid and Cs_2CO_3 in a similar fashion as Example 11.

- [00136] $\text{C}_{19}\text{H}_{18}\text{N}_4\text{O}_2$. MS. m/z 335.1 (M+1). ^1H NMR ($\text{MeOH}-d_4$) δ 8.65 (d, $J = 6.2$ Hz, 1H), 7.93 (d, $J = 6.2$ Hz, 1H), 7.16 (d, $J = 1.5$ Hz, 1H), 6.92 (d, $J = 1.5$ Hz, 1H), 2.52 (s, 3H), 2.43 (s, 3H), 2.40 (s, 3H), 2.27 (s, 3H).
- 10

Example 16

4-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)cinnoline-3-carboxylic acid



15

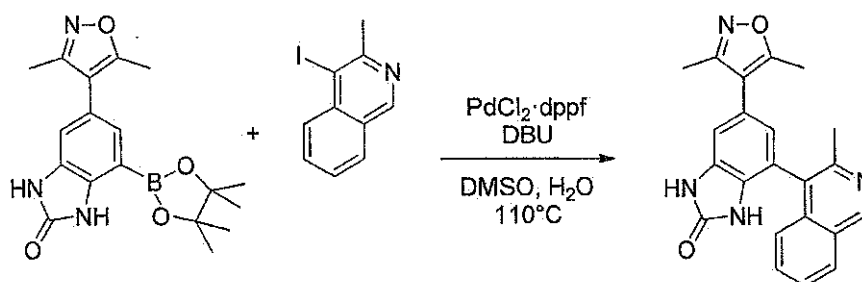
- [00137] 6-(3,5-dimethylisoxazol-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one (100.0, 0.282 mmol) and 5-bromo-8-chloro-6-methylquinoline (94.0 mg, 0.422 mmol) was treated with $\text{PdCl}_2\text{dppf} \cdot \text{CH}_2\text{Cl}_2$ (20.6 mg, 0.028 mmol) in the presence of 1,8-diazabicycloundec-7-ene (DBU, 300.0 mg, 1.971 mmol, 7.0

equiv) in DMSO (1 mL) and water (1 mL). The reaction mixture was heated at 110°C for 12 min in oil bath. The reaction mixture was injected into Gilson preparative HPLC to give 4-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)cinnoline-3-carboxylic acid.

- 5 [00138] $C_{21}H_{15}N_5O_4$. MS. m/z 402.0 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 8.67 (d, $J = 8.8$ Hz, 1H), 8.09 (t, $J = 8.8$ Hz, 1H), 7.92 (d, $J = 8.8$ Hz, 1H), 7.70 (d, $J = 8.8$ Hz, 1H), 7.17 (s, 1H), 6.96 (s, 1H), 2.44 (s, 3H), 2.29 (s, 3H).

Example 17

- 10 6-(3,5-dimethylisoxazol-4-yl)-4-(3-methylisoquinolin-4-yl)-1H-benzo[d]imidazol-2(3H)-one

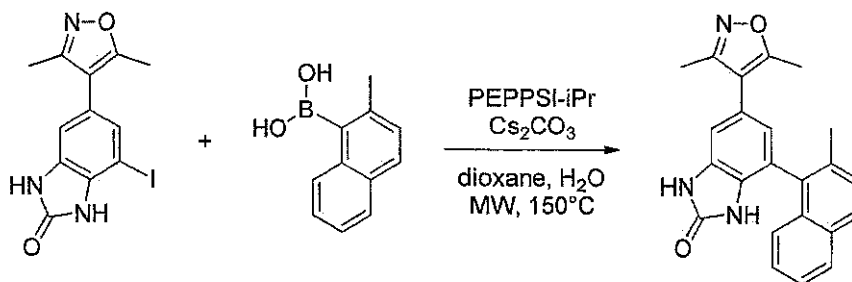


[00139] Synthesized in a similar fashion as that of Example 16.

- [00140] $C_{22}H_{18}N_4O_2$. MS. m/z 371.1 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 9.26 (s, 1H), 8.16 (d, $J = 8.6$ Hz, 1H), 7.70 (t, $J = 8.6$ Hz, 1H), 7.64 (t, $J = 8.6$ Hz, 1H), 7.42 (d, $J = 8.6$ Hz, 1H), 2.50 (s, 3H), 2.45 (s, 3H), 2.29 (s, 3H).
- 15

Example 18

6-(3,5-dimethylisoxazol-4-yl)-4-(2-methylnaphthalen-1-yl)-1H-benzo[d]imidazol-2(3H)-one

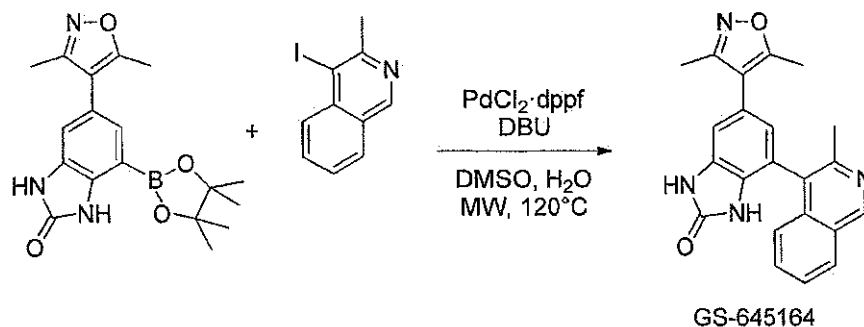


5 [00141] In a 2-5 mL Smith Process Vial, 6-(3,5-dimethylisoxazol-4-yl)-4-iodo-1H-benzo[d]imidazol-2(3H)-one (100.0 mg 0.282 mmol), (2-methylnaphthalen-1-yl)boronic acid (176.0 mg, 0.946 mmol, 3.36 equiv), PEPPSI-iPr (19.2 mg, 0.028 mmol, 0.1 equiv) and Cs₂CO₃ (337.0 mg, 1.126 mmol, 4 equiv) were placed. The mixture was suspended in 1,4-dioxane (1.5 mL) and water (0.5 mL) under N₂. The mixture was heated at 150°C for 75 min
 10 using microwave reactor (Biotage Optimizer). After an aqueous work up, the crude product was purified by a silica-gel column chromatography (hexane / EtOAc 20:80) to give 6-(3,5-dimethylisoxazol-4-yl)-4-(2-methylnaphthalen-1-yl)-1H-benzo[d]imidazol-2(3H)-one.

[00142] C₂₃H₁₉N₃O₂. MS. m/z 370.1 (M+1). ¹H NMR (400 MHz, Methanol-d₄) δ 7.88 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.38 – 7.33 (m, 2H), 7.10
 15 (s, 1H), 6.82 (s, 1H), 2.43 (s, 3H), 2.28 (s, 6H).

Example 19

4-(2-(difluoromethyl)-3-methylquinolin-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



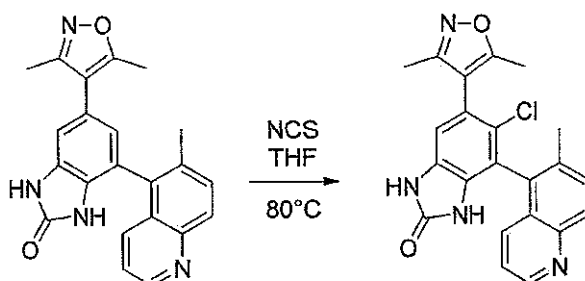
5 [00143] The title compound was synthesized in a similar fashion as that of Example 17.

[00144] $C_{23}H_{17}FN_4O_2$. MS. m/z 421.1 ($M+1$). ^1H NMR (400 MHz, Methanol- d_4) δ 8.18 (d, $J = 9.0$ Hz, 1H), 7.83 – 7.74 (m, 1H), 7.63 – 7.57 (m, 1H), 7.45 (d, $J = 9.4$ Hz, 1H), 7.23 – 6.87 (m, 2H), 2.47 – 2.40 (m, 6H), 2.30 (s, 3H).

10

Example 20

Preparation of 4-chloro-5-(3,5-dimethylisoxazol-4-yl)-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one



15

[00145] In 0.5 -2 mL Smith Process Vial, the intermediate (25.0 mg, 0.067 mmol) and NCS (36.3 mg, 0.135 mmol) were dissolved into THF (2 mL). The mixture was heated at 80

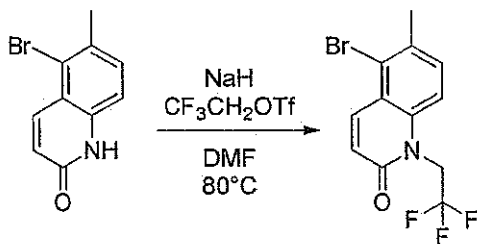
°C for 2 h in an oil bath. The reaction mixture was directly injected into Gilson preparative HPLC (5-95% acetonitrile: water with 0.05% trifluoroacetic acid, on a Phenomenex Luna C18 column) to give the desired product.

- [00146] C₁₉H₁₈N₄O₂. MS. *m/z* 405.1 (M+1), 407.1 (M+2+1). ¹H NMR (400 MHz, Methanol-*d*₄) δ 9.25 – 9.05 (d, *J* = 5.8 Hz, 1H), 8.47 – 8.40 (m, 1H), 8.30 (d, *J* = 9.0 Hz, 1H), 8.20 (d, *J* = 9.0 Hz, 1H), 7.96 – 7.90 (m, 1H), 7.19 (s, 1H), 2.40 (s, 3/2H), 2.39 (s, 3/2H), 2.38 (s, 3/2H), 2.34 (s, 3/2H), 2.21 (s, 3/2H), 2.19 (s, 3/2H).

Example 21

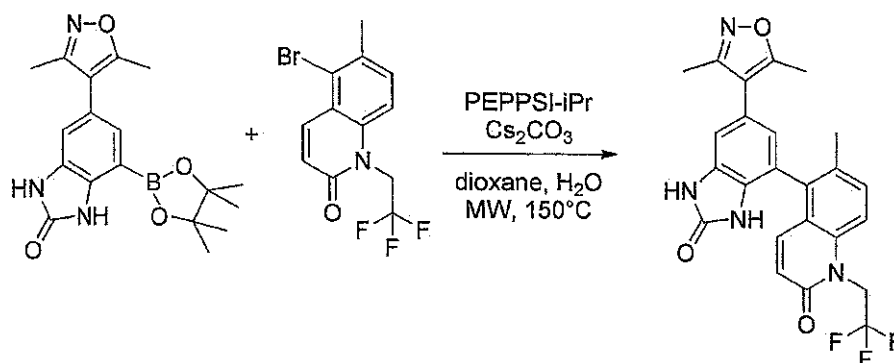
- 10 5-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-6-methyl-1-(2,2,2-trifluoroethyl)quinolin-2(1H)-one

Step 1:



- [00147] 5-Bromo-6-methylquinolin-2(1H)-one (103.5 mg, 0.435 mmol) was suspended into DMF (3 mL). To the suspension, was added NaH (17.4 mg 60% in mineral oil) at room temperature. After 2 h stirring, CF₃CH₂OTf (201.8 mg, 0.869 mmol) was added into the mixture at room temperature. The reaction mixture was stirred for 2 h at the same temperature. The reaction mixture was quenched with water (30 mL). The whole was extracted with AcOEt (30 mL x 3). Organic layer was washed with brine (30 mL) and dried over Na₂SO₄. The solvent was removed under a reduced pressure to give the crude product. Gilson PHPLC purification gave 5-bromo-6-methyl-1-(2,2,2-trifluoroethyl)quinolin-2(1H)-one.

- [00148] ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.41 (d, *J* = 10.0 Hz, 1H), 7.58 (s, 2H), 6.77 (d, *J* = 10.0 Hz, 1H), 5.20 (q, *J* = 8.7 Hz, 2H), 2.52 (d, *J* = 1.0 Hz, 3H).

Step 2:

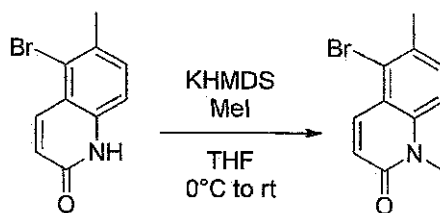
[00149] In a 2-5 mL Smith Process Vial, the boronic acid pinacol ester (29.0 mg 0.82 mmol), the bromide (26.1 mg, 0.082 mmol, 1 equiv), PEPPSI-iPr (2.8 mg, 0.004 mmol, 0.05 equiv) and Cs₂CO₃ (53.2 mg, 0.163 mmol, 2 equiv) were placed. The mixture was suspended in 1,4-dioxane and water under N₂. The mixture was heated at 150°C for 20 min using microwave reactor (Biotage Optimizer). To the mixture were added EtOAc (70 mL) and water (30 mL). The whole was filtered through Celite (3 g) and the filtrate was washed with brine (30 mL), dried over Na₂SO₄ and concentrated under a reduced pressure. Obtained crude material was purified by Gilson preparative HPLC to give the desired product (23.0 mg, 60%).

[00150] C₂₄H₁₉F₃N₄O₃. MS. m/z 469.1 (M+1). ¹H NMR (400 MHz, Methanol-*d*₄) δ 7.70 (d, *J* = 9.2 Hz, 1H), 7.67 (d, *J* = 9.2 Hz, 1H), 7.52 (d, *J* = 10.0 Hz, 1H), 7.12 (s, 1H), 6.82 (s, 1H), 6.60 (d, *J* = 10.0 Hz, 1H), 5.26 (q, *J* = 13.3 Hz, 2H), 2.43 (s, 3H), 2.28 (s, 3H), 2.20 (s, 3H).

Example 22

5-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-1,6-dimethylquinolin-2(1H)-one

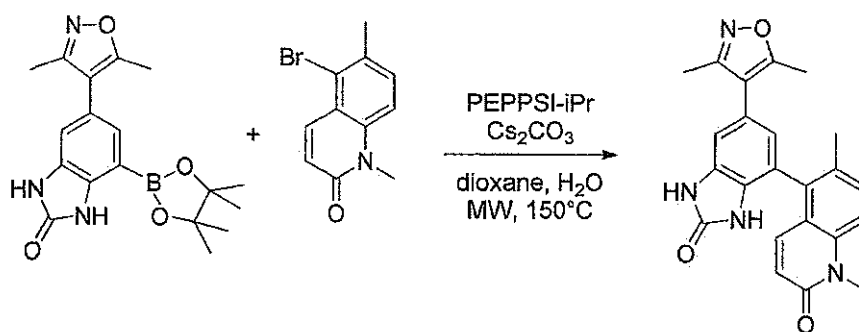
20 Step 1:



[00151] 5-bromo-6-methylquinolin-2(1H)-one (500.0 mg, 2.1 mmol) in THF (10 mL) was treated with KHMDS (2.31 mL, 2.31 mmol, 1.1 equiv) at 0°C for 15 min. To the reaction mixture was added MeI (0.26 mL 596.2 mg, 4.2 mmol, 2 equiv) was added into the mixture at 0°C. The reaction mixture was allowed to warm up to room temperature and stirred for overnight at the same temperature to form a precipitation. The precipitation was filtered off using a glass filter. The filtrate was concentrated and purified by a silica-gel column chromatography (hexane / EtOAc 50:50 to 0:100) to give 5-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-1,6-dimethylquinolin-2(1H)-one as colorless crystals.

[00152] $C_{11}H_{10}BrNO$. MS. m/z 469.1 (M+1).

Step 2:

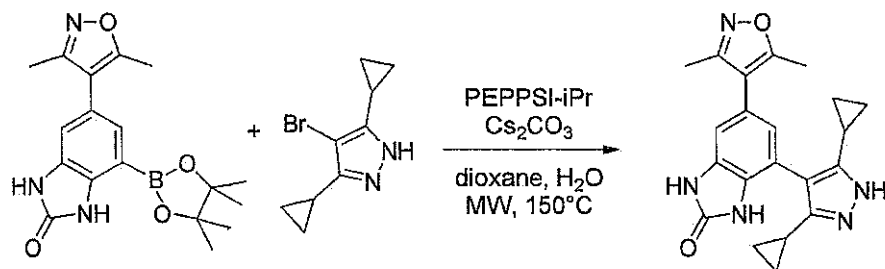


[00153] 5-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-1,6-dimethylquinolin-2(1H)-one was synthesized in a similar fashion as that of Example 21.

[00154] $C_{23}H_{20}N_4O_3$. MS. m/z 401.1 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 7.68 (d, $J = 9.6$ Hz, 1H), 7.63 (d, $J = 9.6$ Hz, 1H), 7.45 (d, $J = 9.6$ Hz, 1H), 7.11 (s, 1H), 6.80 (s, 1H), 6.58 (d, $J = 9.6$ Hz, 1H), 3.80 (s, 3H), 2.43 (s, 3H), 2.28 (s, 3H), 2.20 (s, 3H).

Example 23

4-(3,5-dicyclopropyl-1H-pyrazol-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



5 [00155] The compound of Example 23 was synthesized in a similar fashion as that of Example 22.

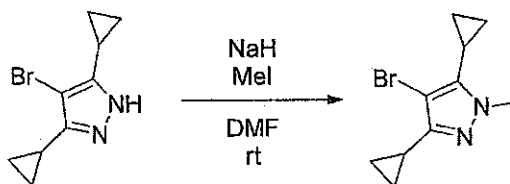
[00156] $C_{21}H_{21}N_5O_2$. MS. m/z 376.1 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 7.05 (s, 1H), 6.95 (s, 1H), 2.33 (s, 3H), 2.28 (s, 3H), 1.86-1.76 (m, 2H), 1.00-0.90 (m, 4H), 0.87-0.78 (m, 4H).

10

Example 24

4-(3,5-dicyclopropyl-1-methyl-1H-pyrazol-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

Step 1:



15

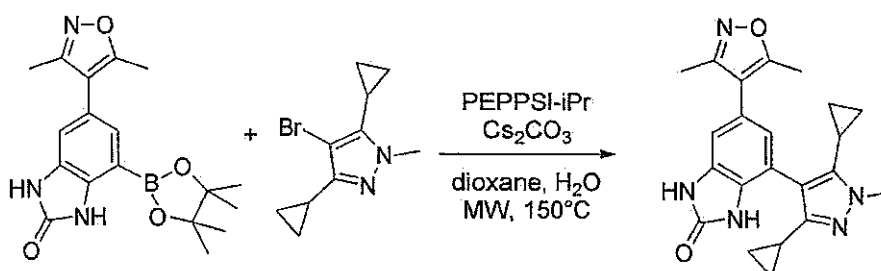
[00157] 4-Bromo-3,5-dicyclopropyl-1-methyl-1H-pyrazole (50.0 mg, 0.22 mmol) was dissolved into DMF (3 mL). To the solution, was added NaH (17.6 mg 60% in mineral oil, 0.44 mmol, 2 equiv) at room temperature. After 30 min stirring, MeI (62.5 mg, 0.44 mmol, 2 equiv) was added into the mixture at room temperature. The reaction mixture was stirred for 20 min at the same temperature. The reaction mixture was quenched with water (30 mL). The

20

whole was extracted with AcOEt (30 mL x 3). Organic layer was washed with brine (30 mL) and dried over Na₂SO₄. The solvent was removed under a reduced pressure to give the crude product. A silica-gel column chromatography (hexane / EtOAc 87:13 to 70:30) purification gave 4-bromo-3,5-dicyclopropyl-1-methyl-1H-pyrazole (51.8 mg, 97.6%).

5 [00158] C₁₀H₁₃BrN₂. MS. m/z 241.0 (M-1+1), 243.0 (M+1+1).

Step 2:



[00159] 4-(3,5-dicyclopropyl-1-methyl-1H-pyrazol-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one was synthesized in a similar fashion as that of Example 21.

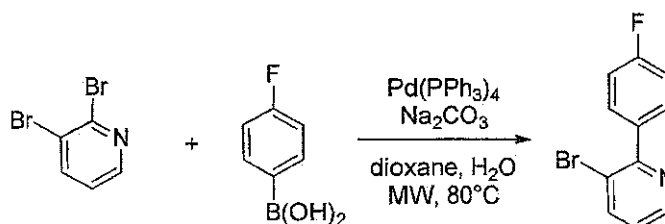
[00160] C₂₃H₂₀N₄O₃. MS. m/z 390.1 (M+1). ¹H NMR (400 MHz, Methanol-*d*₄) δ 6.98 (s, 1H), 6.85 (s, 1H), 3.87 (s, 3H), 2.43 (s, 3H), 2.27 (s, 3H), 1.88-1.80 (m, 1H), 1.69-1.60 (m, 1H), 1.00-0.60 (m, 6H), 0.38-0.28 (m, 2H).

15

Example 25

6-(3,5-dimethylisoxazol-4-yl)-4-(2-(4-fluorophenyl)pyridin-3-yl)-1H-benzo[d]imidazol-2(3H)-one

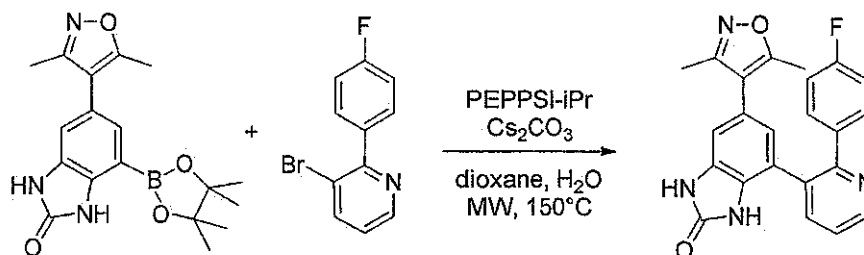
Step 1:



- [00161] In a 2-5 mL Smith Process Vial, 2,3-dibromopyridine (300.0 mg, 1.266 mmol), 4-fluorophenyl boronic acid (177.2 mg, 1.266 mmol, 1 equiv) and Pd(PPh₃)₄ (73.2 mg, 0.063 mmol, 0.05 equiv) were placed. The mixture was suspended in 1,4-dioxane (3 mL) and 2M-Na₂CO₃ (1 mL) under a nitrogen atmosphere. The mixture was heated at 80°C for 10 min using the microwave reactor. To the mixture were added EtOAc (70 mL) and water (30 mL). The whole was filtered through Celite (3 g) and the filtrate was washed with brine (30 mL), dried over Na₂SO₄ and concentrated under a reduced pressure. Obtained crude material was purified by Gilson preparative HPLC to give 3-bromo-2-(4-fluorophenyl)pyridine.

[00162] C₁₁H₇BrFN. MS. m/z 241.0 (M-1+1), 243.0 (M+1+1).

10 Step 2:



[00163] This transformation was performed in a similar fashion as that of Example 21.

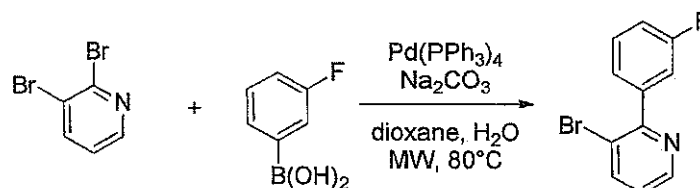
- [00164] C₂₃H₁₇FN₄O₂. MS. m/z 401.1 (M+1). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.68 (dd, 1H, *J* = 4.8, 1.6 Hz), 7.77 (dd, 1H, *J* = 8.0, 1.6 Hz), 7.55 (dd, 1H, *J* = 8.0, 4.6 Hz), 7.42-7.35 (m, 2H), 7.00 (t, 2H, *J* = 8.0 Hz), 6.92 (d, 1H, *J* = 1.0 Hz), 6.65 (d, 1H, *J* = 1.0 Hz), 2.20 (s, 3H), 2.05 (s, 3H).

Example 26

6-(3,5-dimethylisoxazol-4-yl)-4-(2-(3-fluorophenyl)pyridin-3-yl)-1H-benzo[d]imidazol-2(3H)-one

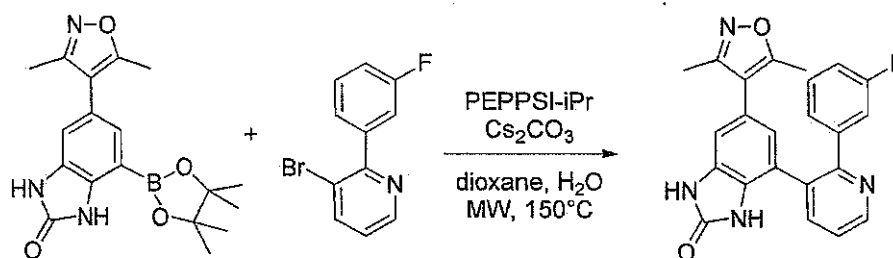
Step 1:

5



[00165] 3-Bromo-2-(3-fluorophenyl)pyridine was synthesized in a similar fashion with 3-bromo-2-(4-fluorophenyl)pyridine. $\text{C}_{11}\text{H}_7\text{BrFN}$. MS. m/z 241.0 ($M-1+1$), 243.0 ($M+1+1$).

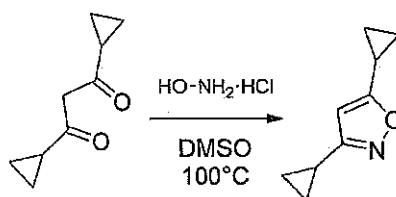
Step 2:



10 [00166] This transformation was performed in a similar fashion as that of Example 21.

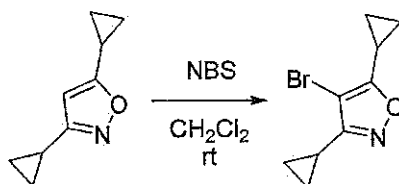
[00167] $\text{C}_{23}\text{H}_{17}\text{FN}_4\text{O}_2$. MS. m/z 401.1 ($M+1$). ^1H NMR (400 MHz, Methanol- d_4) δ 8.70 (dd, 1H, $J = 4.8, 1.6$ Hz), 7.98 (dd, 1H, $J = 8.0, 1.6$ Hz), 7.57 (dd, 1H, $J = 8.0, 4.8$ Hz), 7.30-7.22 (m, 1H), 7.17-7.10 (m, 2H), 7.06-6.96 (m, 1H), 6.93 (d, 1H, $J = 1.0$ Hz), 6.68 (d, 1H, $J = 1.0$ Hz), 2.21 (s, 3H), 2.06 (s, 3H).

15

Example 27**4-(3,5-dicyclopropylisoxazol-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one**5 Step 1:

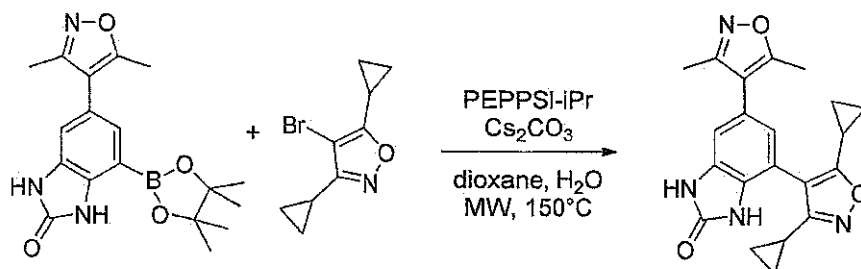
[00168] 1,3-Dicyclopropylpropane-1,3-dione (300.0 mg, 1.971 mmol) and hydroxylamine hydrochloride (162.0 mg, 2.365 mmol, 2 equiv) were heated at 100°C in DMSO (1 mL) in oil bath. After the reaction completed, the reaction mixture was directly
 10 injected into Gilead preparative HPLC to give 4-bromo-3,5-dicyclopropylisoxazole.

[00169] C₉H₁₁ON. MS. m/z 228.0 (M-1+1), 230.0 (M+1+1).

Step 2:

[00170] 3,5-Dicyclopropylisoxazole (70.0 mg, 0.469 mmol) was treated with NBS (167.0 mg, 0.938 mmol, equiv) in CH₂Cl₂ at room temperature for 12 h. The solvent was removed under a reduced pressure and the residue was directly loaded onto a silica gel column chromatography (hexane EtOAc 87:13) to give 4-bromo-3,5-dicyclopropylisoxazole.
 15

[00171] C₉H₁₀BrON. MS. m/z 228.0 (M-1+1), 230.0 (M+1+1).

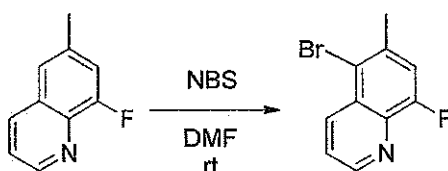
Step 3:

[00172] This transformation was performed in a similar fashion as that of Example 21.

[00173] $C_{21}H_{20}N_4O_3$. MS. m/z 377.1 ($M+1$). ^1H NMR (400 MHz, Methanol- d_4) δ 7.05 (d, 1H, $J = 1.0$ Hz), 6.95 (d, 1H, $J = 1.0$ Hz), 2.43 (s, 3H), 2.28 (s, 3H), 1.90 (quin, 1H, $J = 6.4$ Hz), 1.60 (quin, 1H, $J = 6.4$ Hz), 1.01 (d, 4H, $J = 6.4$ Hz), 0.91 (d, 4H, $J = 6.4$ Hz).

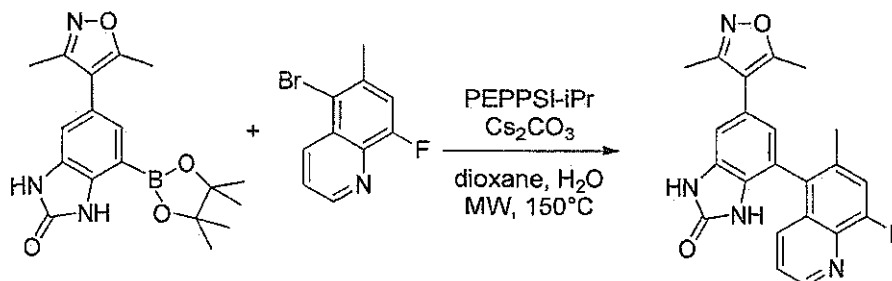
Example 28

6-(3,5-dimethylisoxazol-4-yl)-4-(8-fluoro-6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one

Step 1:

[00174] 3,5-Dicyclopropylisoxazole (70.0 mg, 0.469 mmol) was treated with NBS (167.0 mg, 0.938 mmol, 2 equiv) in CH_2Cl_2 at room temperature for 12 h. The solvent was removed under a reduced pressure and the residue was directly loaded onto a silica gel column chromatography (hexane EtOAc 87:13) to give 5-bromo-8-fluoro-6-methylquinoline (68.7 mg, 64.2%).

[00175] $C_9H_{10}BrON$. MS. m/z 239.9 ($M-1+1$), 241.9 ($M+1+1$).

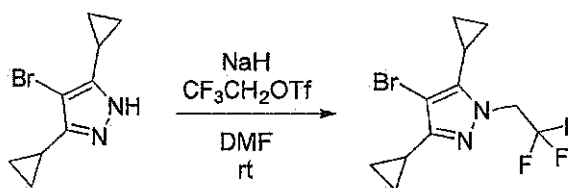
Step 2:

[00176] This transformation was performed in a similar fashion as that of Example 21.

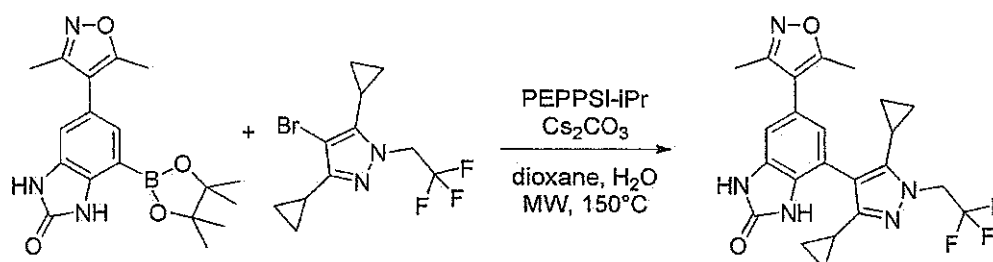
[00177] $C_{22}H_{17}FN_4O_2$. MS. m/z 398.1 ($M+1$). ^1H NMR (400 MHz, Methanol- d_4) δ
 5 8.93 (d, 1H, $J = 4.0$ Hz), 8.08 (d, 1H, $J = 8.0$ Hz), 7.70 (d, 1H, $J = 11.2$ Hz), 7.67 (dd, 1H, $J = 8.0, 4.0$ Hz), 7.15 (d, 1H, $J = 1.0$ Hz), 6.88 (d, 1H, $J = 1.0$ Hz), 2.43 (s, 3H), 2.38 (s, 3H), 2.28 (s, 3H).

Example 29

10 **-(3,5-dicyclopropyl-1-(2,2,2-trifluoroethyl)-1H-pyrazol-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one**

Step 1:

[00178] 4-Bromo-3,5-dicyclopropyl-1-(2,2,2-trifluoroethyl)-1H-pyrazole was
 15 synthesized in a similar fashion with 5-bromo-6-methyl-1-(2,2,2-trifluoroethyl)quinolin-2(1H)-one. $C_{11}H_{12}BrF_3N_2$. MS. m/z 309.0 ($M-1+1$), 311.0 ($M+1+1$).

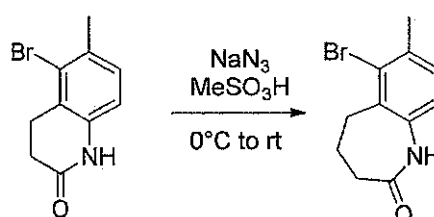
Step 2:

[00179] This transformation was performed in a similar fashion as that of Example 21.

[00180] $C_{23}H_{22}F_3N_5O_2$. MS. m/z 458.1 ($M+1$). ^1H NMR (400 MHz, Methanol- d_4) δ
 5 7.00 (d, 1H, $J = 1.0$ Hz), 6.85 (d, 1H, $J = 1.0$ Hz), 4.95 (q, 2H, $J = 9.6$ Hz), 2.43 (s, 3H),
 2.27 (s, 3H), 1.90-1.81 (m, 1H), 1.66-1.61 (m, 1H), 1.40-1.26 (m, 2H), 0.94-0.68 (m, 6H),
 0.42-0.32 (m, 2H).

Example 30

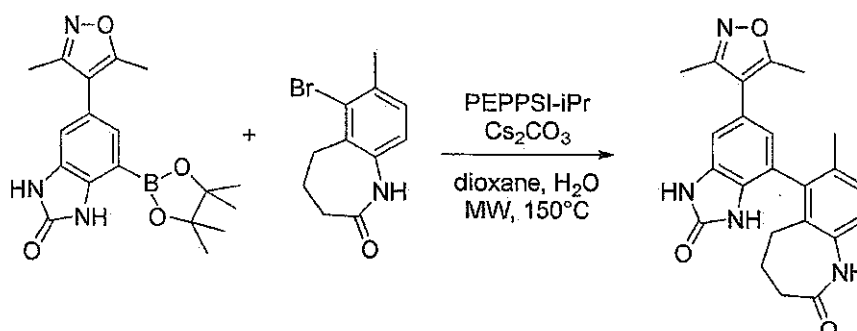
10 6-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-7-methyl-
 4,5-dihydro-1H-benzo[b]azepin-2(3H)-one

Step 1:

[00181] 5-Bromo-6-methyl-3,4-dihydroquinolin-2(1H)-one (477.7 mg, 1.998 mmol)
 15 was treated with NaN_3 (194.8 mg, 0.938 mmol, 1.5 equiv) in $MeSO_3H$ (3 g) at $0^\circ C$ to room
 temperature for 1 h. The mixture was neutralized with $NaHCO_3$ and extracted with EtOAc
 (30 mL x 3). The organic layer was washed with brine (30 mL) and dried over Na_2SO_4 . The
 solvent was removed under a reduced pressure and the crude product was recrystallized from
 EtOAc (10 mL) to give 6-bromo-7-methyl-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one.

20 [00182] $C_{11}H_{12}BrON$. MS. m/z 254.0 ($M-1+1$), 256.0 ($M+1+1$).

Step 2:



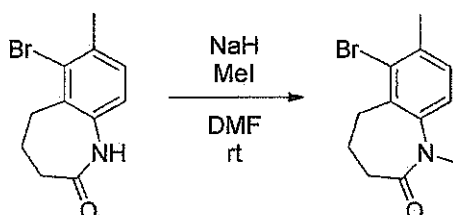
[00183] This transformation was performed in a similar fashion as that of Example 21.

[00184] $C_{23}H_{22}N_4O_3$. MS. m/z 403.1 ($M+1$). ^1H NMR (400 MHz, Methanol- d_4) δ 8.93 (d, 1H, $J = 4.0$ Hz), 7.24 (d, 1H, $J = 8.0$ Hz), 7.04 (d, 1H, $J = 8.0$ Hz), 7.03 (d, 1H, $J = 1.0$ Hz), 6.73 (d, 1H, $J = 1.0$ Hz), 2.60-2.22 (m, 4H), 2.41 (s, 3H), 2.26 (s, 3H), 2.05 (s, 3H), 2.04-1.94 (m, 3H).

Example 31

10 6-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-7-methyl-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one

Step 1:

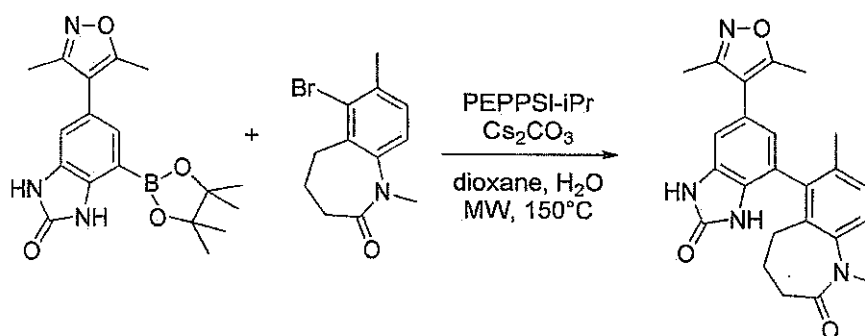


[00185] 6-Bromo-7-methyl-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one (100.0 mg, 1.998 mmol) was treated with NaH (18.9 mg, 0.472 mmol, 1.2 equiv) in DMF (3 mL) at 0°C to room temperature for 30 min. To the mixture was added MeI (111.7 mg, 0.787 mmol, 2 equiv). The mixture was stirred at to room temperature for 1 h. The mixture was quenched with water and extracted with EtOAc (30 mL x 3). The organic layer was washed with brine (30 mL) and dried over Na_2SO_4 . The solvent was removed under a reduced pressure and the

crude product was purified by a silica-gel column chromatography (hexane / EtOAc 87:13 to 50:50) to give 6-bromo-1,7-dimethyl-4,5-dihydro-1H-benzo[b]azepin-2(3H)-one (88.5 mg, 83.9%).

[00186] ^1H NMR (400 MHz, CDCl_3) δ 7.16 (d, 1H, $J = 8.0$ Hz), 7.03 (d, 1H, $J = 8.0$ Hz), 3.32 (s, 3H), 2.43 (s, 3H), 2.40-1.90 (broad, 6H).

Step 2:



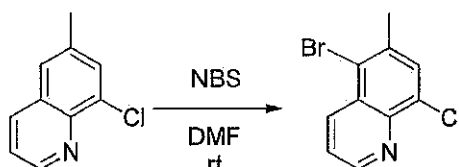
[00187] This transformation was performed in a similar fashion as that of Example 21.

[00188] $\text{C}_{24}\text{H}_{24}\text{N}_4\text{O}_3$. MS. m/z 417.1 ($M+1$). ^1H NMR (400 MHz, Methanol- d_4) δ 7.34 (d, 1H, $J = 8.0$ Hz), 7.30 (d, 1H, $J = 8.0$ Hz), 7.04 (d, 1H, $J = 1.0$ Hz), 6.73 (broad, 1H), 3.36 (s, 3H), 2.60-2.20 (m, 4H), 2.41 (s, 3H), 2.26 (s, 3H), 2.07 (s, 3H).

Example 32

4-(8-chloro-6-methylquinolin-5-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

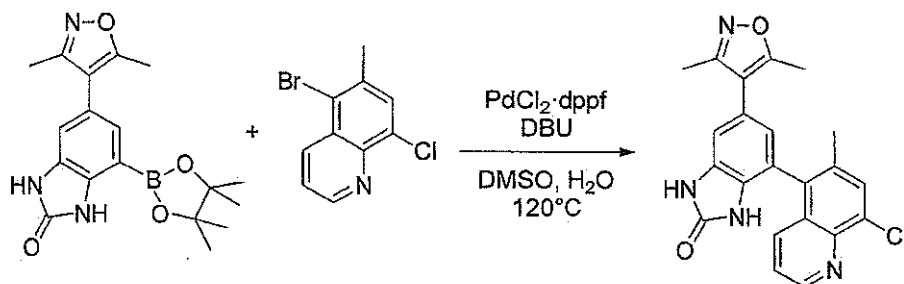
Step 1:



[00189] 5-Bromo-8-chloro-6-methylquinoline was synthesized in a similar fashion, using 5-bromo-8-fluoro-6-methylquinoline.

$C_{10}H_8ClN$. MS. m/z 258.0 (M-1+1), 256.1 (M+1+1), 260.0 (M+1+2).

Step 2:



5

[00190] A mixture of 6-(3,5-Dimethylisoxazol-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one (100.0, 0.282 mmol) and 5-bromo-8-chloro-6-methylquinoline (72.2 mg, 0.282 mmol) was treated with $PdCl_2dppf \cdot CH_2Cl_2$ (20.9 mg, 0.028 mmol) in the presence of 1,8-Diazabicycloundec-7-ene (DBU, 204.0 mg, 1.34 mmol, 4.76 equiv) in DMSO (0.2 mL) and water (0.2 mL). The reaction mixture was heated at 120°C in oil bath. The reaction mixture was diluted with THF (3 mL) and purified by Gilson preparative HPLC to give 4-(8-chloro-6-methylquinolin-5-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

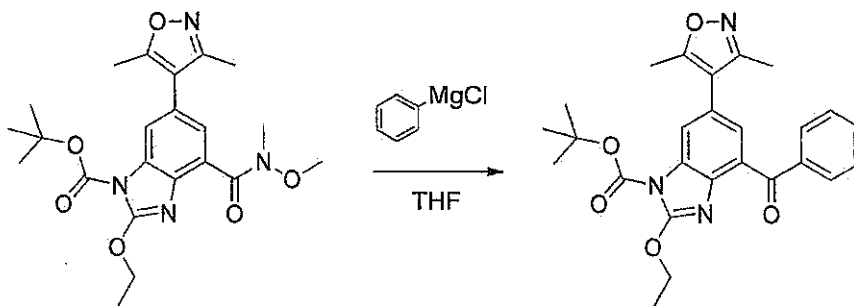
[00191] $C_{22}H_{17}ClN_4O_2$. ^1H NMR (400 MHz, Methanol- d_4) δ 8.97 (d, 1H, J = 4.8, 1.6 Hz), 8.08 (d, 1H, J = 8.0 Hz), 8.09 (dd, 1H, J = 9.6, 1.6 Hz), 8.08 (s, 1H), 7.66 (dd, 1H, J = 9.6, 4.8 Hz), 7.16 (d, 1H, J = 1.0 Hz), 6.89 (d, 1H, J = 1.0 Hz), 2.44 (s, 3H), 2.36 (s, 3H), 2.28 (s, 3H).

15

Example 33

6-(3,5-dimethylisoxazol-4-yl)-4-((7-fluoroquinolin-2-yl)(hydroxy)(phenyl)methyl)-1H-benzo[d]imidazol-2(3H)-one

Step 1:



5

[00192] *Tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-

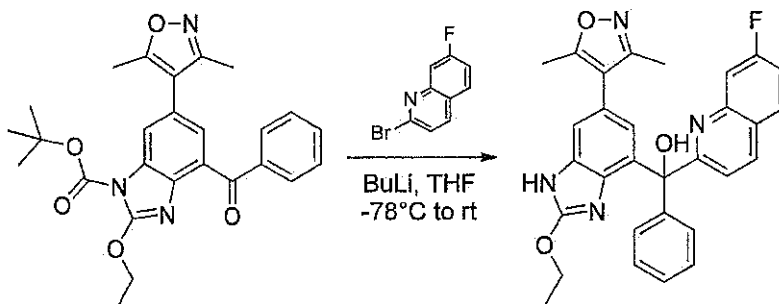
(methoxy(methyl)carbamoyl)-1H-benzo[d]imidazole-1-carboxylate was dissolved in THF (3 mL). To the solution was added a solution of phenyl magnesium chloride (2M in THF, 0.508 mmol, 0.254 mmol) at -78°C. after the addition, the reaction was allowed to warm up to room temperature. The reaction was stirred for 17 hat the same temperature. The reaction mixture was quenched with water (30 mL). The whole was extracted with AcOEt (30 mL x 3). Organic layer was washed with brine (30 mL) and dried over Na₂SO₄. The solvent was removed under a reduced pressure to give the crude product. The crude product was purified by a silica gel column chromatography (hexane: EtOAc, 7:1 to 3:1) to give *tert*-butyl 4-benzoyl-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate.

10

15

[00193] C₂₆H₂₇N₃O₅. MS. m/z 462.2 (M+1).

Step 2:

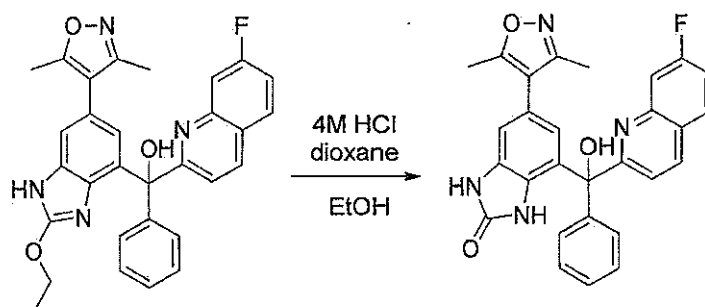


[00194] To a solution of 7-fluoro-2-bromoquinoline (54.1 mg) in THF (2 mL) was added BuLi (1.6 M, 0.25 mL) at -78°C. After 5 min, a solution of phenyl ketone (60.0 mg) in THF (1 mL) was added at -78°C. The reaction was immediately allowed to warm up to room temperature and stirred for 30 min. The reaction mixture was quenched with water (30 mL).

5 The whole was extracted with AcOEt (30 mL x 3). Organic layer was washed with brine (30 mL) and dried over Na₂SO₄. The solvent was removed under a reduced pressure to give the crude product. The crude product was treated with TFA to cleave the Boc group. The crude product was purified by a silica gel column chromatography (hexane: EtOAc, 7:1 to 3:1) to give tert-butyl 4-benzoyl-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate.

[00195] C₂₆H₂₇N₃O₅. MS. m/z 509.2 (M+1).

Step 3:

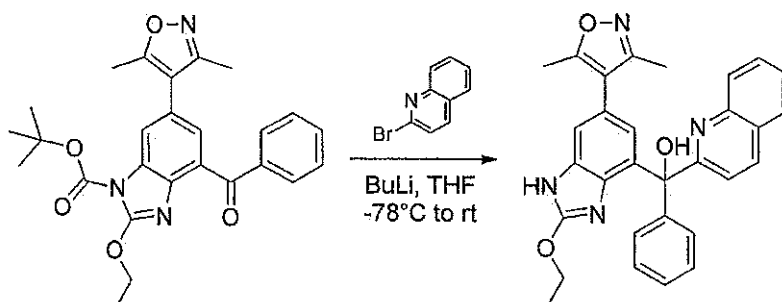


[00196] *Tert*-butyl 4-benzoyl-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate (18.0 mg) was dissolved into EtOH (2 mL) and 4M HCl/dioxane (2 mL). The solution was heated at 70°C for 30 min. The reaction mixture was quenched with water (30 mL). The whole was extracted with EtOAc (30 mL x3). Combined organic layers were washed with brine (50 mL). The solvent was removed under a reduced pressure to give a crude product. The crude product was purified by a silica gel column chromatography (hexane: EtOAc, 7:1 to 3:1) to give *tert*-butyl 4-benzoyl-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate.

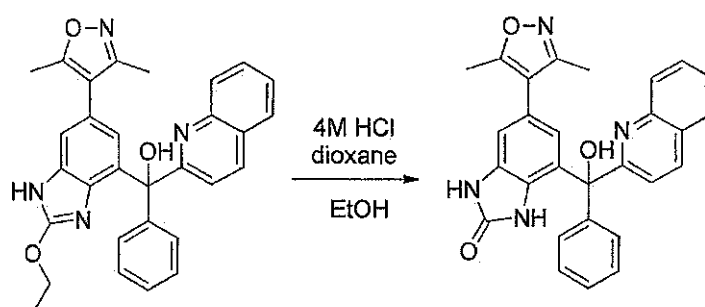
[00197] C₂₈H₂₁FN₄O₃. MS. m/z 481.1 (M+1). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.31 (1, *J* = 8.7 Hz, 1H), 8.13 (dd, *J* = 9.2, 5.3 Hz, 1H), 7.67 – 7.56 (m, 3H), 7.40 – 7.25 (m, 5H), 6.98 (d, *J* = 1.6 Hz, 1H), 6.61 (d, *J* = 1.6 Hz, 1H), 2.28 (s, 3H), 2.11 (s, 3H).

Example 34

6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(phenyl)(quinolin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one



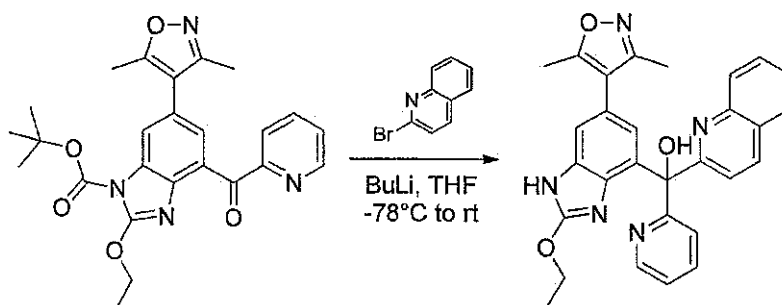
- 5 [00198] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(phenyl)(quinolin-2-yl)methanol was synthesized in the similar fashion with tert-butyl 4-benzoyl-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate. $C_{30}H_{26}N_4O_3$. MS. m/z 491.2 (M+1).



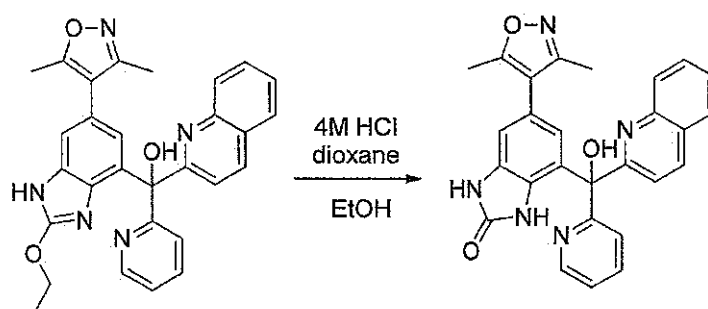
- 10 [00199] 6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(phenyl)(quinolin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one was synthesized in the similar fashion as that of Example 33.
- $C_{28}H_{22}N_4O_3$. MS. m/z 463.1 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 8.30 (d, J = 8.6 Hz, 1H), 8.09 (d, J = 8.6 Hz, 1H), 7.93 (d, J = 8.6 Hz, 1H), 7.77 (ddd, J = 8.6, 7.0, 1.2 Hz, 1H), 7.61 (ddd, J = 8.6, 7.0, 1.2 Hz, 1H), 7.54 (d, J = 8.6 Hz, 1H), 7.40-7.26 (m, 5H), 6.98 (d, J = 1.5 Hz, 1H), 6.61 (d, J = 1.5 Hz, 1H), 2.27 (s, 3H), 2.10 (s, 3H).
- 15

Example 35

6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(pyridin-2-yl)(quinolin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one



- 5 [00200] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)(quinolin-2-yl)methanol was synthesized in the similar fashion with tert-butyl 4-benzoyl-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate. $C_{29}H_{25}N_5O_3$. MS. m/z 492.2 (M+1).



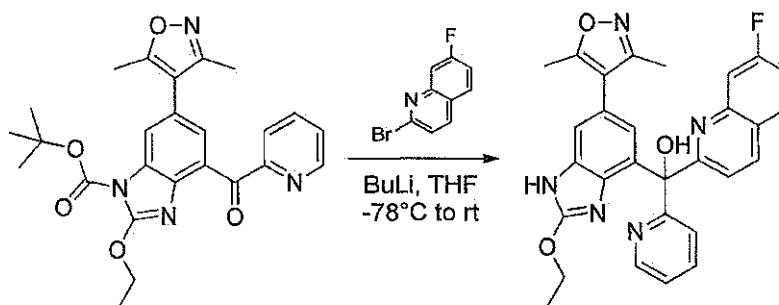
- 10 [00201] 6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(pyridin-2-yl)(quinolin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one was synthesized in the similar fashion as that of Example 33.

- $C_{28}H_{22}N_4O_3$. MS. m/z 463.1 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 8.78 (dd, J = 6.6, 1.0 Hz, 1H), 8.66 (d, J = 8.8 Hz, 1H), 8.47 (td, J = 8.8, 1.0 Hz, 1H), 8.15 – 8.03 (m, 3H),
 15 8.00 – 7.83 (m, 3H), 7.76 (t, J = 8.0 Hz, 1H), 7.07 (d, J = 1.0 Hz, 1H), 6.46 (d, J = 1.0 Hz, 1H), 2.22 (s, 3H), 2.04 (s, 3H).

Example 36

6-(3,5-dimethylisoxazol-4-yl)-4-((7-fluoroquinolin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one

Step 1:

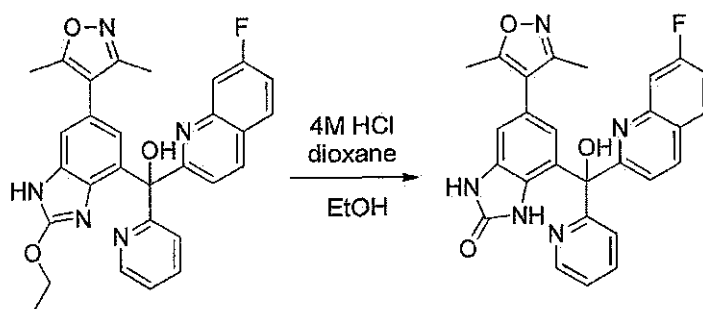


5

[00202] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(7-fluoroquinolin-2-yl)(pyridin-2-yl)methanol was synthesized in the similar fashion with tert-butyl 4-benzoyl-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate.

10 [00203] $C_{29}H_{24}FN_5O_3$. MS. m/z 510.2 (M+1).

Step 2:

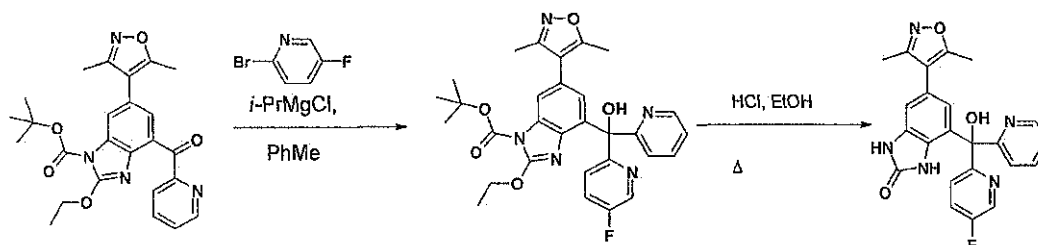


15 [00204] 6-(3,5-dimethylisoxazol-4-yl)-4-((7-fluoroquinolin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one was synthesized in the similar fashion as that of Example 33.

$C_{27}H_{20}FN_5O_3$. MS. m/z 482.1 ($M+1$). ^1H NMR (400 MHz, Methanol- d_4) δ 8.52 (ddd, $J = 4.9$, 1.8, 0.9 Hz, 1H), 8.26 (dd, $J = 8.9$, 0.8 Hz, 1H), 8.04 (dd, $J = 9.2$, 5.3 Hz, 1H), 7.84 (td, $J = 7.8$, 1.8 Hz, 1H), 7.76 (d, $J = 7.8$ Hz, 1H), 7.72 (d, $J = 7.8$ Hz, 1H), 7.59 (dd, $J = 8.9$, 1.8 Hz, 1H), 7.54 (d, $J = 8.9$, 0.8 Hz, 1H), 7.33 (ddd, $J = 7.5$, 4.9, 1.2 Hz, 1H), 6.96 (d, $J = 1.6$ Hz, 1H), 6.72 (d, $J = 1.6$ Hz, 1H), 2.28 (s, 3H), 2.11 (s, 3H).

Example 37

6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one



10

[00205] To isopropyl magnesium chloride (1.32 mL, 2.64 mmol, 2 M in THF) in toluene (4mL) was added 2-bromo-5-fluoropyridine (388 mg, 2.05 mmol) in toluene (1 mL). After 3.5 hours the Grignard solution (1 mL, 0.65 mmol) was added to tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxycarbonyl-1H-benzo[d]imidazole-1-carboxylate (60 mg, 0.13 mmol) in a 1:1 mixture of toluene/2-methyl-THF (6 mL) at 0°C and the mixture was allowed to warm to 20°C. After 16 hours, the reaction was quenched with saturated $NH_4Cl_{(aq)}$ (10 mL), extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The resulting residue (100 mg) was submitted to deprotection directly.

[00206] To 100 mg crude tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-((5-fluoropyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-1H-benzo[d]imidazole-1-carboxylate (100 mg) in ethanol (3 mL) was added hydrochloric acid (0.2 mL, 0.8 mmol, 4 M in 1,4-dioxane). The mixture was heated to 70°C for 0.5 hours and then concentrated *in vacuo*. Purification by reverse-phase HPLC (25-50% acetonitrile/water with 0.01% trifluoroacetic acid, Gemini C18 5 μ) afforded the TFA salt of 6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one as a light yellow solid.

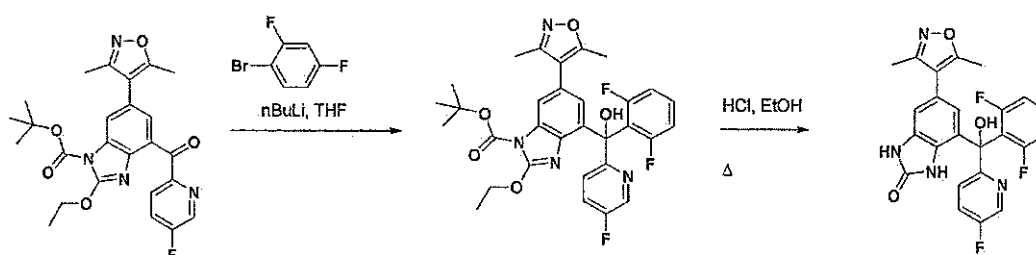
25

[00207] $C_{23}H_{18}FN_5O_3$, 432.1 (M+H). ^1H NMR (400 MHz, d_3 -acetonitrile) δ 10.72 (s, 1H), 9.80 (s, 1H), 8.6 (m, 1H), 7.87 (m, 1H), 7.75 (m, 1H), 7.62 (m, 1H), 6.87 (s, 1H), 6.51 (s, 1H), 2.30 (s, 3H), 2.11 (s, 3H). ^{19}F NMR (376 MHz, d_3 -acetonitrile) δ -74.7, -130.95.

5

Example 38

4-((2,6-difluorophenyl)(5-fluoropyridin-2-yl)(hydroxy)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



[00208] To 1-bromo-2,4-difluorobenzene (0.02 ml, 0.16 mmol) in THF (0.52 mL) at -78°C was added *n*-butyllithium (0.12 mL, 0.18 mmol, 1.6 M in hexanes). After 30 minutes, *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(5-fluoropicolinoyl)-1H-benzo[d]imidazole-1-carboxylate (50 mg, 0.10 mmol) in THF (1 mL) was added drop-wise to the reaction. After 60 minutes, the reaction was warmed, quenched with saturated $NH_4Cl_{(aq)}$ (10 mL), extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. To the crude residue in ethanol (3.5 mL) was added hydrochloric acid (0.35 mL, 1.4 mmol, 4 M in 1,4-dioxane) and the mixture was heated to 70°C in a microwave reactor for 45 minutes. Purification by reverse-phase HPLC (40-50% acetonitrile/water with 0.01% trifluoroacetic acid, Gemini C18 5 μ) gave the trifluoroacetate salt of 4-((2,6-difluorophenyl)(5-fluoropyridin-2-yl)(hydroxy)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one as a white solid.

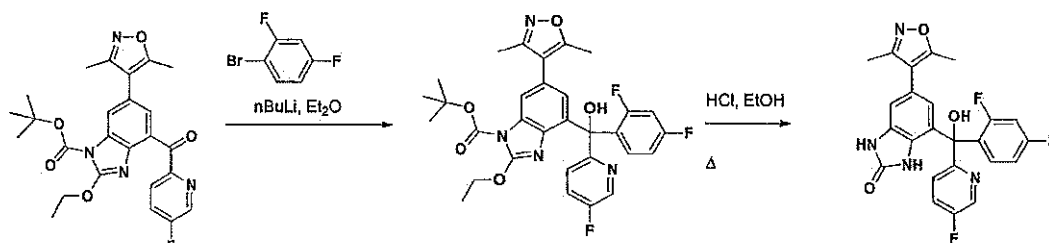
20

[00209] $C_{24}H_{17}F_3N_4O_3$, 467.03 (M+H). ^1H NMR (400 MHz, d_3 -acetonitrile) δ 8.74 (s, 1H), 8.65 (s, 1H), 8.49 (s, 1H), 7.55 (m, 1H), 6.95 (m, 3H), 6.70 (s, 1H), 2.35 (s, 3H), 2.22 (s, 3H). ^{19}F NMR (377 MHz, d_3 -acetonitrile) δ -77, -107, -131.

25

Example 39

4-((2,4-difluorophenyl)(5-fluoropyridin-2-yl)(hydroxy)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



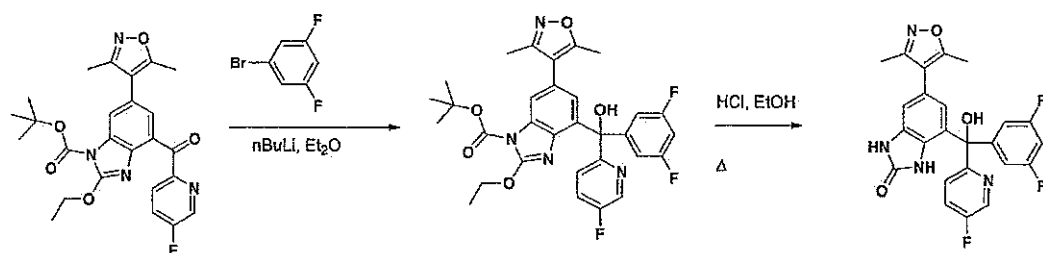
- 5 [00210] In a synthetic process following that described for Example 40, reaction of tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(5-fluoropicolinoyl)-1H-indole-1-carboxylate (50 mg, 0.13 mmol) with the organolithium species resulting from metal-halogen exchange with 1-bromo-2,4-difluorobenzene in diethyl ether gave, after silica gel chromatography, 4-((2,4-difluorophenyl)(5-fluoropyridin-2-yl)(hydroxy)methyl)-6-(3,5-
- 10 dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one as a white solid.

[00211] $C_{24}H_{17}F_3N_4O_3$, 467.1 (M+H). ^1H NMR (400 MHz, d_3 -acetonitrile) δ 8.68 (s, 1H), 8.49 (s, 1H), 7.56 (m, 1H), 7.45 (m, 1H), 7.12 (m, 1H), 6.99-6.89 (m, 3H), 6.50 (s, 1H), 5.56 (s, 1H), 2.29 (s, 3H), 2.12 (s, 3H). ^{19}F NMR (377 MHz, d_3 -acetonitrile) δ -105, -111, -132.

15

Example 40

4-((3,5-difluorophenyl)(5-fluoropyridin-2-yl)(hydroxy)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

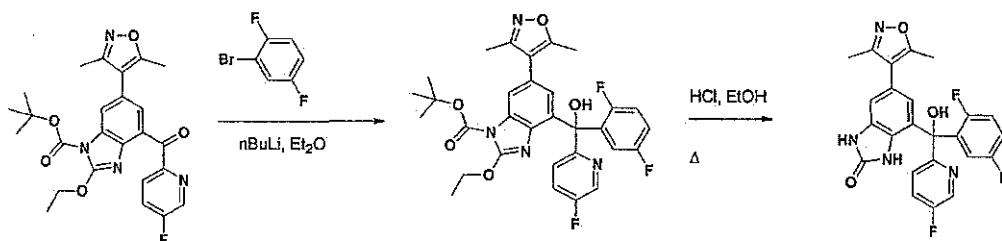


[00212] In a synthetic process following that described for Example 40, reaction of tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(5-fluoropicolinoyl)-1H-indole-1-carboxylate (50 mg, 0.13 mmol) with the organolithium species resulting from metal halogen exchange of 1-bromo-3,5-difluorobenzene in diethyl ether gave, after purification of final material by reverse-phase HPLC (40-50% acetonitrile/water with 0.01% trifluoroacetic acid, Gemini C18 5 μ) the trifluoroacetate salt of 4-((3,5-difluorophenyl)(5-fluoropyridin-2-yl)(hydroxy)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one as a white solid.

[00213] C₂₄H₁₇F₃N₄O₃. 467.1 (M+H). ¹H NMR (400 MHz, *d*₆-DMSO) δ 10.73 (s, 1H), 9.76 (s, 1H), 8.52 (m, 1H), 7.77 (m, 1H), 7.09 (m, 1H), 6.92 (s, 1H), 6.33 (s, 1H), 2.25 (s, 3H), 2.07 (s, 3H). ¹⁹F NMR (377 MHz, *d*₆-DMSO) δ -75, -111, -130.

Example 41

4-((2,5-difluorophenyl)(5-fluoropyridin-2-yl)(hydroxy)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



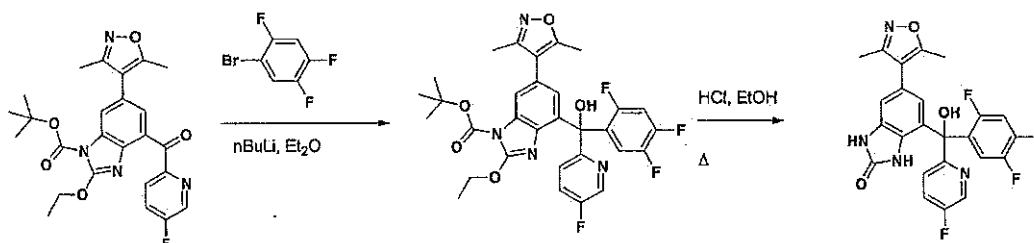
[00214] In a synthetic process following that described for Example 40, reaction of tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(5-fluoropicolinoyl)-1H-indole-1-carboxylate (50 mg, 0.13 mmol) with the organolithium species resulting from metal halogen exchange of 1-bromo-2,5-difluorobenzene in diethyl ether gave after purification of final material by reverse-phase HPLC (40-50% acetonitrile/water with 0.01% trifluoroacetic acid, Gemini C18 5 μ) the trifluoroacetate salt of 4-((2,5-difluorophenyl)(5-fluoropyridin-2-yl)(hydroxy)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one as a white solid.

[00215] $C_{24}H_{17}F_3N_4O_3$. 466.9 (M+H). ^1H NMR (400 MHz, d_6 -DMSO) δ 10.74 (s, 1H), 9.87 (s, 1H), 8.48 (m, 1H), 7.75 (m, 1H), 7.64 (m, 1H), 7.30 (s, 1H), 7.21-7.07 (m, 3H), 6.86 (s, 1H), 6.38 (s, 1H), 2.26 (s, 3H), 2.07 (s, 3H). ^{19}F NMR (377 MHz, d_6 -DMSO) δ -76, -114, -120, -130.

5

Example 42

6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(hydroxy)(2,4,5-trifluorophenyl)methyl)-1H-benzo[d]imidazol-2(3H)-one



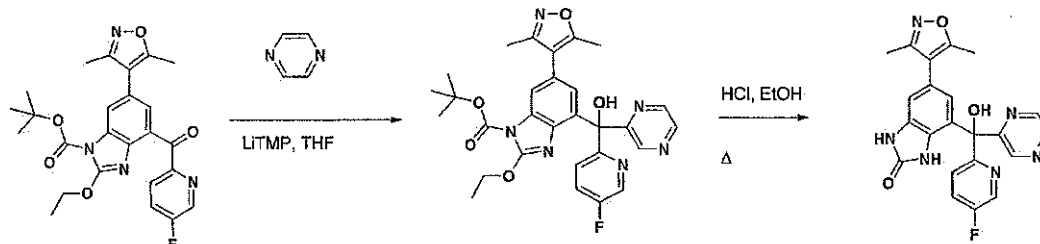
10 [00216] In a synthetic process following that described for Example 40, reaction of tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(5-fluoropicolinoyl)-1H-indole-1-carboxylate (50 mg, 0.13 mmol) with the organolithium species resulting from metal halogen exchange of 1-bromo-2,4,5-trifluorobenzene in diethyl ether gave, after purification of final material by reverse-phase HPLC (40-50% acetonitrile/water with 0.01% trifluoroacetic acid, 15 Gemini C18 5 μ), the trifluoroacetate salt of 6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(hydroxy)(2,4,5-trifluorophenyl)methyl)-1H-benzo[d]imidazol-2(3H)-one as a white solid.

[00217] $C_{24}H_{16}F_4N_4O_3$. 485.12 (M+H). ^1H NMR (400 MHz, d_3 -acetonitrile), 8.69 (s, 1H), 8.49 (s, 1H), 7.59 (m, 1H), 7.13 (m, 1H), 6.98 (s, 1H), 6.52 (m, 1H), 2.29 (s, 3H), 2.13 (s, 3H). ^{19}F NMR (377 MHz, d_3 -acetonitrile) δ -77, -110, -137, -135, -145.

20

Example 43

6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(hydroxy)(pyrazin-2-yl)methyl)-
1H-benzo[d]imidazol-2(3H)-one

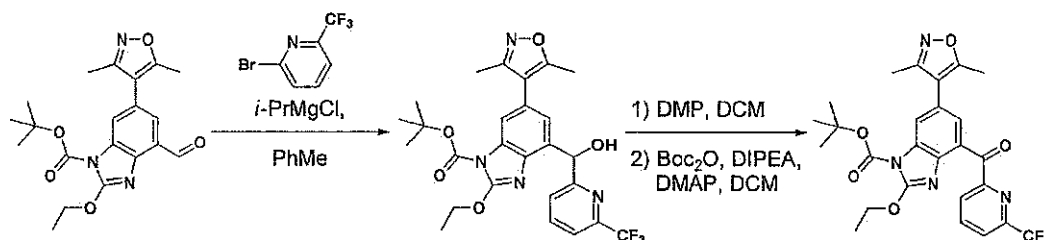


- 5 [00218] In a synthetic process following that described for Example 40, reaction of tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(5-fluoropicolinoyl)-1H-indole-1-carboxylate (50 mg, 0.13 mmol) with the organolithium species resulting from deprotonation of pyrazine by LiTMP in THF (using the literature method described in *J. Org. Chem.* **1995**, *60*, 3781-3786.) Following final deprotection, the combined organics were
- 10 washed with water (30 mL) and brine (30 mL), and dried over Na₂SO₄. Purification by flash chromatography (0-100% hexanes/ethyl acetate) gave 6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(hydroxy)(pyrazin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one as a white solid.

- [00219] C₂₂H₁₇FN₆O₃. 433.1 (M+H). ¹H NMR (400 MHz, d₃-acetonitrile), 8.88 (s, 1H), 8.56-8.44 (m, 3H), 7.72 (m, 1H), 7.61 (m, 1H), 6.97 (s, 1H), 6.57 (m, 1H), 2.29 (s, 3H), 2.13 (s, 3H). ¹⁹F NMR (377 MHz, d₃-acetonitrile) δ -130.
- 15

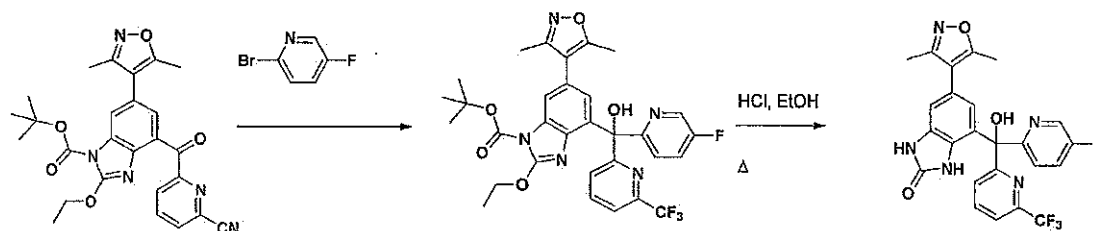
Example 44

- 20 6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(hydroxy)(6-(trifluoromethyl)pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one

Step 1:

- [00220] To isopropylmagnesium chloride (0.63 mL, 1.26 mmol, 2 M in THF) in toluene (1.4 mL) was added 2-bromo-5-trifluoromethyl pyridine (300 mg, 1.6 mmol) in toluene (4 mL). After 3.5 hours, the Grignard solution (1.9 mL, 0.8 mmol) was added to *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-formyl-1H-indole-1-carboxylate (100 mg, 0.26 mmol) in toluene (9 mL) at 0°C and the mixture was allowed to warm to 20°C. After 16 hours, the reaction was quenched with saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL), extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The resulting unpurified product, 100 mg, was treated to oxidation in 10mL DCM with Dess-Martin periodinane reagent (154.1 mg, 0.34 mmol). After 15 minutes, the reaction was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3_{(\text{aq})}$ (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organics were washed with water (30 mL) and brine (30 mL), and dried over Na_2SO_4 . Purification by flash chromatography (0-50% ethyl acetate/hexane) afforded *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(6-(trifluoromethyl)picolinoyl)-1H-benzo[d]imidazole-1-carboxylate (30 mg, 23%) as an amber residue contaminated with unreacted aldehyde.

[00221] $\text{C}_{26}\text{H}_{25}\text{F}_3\text{N}_4\text{O}_5$: 531.0 (M+H).

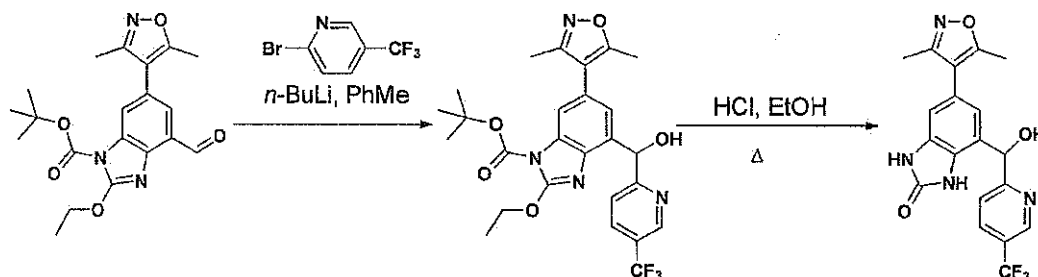
Step 2:

- [00222] To isopropylmagnesium chloride (1.32 mL, 2.64 mmol, 2 M in THF) in
 5 toluene (4mL) was added 2-bromo-5-fluoropyridine (388 mg, 2.05 mmol) in toluene (1 mL).
 After 3.5 hours the Grignard solution (1 mL, 0.65 mmol) was added to tert-butyl 6-(3,5-
 dimethylisoxazol-4-yl)-2 ethoxycarbonyl-1H-benzo[d]imidazole-1-carboxylate (30 mg, 0.13
 mmol) in toluene (6 mL) at 0°C and the mixture was allowed to warm to 20°C. After 16
 hours, the reaction was quenched with saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL), extracted with ethyl
 10 acetate (3 x 10 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. The resulting residue
 (100 mg) was dissolved in ethanol (3 mL) to which was added hydrochloric acid (0.2 mL, 0.8
 mmol, 4 M in 1,4-dioxane). The mixture was heated to 70°C for 0.75 hours and then
 concentrated *in vacuo*. Purification by reverse-phase HPLC (25-50% acetonitrile/water with
 0.01% trifluoroacetic acid, Gemini C18 5 μ) afforded the TFA salt of 6-(3,5-
 15 dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(hydroxy))(6-(trifluoromethyl)pyridin-2-
 yl)methyl)-1H-benzo[d]imidazol-2(3H)-one as a light yellow solid.

- [00223] $\text{C}_{24}\text{H}_{17}\text{F}_4\text{N}_5\text{O}_3$. 500.12 (M+H). ^1H NMR (400 MHz, d_3 -acetonitrile) δ 8.82 (s, 1H), 8.76 (s, 1H), 8.45 (d, $J = 2.7$ Hz, 1H), 8.05 (m, 1H), 7.86 (m, 1H), 7.75 (m, 2H), 7.62 (m, 1H), 6.93 (s, 1H), 6.58 (s, 1H), 6.93 (s, 1H), 6.25 (s, 1H), 2.31 (s, 3H), 2.16 (s, 3H). ^{19}F
 20 NMR (377 MHz, d_3 -acetonitrile) δ -68, -76, -131.

Example 45

tert-Butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(hydroxy(5-(trifluoromethyl)pyridin-2-yl)methyl)-1H-benzo[d]imidazole-1-carboxylate



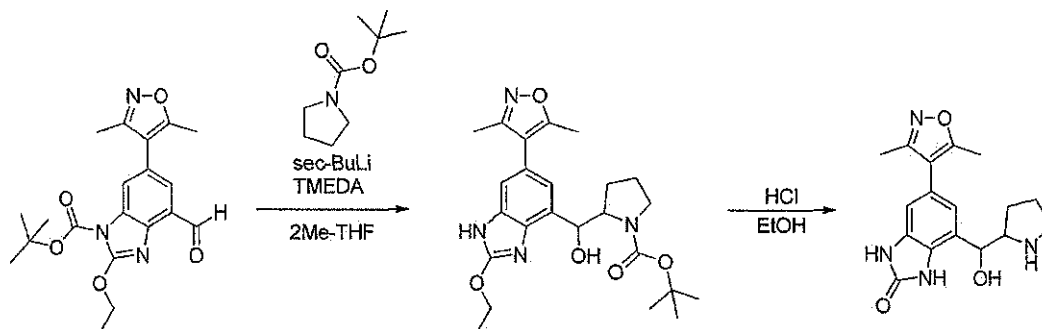
5 [00224] To 2-bromo-5-trifluoromethyl pyridine (200 mg, 0.89 mmol) in THF (4 mL) at -78°C was added *n*-butyllithium (0.36 mL, 0.9 mmol, 2.5M in hexanes). After 15 minutes, *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-formyl-1H-indole-1-carboxylate (60 mg, 0.16 mmol) in THF (1 mL) was added drop-wise to the reaction. After 60 minutes, the reaction was warmed, quenched with water (10 mL), extracted with ethyl acetate (3 x 10 mL), dried over Na₂SO₄, and concentrated *in vacuo*. Purification of the resulting residue by flash column (0-50% ethyl acetate/hexanes) afforded 30 mg *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(hydroxy(5-(trifluoromethyl)pyridin-2-yl)methyl)-1H-benzo[d]imidazole-1-carboxylate that was submitted to directly to final deprotection.

15 [00225] 30 mg (0.056 mmol) *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(hydroxy(5-(trifluoromethyl)pyridin-2-yl)methyl)-1H-benzo[d]imidazole-1-carboxylate was dissolved in 3 mL ethanol, and hydrochloric acid (0.1 mL, 0.4 mmol, 4 M in 1,4-dioxane) was added. The mixture was heated to 70°C for 0.5 hours and then concentrated *in vacuo*. Purification by reverse-phase HPLC (25-50% acetonitrile/water with 0.01% trifluoroacetic acid, Gemini C18 5μ) afforded the TFA salt of 6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(5-(trifluoromethyl)pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one as a light yellow solid.

20 [00226] C₁₉H₁₅F₃N₄O₃. 405.1 (M+H). ¹H NMR (400 MHz, d₃-acetonitrile) δ 8.91 (s, 1H), 8.76 (s, 1H), 8.3 (s, 1H), 7.98 (d, *J* = 8.1, 1H), 7.70 (d, *J* = 8.1, 1H), 6.71 (m, 2H), 5.98 (s, 1H), 2.24 (s, 3H), 2.08 (s, 3H). ¹⁹F NMR (376 MHz, d₃-acetonitrile) δ -63.45, -74.7.

Example 46

6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(pyrrolidin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one

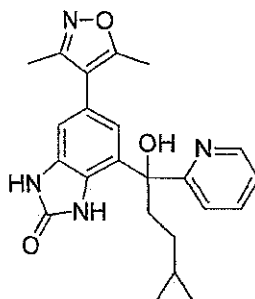


- 5 [00227] N-Boc-pyrrolidine (150mg, 0.39 mmol) and TMEDA (0.2 mL, 158 mg, 1.36 mmol) was dissolved in dry MeTHF (2.6 mL) under Ar and cooled to -78 °C. Sec-BuLi (1.4M, 0.97 mL, 1.36 mmol) was added dropwise and the reaction was allowed to stir at -78 °C for 40 mins. tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-formyl-1H-benzo[d]imidazole-1-carboxylate (150 mg, 0.39 mmol) was dissolved in MeTHF (0.5 mL) and added dropwise via syringe to the reaction and allowed to stir at -78 °C for 10 minutes. The reaction was quenched with water and extracted three times with EtOAc, combined organic layers were washed once with brine, concentrated, and purified by reverse-phase HPLC to give tert-butyl 2-((6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(hydroxy)methyl)pyrrolidine-1-carboxylate (53 mg, 30%) as a white powder. The solid (50 mg, 0.11 mmol) was dissolved in EtOH (5 mL) and HCl (1 mL) and heated for 12 hours at 65 °C. The reaction was cooled and concentrated to afford the desired product as a white powder.

- [00228] $C_{17}H_{20}N_4O_3$ 329.3 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.93 (s, 2H), 10.83 (d, J = 11.8 Hz, 2H), 9.07 (s, 2H), 8.47 (s, 1H), 7.03 (d, J = 1.5 Hz, 1H), 6.99 (s, 1H), 6.86 (s, 1H), 6.84 (d, J = 1.6 Hz, 1H), 6.38 (d, J = 4.0 Hz, 1H), 6.10 (d, J = 4.2 Hz, 1H), 5.28 (s, 1H), 4.98 (s, 1H), 3.70 (d, J = 7.6 Hz, 1H), 3.25 – 3.07 (m, 4H), 2.39 (s, 3H), 2.38 (s, 2H), 2.21 (s, 3H), 2.20 (s, 2H), 1.96 (q, J = 7.4 Hz, 3H), 1.86 (s, 2H), 1.77 (s, 2H), 1.67 (s, 1H). (1:1.4 mixture of diastereomers)

Example 47

4-(3-cyclopropyl-1-hydroxy-1-(pyridin-2-yl)propyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



5 [00229] Magnesium metal (39.0 mg, 2.0 mmol) and iodine (one crystal) was taken up in dry diethyl ether (1.2 mL) and (2-bromoethyl)cyclopropane (200 mg, 1.3 mmol) was added dropwise until iodine color faded. The remainder was then added dropwise over 15 minutes to maintain a gentle reflux and then cooled to 0 °C. (2-cyclopropylethyl)magnesium bromide (1.1 M, 0.38 mL, 0.41 mmol) was added to a cooled (0 °C) solution of (6-(3,5-

10 dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanone (50 mg, 0.14 mmol) in dry THF (1.0 mL) under argon and allowed to stir for 10 minutes. The reaction was quenched with water, extracted three times with EtOAc, and combined organic layers were concentrated and purified by reverse-phase HPLC to give 3-cyclopropyl-1-(6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)-1-(pyridin-2-yl)propan-1-ol

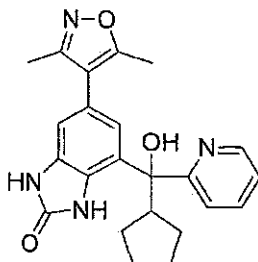
15 intermediate. The intermediate was taken up in EtOH (1.5 mL) and 0.2mL concentrated HCl and heated to 65 °C for 2 hours and concentrated to afford the desired product as a white powder.

[00230] $C_{23}H_{24}N_4O_3$ 405.2 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 8.73 (ddd, J = 5.8, 1.6, 0.7 Hz, 1H), 8.43 (td, J = 8.0, 1.6 Hz, 1H), 8.09 (dt, J = 8.2, 1.0 Hz, 1H), 7.87 (ddd, J = 7.4, 5.7, 1.2 Hz, 1H), 7.13 (d, J = 1.5 Hz, 1H), 6.96 (d, J = 1.4 Hz, 1H), 2.68 (ddd, J = 10.6, 8.6, 5.1 Hz, 2H), 2.40 (s, 3H), 2.23 (s, 3H), 1.37 (ddd, J = 11.8, 7.2, 4.7 Hz, 1H), 1.26 – 1.13 (m, 1H), 0.76 – 0.66 (m, 1H), 0.43 (ddt, J = 8.7, 5.4, 2.4 Hz, 2H), 0.06 – -0.05 (m, 2H).

20

Example 48

6-(3,5-dimethylisoxazol-4-yl)-4-(2-ethyl-1-hydroxy-1-(pyridin-2-yl)butyl)-1H-benzo[d]imidazol-2(3H)-one



5

[00231] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanone (50 mg, 0.14 mmol) was dissolved in dry THF (1.4 mL) and cooled to 0 °C. Pentan-3-ylmagnesium bromide (2.0 M, 0.21 mL, 0.41 mmol) was added dropwise and the reaction was allowed to stir for 10 mins and then quenched with water. Reaction was

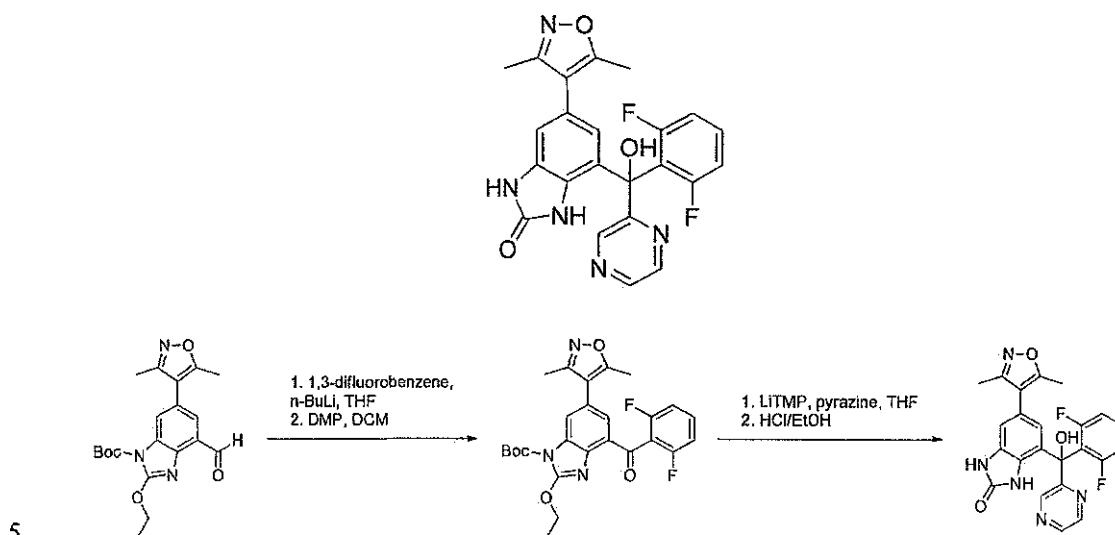
10 extracted three times with EtOAc and combined organic layers were washed once with water, concentrated, and purified by reverse-phase HPLC to give 1-(6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)-2-ethyl-1-(pyridin-2-yl)butan-1-ol intermediate. The intermediate was taken up in EtOH (1.5 mL) and 0.2mL concentrated HCl and heated to 65 °C for 2 hours and concentrated to afford the desired product as a white powder.

15 [00232] $C_{23}H_{26}N_4O_3$ 407.3 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 8.78 (d, J = 5.6 Hz, 1H), 8.54 (t, J = 7.6 Hz, 1H), 8.23 (d, J = 7.8 Hz, 1H), 7.98 (t, J = 6.4 Hz, 1H), 7.21 (d, J = 1.2 Hz, 1H), 6.97 (d, J = 1.1 Hz, 1H), 2.71 (s, 1H), 2.41 (s, 3H), 2.25 (s, 3H), 1.88 – 1.76 (m, 1H), 1.59 – 1.29 (m, 3H), 1.09 (t, J = 7.4 Hz, 3H), 0.85 (t, J = 7.5 Hz, 3H).

20

Example 49

4-((2,6-difluorophenyl)(hydroxy)(pyrazin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



[00233] n-BuLi (0.58 mL, 0.93 mmol) was added dropwise to a solution of 1,3-difluorobenzene (0.102 mL, 0.1 mmol) in THF (5 mL) cooled to -78 °C and allowed to stir for 1 hour. tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-formyl-1H-benzo[d]imidazole-1-carboxylate (200 mg, 0.52 mmol) in THF was added and the reaction was allowed to stir for 5 mins at -78 °C, quenched with ammonium chloride, extracted with EtOAc and concentrated. The crude was then taken up in DCM (2 mL), Des-Martin periodinane (290 mg, 0.78 mmol) was added and the reaction was allowed to stir for 15 mins. The reaction was quenched with sat. Na₂S₂O₃, extracted with EtOAc, concentrated and purified by silica gel chromatography to give tert-butyl 4-(2,6-difluorobenzoyl)-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate.

[00234] n-BuLi (0.21 mL, 0.33 mmol) was added dropwise to a solution of 2,2,6,6-tetramethylpiperidine (0.06 mL, 0.33 mmol) in THF (0.7 mL) at 0 °C and was allowed to stir for 5 minutes. Pyrazine (24 mg, 0.3 mmol) in THF (0.4 mL) was added and the reaction was stirred for an additional 5 minutes and then cooled to -78 °C. tert-butyl 4-(2,6-difluorobenzoyl)-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate (50 mg, 0.10 mmol) in THF (0.4 mL) was added, the solution was allowed to stir

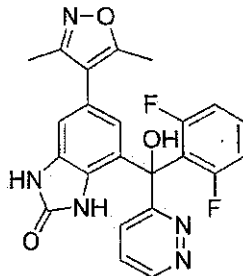
for 5 minutes and then quenched with water. Solution was extracted three times with EtOAc, washed once with brine and concentrated. Crude was purified by reverse-phase HPLC and then taken up in EtOH (3 mL) and HCl (0.1 mL) and heated to 65 °C for 2 hours. Reaction was cooled and concentrated to afford desired product as a pale brown powder.

5. [00235] $C_{25}H_{21}F_2N_5O_3$ 478.5 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 9.02 (s, 1H), 8.57 (d, J = 26.1 Hz, 2H), 7.44 (tt, J = 8.3, 5.9 Hz, 1H), 7.02 – 6.89 (m, 4H), 2.33 (s, 3H), 2.16 (s, 3H).

Example 50

- 10 4-((2,6-difluorophenyl)(hydroxy)(pyridazin-3-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

[00236] The following compound was made in a similar fashion as that of Example 49, but using pyridazine instead of pyrazine.



- 15 [00237] $C_{25}H_{21}F_2N_5O_3$ 478.5 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 9.48 (s, 1H), 8.88 – 8.81 (m, 1H), 8.42 (dd, J = 8.7, 5.0 Hz, 1H), 7.54 (tt, J = 8.4, 6.1 Hz, 1H), 7.05 (dd, J = 10.6, 8.6 Hz, 2H), 6.98 (d, J = 1.5 Hz, 1H), 6.91 – 6.87 (m, 1H), 2.32 (s, 3H), 2.15 (s, 3H).

Example 51,

Example 52, and

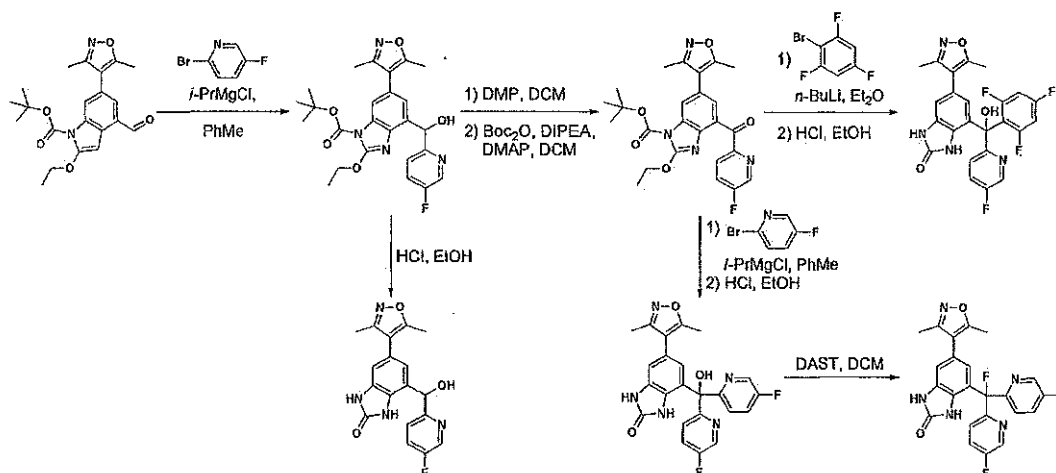
Example 53

6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(hydroxy)methyl)-1H-benzo[d]imidazol-2(3H)-one;

6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(hydroxy)(2,4,6-trifluorophenyl)methyl)-1H-benzo[d]imidazol-2(3H)-one;

and

6-(3,5-dimethylisoxazol-4-yl)-4-(fluorobis(5-fluoropyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one



[00238] To isopropylmagnesium chloride (0.63 mL, 1.26 mmol, 2 M in tetrahydrofuran) in toluene (1.4 mL) was added 2-bromo-5-fluoropyridine (184.6 mg, 1.05 mmol) in toluene (0.48 mL). After 3.5 hours, the Grignard solution (1.9 mL, 0.65 mmol) was added to *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-formyl-1H-indole-1-carboxylate (62.2 mg, 0.16 mmol) in tetrahydrofuran (9 mL) at 0°C and the mixture was allowed to warm to 20°C. After 16 hours, the reaction was quenched with saturated NH₄Cl(aq) (10 mL), extracted with ethyl acetate (3 x 10 mL), dried over Na₂SO₄, and concentrated in vacuo. Purification by flash chromatography (0-50% ethyl acetate/hexane) afforded *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-((5-fluoropyridin-2-yl)(hydroxy)methyl)-1H-benzo[d]imidazole-1-carboxylate as a yellow residue.

[00239] To *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-((5-fluoropyridin-2-yl)(hydroxy)methyl)-1H-benzo[d]imidazole-1-carboxylate (41.2 mg, 0.09 mmol) in ethanol (5 mL) was added hydrochloric acid (0.66 mL, 2.64 mmol, 4 M in 1,4-dioxane). The mixture was heated to 60°C for 6 hours and then concentrated *in vacuo*. Purification by reverse-phase HPLC (25-50% acetonitrile/water with 0.01% trifluoroacetic acid, Gemini C18 5 μ) afforded 6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(hydroxy)methyl)-1H-benzo[d]imidazol-2(3H)-one as a white solid.

[00240] $C_{18}H_{15}FN_4O_3$. 335.03 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.73 (s, 1H), 10.70 (s, 1H), 8.45 (d, J = 2.9 Hz, 1H), 7.80 (dd, J = 8.7, 4.7 Hz, 1H), 7.73 (td, J = 8.8, 2.9 Hz, 1H), 6.81 (d, J = 1.6 Hz, 1H), 6.74 (d, J = 1.5 Hz, 1H), 6.03 (s, 1H), 2.31 (s, 3H), 2.12 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -76.42, -131.97.

[00241] To *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-((5-fluoropyridin-2-yl)(hydroxy)methyl)-1H-benzo[d]imidazole-1-carboxylate (57 mg, 0.12 mmol) in dichloromethane (6 mL) was added Dess-Martin periodinane (154.1 mg, 0.34 mmol). After 15 minutes, the reaction was quenched with saturated Na₂S₂O₃(aq) (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organics were washed with water (30 mL) and brine (30 mL), and dried over Na₂SO₄. To the crude solution was added N,N-diisopropylethylamine (0.05 mL, 0.26 mmol), 4-(dimethylamino)pyridine (6.8 mg, 0.05 mmol), and di-*tert*-butyl dicarbonate (120.9 mg). After 90 minutes, the reaction mixture was washed with water (2 x 30 mL), dried over Na₂SO₄, and concentrated *in vacuo*. Purification by flash chromatography (0-50% ethyl acetate/hexane) afforded *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(5-fluoropicolinoyl)-1H-benzo[d]imidazole-1-carboxylate as an amber residue.

[00242] To 1-bromo-2,4,6-trifluorobenzene (0.02 mL, 0.16 mmol) in diethyl ether (0.52 mL) at -78°C was added *n*-butyllithium (0.12 mL, 0.18 mmol, 1.6 M in hexanes). After 30 minutes, *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(5-fluoropicolinoyl)-1H-benzo[d]imidazole-1-carboxylate (50 mg, 0.10 mmol) in diethyl ether (1 mL) was added drop-wise to the reaction. After 60 minutes, the reaction was warmed, quenched with saturated NH₄Cl(aq) (10 mL), extracted with ethyl acetate (3 x 10 mL), dried over Na₂SO₄, and concentrated *in vacuo*. To the crude residue in ethanol (3.5 mL) was added hydrochloric acid (0.35 mL, 1.4 mmol, 4 M in 1,4-dioxane) and the mixture was heated to 70°C in a microwave reactor for 45 minutes. Purification by reverse-phase HPLC (40-50%

acetonitrile/water with 0.01% trifluoroacetic acid, Gemini C18 5 μ) afforded 6-(3,5-dimethylisoxazol-4-yl)-4-((5-fluoropyridin-2-yl)(hydroxy)(2,4,6-trifluorophenyl)methyl)-1H-benzo[d]imidazol-2(3H)-one as a white solid.

[00243] $C_{24}H_{16}F_4N_4O_3$, 485.12 (M+1). ^1H NMR (400 MHz, chloroform-*d*) δ 9.40 (s, 1H), 9.18 (s, 1H), 8.48 (d, *J* = 2.7 Hz, 1H), 7.40 (td, *J* = 8.3, 2.8 Hz, 1H), 7.15 (dd, *J* = 8.8, 4.2 Hz, 1H), 6.99 (s, 1H), 6.68 – 6.56 (m, 3H), 2.31 (s, 3H), 2.16 (s, 3H). ^{19}F NMR (377 MHz, chloroform-*d*) δ -76.51, -102.54 – -103.06 (m), -106.62 (p, *J* = 7.9 Hz), -127.18 (dd, *J* = 7.3, 3.8 Hz).

[00244] To isopropylmagnesium chloride (0.34 mL, 0.57 mmol, 2 M in tetrahydrofuran) in toluene (0.26 mL) was added 2-bromo-5-fluoropyridine (100 mg, 0.57 mmol) in toluene (0.78 mL). After 4 hours, the Grignard solution (1.2 mL, 0.47 mmol) was added to tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-((5-fluoropyridin-2-yl)(hydroxy)methyl)-1H-benzo[d]imidazole-1-carboxylate (57 mg, 0.12 mmol) in tetrahydrofuran (6 mL) at 0°C. After 60 minutes, the reaction was quenched with saturated $NH_4Cl_{(aq)}$ (10 mL), extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. To the crude dissolved in ethanol (2.5 mL) was added hydrochloric acid (0.29 mL, 1.17 mmol, 4 M in 1,4-dioxane) and the mixture was heated to 70°C in a microwave reactor for 45 minutes. Purification by reverse-phase HPLC (30-45% acetonitrile/water with 0.01% trifluoroacetic acid, Gemini C18 5 μ) afforded 4-(bis(5-fluoropyridin-2-yl)(hydroxy)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one as a white solid.

[00245] $C_{23}H_{17}F_2N_5O_3$, 450.11 (M+1). ^1H NMR (400 MHz, DMSO-*d*₆) δ 10.72 (s, 1H), 9.75 (s, 1H), 8.52 – 8.48 (m, 2H), 7.74 (td, *J* = 8.8, 2.9 Hz, 2H), 7.63 (dd, *J* = 8.9, 4.7 Hz, 2H), 6.84 (d, *J* = 1.2 Hz, 1H), 6.45 (d, *J* = 1.3 Hz, 1H), 2.27 (s, 3H), 2.08 (s, 3H). ^{19}F NMR (376 MHz, DMSO-*d*₆) δ -75.01, -130.07 (dd, *J* = 8.8, 4.4 Hz).

[00246] To 4-(bis(5-fluoropyridin-2-yl)(hydroxy)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one (10.4 mg, 0.02 mmol) in dichloromethane (2.3 mL) added (diethylamino)sulfur trifluoride (9.15 μ L, 0.07 mmol) and stirred for 60 minutes before adding more (diethylamino)sulfur trifluoride (0.01 mL, 0.07 mmol). After 60 minutes from the second addition, the reaction was poured into saturated $NaHCO_{3(aq)}$ (5 mL), the layers were separated, and the aqueous was extracted with dichloromethane (2 x 5 mL). The combined

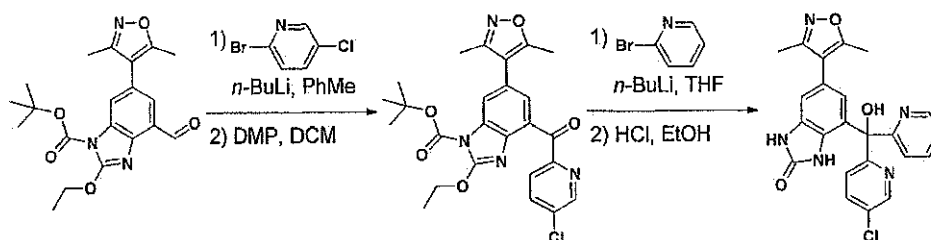
organics were dried over Na₂SO₄ and concentrated *in vacuo*. Purification by reverse-phase HPLC (25-75% acetonitrile/water with 0.01% trifluoroacetic acid, Gemini C18 5μ) afforded 6-(3,5-dimethylisoxazol-4-yl)-4-(fluorobis(5-fluoropyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one as an off-white solid.

- 5 [00247] C₂₃H₁₆F₃N₅O₂. 452.05 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.85 (s, 1H), 10.35 (s, 1H), 8.55 (d, *J* = 2.9 Hz, 2H), 7.82 (td, *J* = 8.6, 2.9 Hz, 2H), 7.64 (dd, *J* = 8.8, 4.4 Hz, 2H), 6.92 (s, 1H), 6.40 (s, 1H), 2.27 (s, 3H), 2.07 (s, 3H). ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -74.14, -127.97 (dt, *J* = 8.3, 4.0 Hz), -136.81.

10

Example 54

4-((5-chloropyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



- [00248] To 2-bromo-5-chloropyridine (55.42 mg, 0.29 mmol) in toluene (1 mL) at -
 15 78°C was added *n*-butyllithium (0.41 mL, 0.65 mmol, 1.6 M in tetrahydrofuran). After 60 minutes, *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-formyl-1H-indole-1-carboxylate (100 mg, 0.26 mmol) in toluene (0.3 mL) was added drop-wise to the reaction. After 60 minutes, the reaction was warmed, quenched with saturated NH₄Cl_(aq) (10 mL), extracted with ethyl acetate (3 x 10 mL), dried over Na₂SO₄, and concentrated *in vacuo*. The crude
 20 material was dissolved in dichloromethane (6 mL) and Dess-Martin periodinane (143.06 mg, 0.34 mmol) was added. After 10 minutes, the reaction was quenched with saturated Na₂S₂O_{3(aq)} (10 mL) and extracted with dichloromethane (3 x 10 mL). The combined organics were washed with water (30 mL) and brine (30 mL), dried over Na₂SO₄, and concentrated *in vacuo*. Purification by flash chromatography (0-50% ethyl acetate/hexanes)
 25 afforded *tert*-butyl 4-(5-chloropicolinoyl)-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate as a yellow residue.

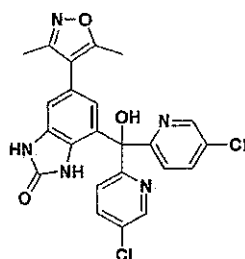
[00249] To 2-bromopyridine (0.02 ml, 0.2 mmol) in tetrahydrofuran (4 mL) at -78°C was added *n*-butyllithium (0.15 mL, 0.24 mmol, 1.6 M in hexanes). After 30 minutes, *tert*-butyl 4-(5-chloropicolinoyl)-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate (33 mg, 0.07 mmol) in tetrahydrofuran (1 mL) was added drop-wise to the reaction. After 30 minutes, the reaction was warmed, quenched with saturated NH₄Cl_(aq) (10 mL), extracted with ethyl acetate (3 x 10 mL), dried over Na₂SO₄, and concentrated *in vacuo*. To the crude residue in ethanol (3 mL) was added hydrochloric acid (0.17 mL, 0.66 mmol, 4 M in 1,4-dioxane) and the mixture was heated to 70°C in a microwave reactor for 45 minutes. Purification by reverse-phase HPLC (23-40% acetonitrile/water with 0.01% trifluoroacetic acid, Gemini C18 5μ) afforded 4-((5-chloropyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one as an off-white solid.

[00250] C₂₃H₁₈ClN₅O₃. 448.22 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.78 (s, 1H), 9.90 (s, 1H), 8.62 – 8.53 (m, 2H), 8.04 – 7.96 (m, 2H), 7.66 (dd, *J* = 8.2, 5.2 Hz, 2H), 7.53 – 7.45 (m, 1H), 6.87 (d, *J* = 1.1 Hz, 1H), 6.44 (d, *J* = 1.6 Hz, 1H), 2.27 (s, 3H), 2.07 (s, 3H).

Example 55

4-(bis(5-chloropyridin-2-yl)(hydroxy)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

[00251] The following analog was prepared in the same fashion as 4-((5-chloropyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one by substituting 2-bromo-5-chloropyridine for 2-bromopyridine.



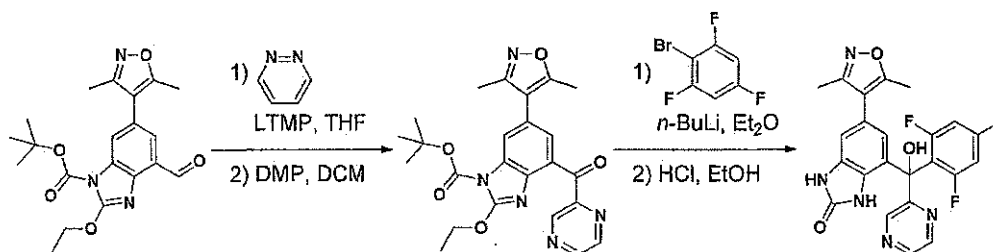
4-(bis(5-chloropyridin-2-yl)(hydroxy)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one as an off-white solid.

[00252] $C_{23}H_{17}Cl_2N_5O_3$, 482.29 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.81 (s, 1H), 9.85 (s, 1H), 8.59 – 8.52 (m, 2H), 8.48 (d, J = 3.3 Hz, 1H), 8.01 (dd, J = 8.3, 2.5 Hz, 1H), 7.77 (d, J = 8.6 Hz, 1H), 7.18 (d, J = 5.0 Hz, 1H), 7.06 (s, 1H), 6.88 (d, J = 1.1 Hz, 1H), 6.34 (d, J = 1.5 Hz, 1H), 2.25 (s, 3H), 2.05 (s, 3H).

5

Example 56

6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(pyrazin-2-yl)(2,4,6-trifluorophenyl)methyl)-1H-benzo[d]imidazol-2(3H)-one



10 [00253] To 2,2,6,6-tetramethylpiperidine (0.27 mL, 1.56 mmol) in tetrahydrofuran (16 mL) at -78°C was added *n*-butyllithium (0.97 mL, 1.56 mmol, 1.6 M in hexanes). After 5 minutes, the reaction was warmed to 0°C . After stirring for 30 minutes, the reaction was cooled to -78°C , and pyrazine (137 mg, 1.69 mmol) in tetrahydrofuran (3.3 mL) and *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-formyl-1H-indole-1-carboxylate (498 mg, 1.3

15 mmol) in tetrahydrofuran (2.6 mL) were added simultaneously in a drop-wise manner. After stirring for 60 minutes, the reaction was quenched with saturated $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 mL), extracted with ethyl acetate (3 x 10 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by flash chromatography (0-100% ethyl acetate/hexane) afforded *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(hydroxy(pyrazin-2-yl)methyl)-1H-

20 benzo[d]imidazole-1-carboxylate. To *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(hydroxy(pyrazin-2-yl)methyl)-1H-benzo[d]imidazole-1-carboxylate (50 mg, 0.11 mmol) in dichloromethane (2.5 mL) was added Dess-Martin periodinane (72.4 mg, 0.16 mmol). After 15 minutes, the reaction was quenched with saturated $\text{Na}_2\text{S}_2\text{O}_3_{(\text{aq})}$ (10 mL) and extracted with dichloromethane (3 x 10 mL), dried over Na_2SO_4 , and concentrated *in vacuo*. Purification by

25 flash chromatography (0-100% ethyl acetate/hexanes) afforded *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(pyrazine-2-carbonyl)-1H-benzo[d]imidazole-1-carboxylate as a yellow oil.

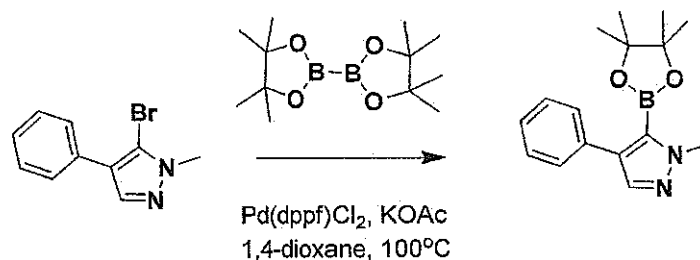
[00254] To 1-bromo-2,4,6-trifluorobenzene (0.01 ml, 0.12 mmol) in diethyl ether (0.5 mL) at -78°C was added *n*-butyllithium (0.13 mL, 0.14 mmol, 1.6 M in hexanes). After 30 *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(pyrazine-2-carbonyl)-1H-benzo[d]imidazole-1-carboxylate (36.6 mg, 0.08 mmol) in diethyl ether (1 mL) was added drop-wise to the reaction. After 90 minutes, the reaction was warmed, quenched with saturated NH₄Cl_(aq) (10 mL), extracted with ethyl acetate (3 x 10 mL), dried over Na₂SO₄, and concentrated *in vacuo*. To the crude residue in ethanol (1.5 mL) was added hydrochloric acid (0.20 mL, 0.79 mmol, 4 M in 1,4-dioxane) and the mixture was heated to 70°C in a microwave reactor for 45 minutes. Purification by reverse-phase HPLC (35-50% acetonitrile/water with 0.01% trifluoroacetic acid, Gemini C18 5μ) afforded 6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(pyrazin-2-yl)(2,4,6-trifluorophenyl)methyl)-1H-benzo[d]imidazol-2(3H)-one as a pale yellow solid.

[00255] C₂₃H₁₆F₃N₅O₃. 468.09 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.74 (s, 1H), 9.89 (s, 1H), 9.12 (d, *J* = 1.2 Hz, 1H), 8.60 – 8.49 (m, 2H), 7.39 (s, 1H), 7.10 (t, *J* = 9.7 Hz, 2H), 6.83 – 6.77 (m, 1H), 6.63 (d, *J* = 1.3 Hz, 1H), 2.28 (s, 3H), 2.09 (s, 3H). ¹⁹F NMR (377 MHz, DMSO-*d*₆) δ -74.73, -100.62 (t, *J* = 9.1 Hz), -108.90 (p, *J* = 8.8 Hz).

Example 57

6-(3,5-dimethylisoxazol-4-yl)-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-1H-benzo[d]imidazol-2(3H)-one

Step 1: 1-Methyl-4-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole

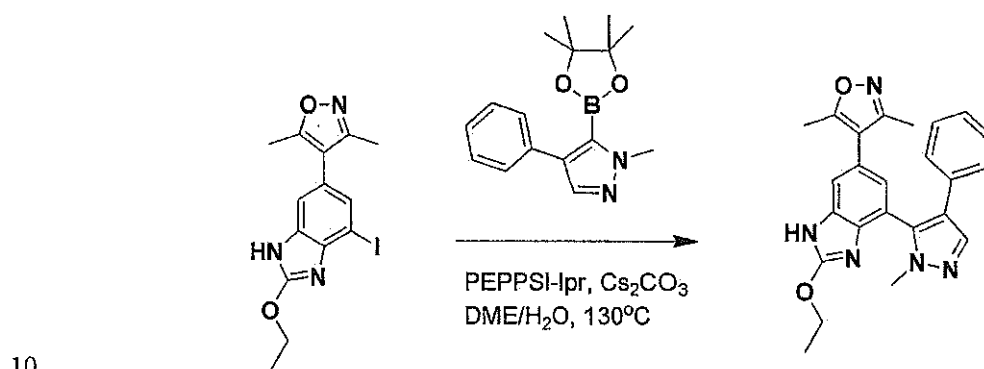


[00256] 5-bromo-1-methyl-4-phenyl-1H-pyrazole (87 mg, 0.37 mmol) and 3,5-Dimethylisoxazole-4-boronic acid pinacol ester (373 mg, 1.47 mmol) was added to a 1,4-dioxane (2 ml). To the above mixture were added Pd(dppf)Cl₂ (27 mg, 0.037 mmol) and

potassium acetate (181 mg, 1.85 mmol). The reaction mixture was heated at 100°C for 2h. The reaction mixture was then diluted with EtOAc (100 ml), washed with brine (50mlX2). The organic solvent was evaporated and the residue was dissolved in DCM and purified with combi-flash column chromatography (product came out at 45% EtOAc/Hexane) to afford 141mg product 1-methyl-4-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole.

[00257] C₁₆H₂₁BN₂O₂. 285.3 (M+1).

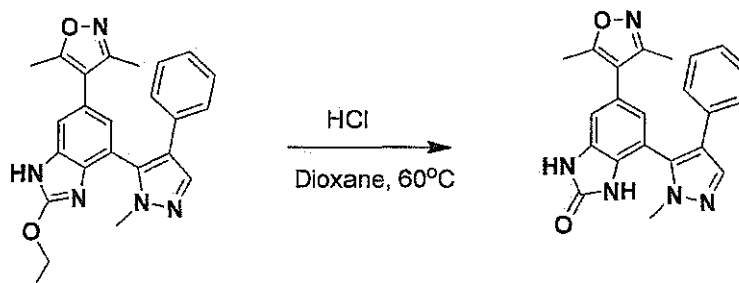
Step 2: Preparation of 4-(2-ethoxy-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole



[00258] 4-(2-ethoxy-4-iodo-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole (100 mg, 0.26 mmol) and 1-methyl-4-phenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (37 mg, 0.13 mmol) was added to a solvent mixture of 1,2-dimethoxyethane (2 ml) and water (1 ml). To the above mixture were added PEPPSI-Ipr (18 mg, 0.026 mmol) and CsCO₃ (127 mg, 0.39 mmol). The reaction mixture was heated at 130°C in microwave reactor for 30mins. The reaction mixture was then filtered and organic solvent was evaporated and the residue was purified with Prep HPLC (0-100% CH₃CN/H₂O) to afford 8 mg product 4-(2-ethoxy-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole.

20 [00259] C₂₄H₂₃N₅O₂. 414.5 (M+1).

Step 3:

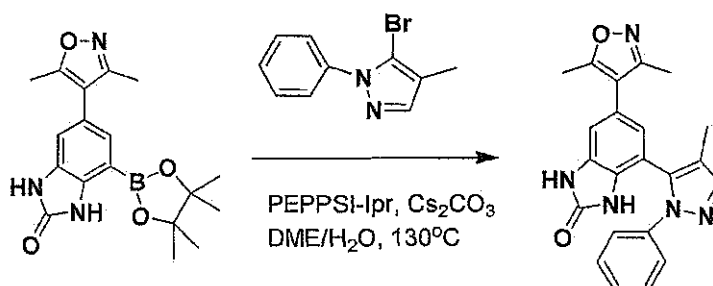


[00260] 4-(2-ethoxy-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-1H-benzo[d]imidazol-6-yl)-3,5-dimethylisoxazole (8mg, 0.019 mmol) was dissolved in dioxane (0.5 ml), to the solution was added concentrated HCl (0.1 ml), heated at 60oC for 2h. Solvent was evaporated and the residue was purified with Prep HPLC (0-100% CH₃CN/H₂O) to afford 2 mg product 6-(3,5-dimethylisoxazol-4-yl)-4-(1-methyl-4-phenyl-1H-pyrazol-5-yl)-1H-benzo[d]imidazol-2(3H)-one.

10 **[00261]** C22H19N5O2. 386.2 (M+1). ¹H NMR (400MHz, CD3OD) δ 8.20 (s, 1H), 7.91 (s, 1H), 7.64 (d, J = 7.6 Hz, 2H), 7.55 (d, J = 7.6 Hz, 2H), 6.94 (s, 1H), 6.86 (s, 1H), 3.87 (s, 3H), 2.39 (s, 3H), 2.22 (s, 3H).

Example 58

15 **6-(3,5-dimethylisoxazol-4-yl)-4-(4-methyl-1-phenyl-1H-pyrazol-5-yl)-1H-benzo[d]imidazol-2(3H)-one**

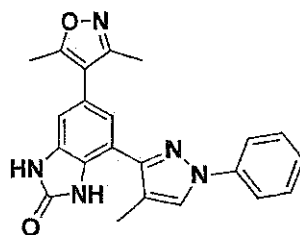


- [00262] 6-(3,5-dimethylisoxazol-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one (30 mg, 0.084 mmol) and 5-bromo-4-methyl-1-phenyl-1H-pyrazole (30 mg, 0.13 mmol) was added to a solvent mixture of 1,2-dimethoxyethane (2 ml) and water (1 ml). To the above mixture were added PEPPSI-Ipr (5.4 mg, 0.008 mmol) and Cs₂CO₃ (83 mg, 0.25 mmol). The reaction mixture was heated at 130°C in microwave reactor for 30 mins. The reaction mixture was then filtered and organic solvent was evaporated and the residue was purified with Prep HPLC (0-100% CH₃CN/H₂O) to afford 3.9 mg product 6-(3,5-dimethylisoxazol-4-yl)-4-(4-methyl-1-phenyl-1H-pyrazol-5-yl)-1H-benzo[d]imidazol-2(3H)-one (yield = 12%).
- 10 [00263] C₂₂H₁₉N₅O₂. 386.3 (M+1). ¹H NMR (400MHz, CD₃OD) δ 8.10 (s, 1H), 7.77 (d, J = 8.0 Hz, 2H), 7.42 (t, J = 8.0 Hz, 2H), 7.23-7.22 (m, 2H), 6.94 (s, 1H), 2.37 (s, 3H), 2.29 (s, 3H), 2.21 (s, 3H).
- [00264] The following compounds were made in similar fashion as that of Example 58.

15

Example 59

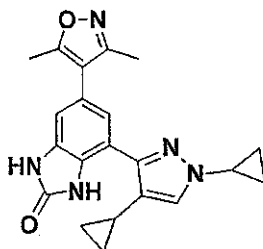
6-(3,5-dimethylisoxazol-4-yl)-4-(4-methyl-1-phenyl-1H-pyrazol-3-yl)-1H-benzo[d]imidazol-2(3H)-one



- [00265] C₂₂H₁₉N₅O₂. 386.1 (M+1). ¹H NMR (400MHz, CD₃OD) δ 7.98 (s, 1H), 7.73 (d, J = 8.4 Hz, 2H), 7.58 (d, J = 8.4 Hz, 2H), 7.48 (s, 1H), 6.94 (s, 1H), 6.90 (s, 1H), 2.34 (s, 3H), 2.19 (s, 3H), 2.10 (s, 3H).
- 20

Example 60

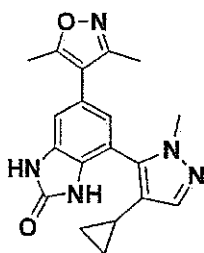
4-(1,4-dicyclopropyl-1H-pyrazol-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



- 5 [00266] $C_{21}H_{21}N_5O_2$. 376.2 (M+1). ^1H NMR (400MHz, CD_3OD) δ 7.62 (s, 1H), 7.48 (s, 1H), 6.97 (s, 1H), 3.71-3.31 (m, 1H), 2.27 (s, 3H), 2.27 (s, 3H), 1.78-1.75 (m, 2H), 1.16-1.06 (m, 2H), 1.05-1.02 (m, 2H), 0.61-0.59 (m, 2H).

Example 61

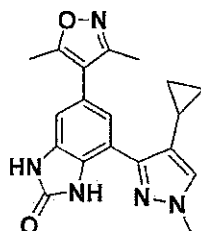
- 10 4-(4-cyclopropyl-1-methyl-1H-pyrazol-5-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



- [00267] $C_{19}H_{19}N_5O_2$. 350.2 (M+1). ^1H NMR (400MHz, CD_3OD) δ 7.19 (s, 1H), 7.00 (s, 1H), 6.86 (s, 1H), 3.59 (s, 3H), 2.34 (s, 3H), 2.18 (s, 3H), 1.45-1.41 (m, 1H), 0.65-0.63 (m, 2H), 0.45-0.38 (m, 2H).
- 15

Example 62

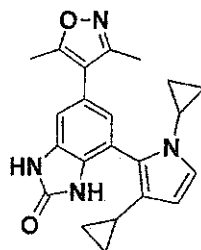
4-(4-cyclopropyl-1-methyl-1H-pyrazol-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



- 5 [00268] $C_{19}H_{19}N_5O_2$. 350.2 (M+1). ^1H NMR (400MHz, CD_3OD) δ 7.53 (s, 1H), 7.30 (s, 1H), 6.87 (s, 1H), 3.82 (s, 3H), 2.18 (s, 3H), 1.72 (s, 3H), 1.72-1.68 (m, 1H); 0.83-0.75 (m, 2H), 0.50-0.42 (m, 2H).

Example 63

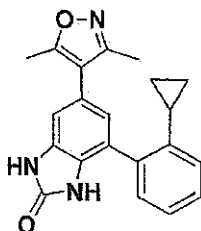
- 10 4-(1,3-dicyclopropyl-1H-pyrrol-2-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



- [00269] $C_{21}H_{21}N_5O_2$. 376.2 (M+1). ^1H NMR (400MHz, CD_3OD) δ 7.23 (s, 1H), 7.09 (s, 1H), 6.99 (s, 1H), 3.48-3.42 (m, 3H), 2.27 (s, 3H), 2.00 (s, 3H), 1.51-1.23 (m, 1H), 0.91-0.85 (m, 2H), 0.80-0.71 (m, 4H), 0.56-0.46 (m, 2H).
- 15

Example 64

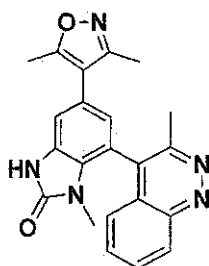
4-(2-cyclopropylphenyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



[00270] $C_{21}H_{19}N_3O_2$. 346.1 (M+1). ^1H NMR (400MHz, CD_3OD) δ 7.35-7.31(m, 1H),
 5 7.25-7.24 (m, 1H), 7.24-7.03 (m, 1H), 6.99 (s, 1H), 6.87 (s, 1H), 2.42 (s, 3H), 2.26 (s, 3H),
 1.77-1.73 (m, 1H), 0.79-0.77 (m, 2H), 0.67 (bs, 2H).

Example 65

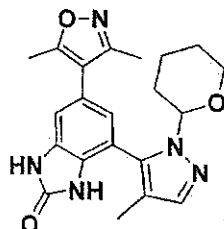
5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(3-methylcinnolin-4-yl)-1H-benzo[d]imidazol-2(3H)-one



[00271] $C_{22}H_{19}N_5O_2$. 386.2 (M+1). ^1H NMR (400MHz, CD_3OD) δ 8.42 (d, J = 8.8
 Hz, 1H), 7.84 (t, J = 7.6 Hz, 1H), 7.73 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8.8 Hz, 1H), 7.14 (s,
 1H), 6.83 (s, 1H), 2.68 (s, 3H), 2.55 (s, 3H), 2.33 (s, 3H), 2.17 (s, 3H).

Example 66

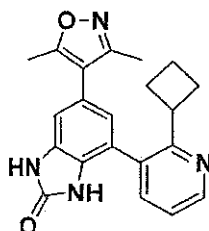
6-(3,5-dimethylisoxazol-4-yl)-4-(4-methyl-1-(tetrahydro-2H-pyran-2-yl)-1H-pyrazol-5-yl)-1H-benzo[d]imidazol-2(3H)-one



- 5 [00272] $C_{21}H_{23}N_5O_3$. 386.2 (M+1). ^1H NMR (400MHz, CD_3OD) δ 7.23 (s, 1H), 7.00 (s, 1H), 6.86 (s, 1H), 3.83-3.57 (m, 1H), 3.38-3.33 (m, 2H), 2.34 (s, 3H), 2.55 (s, 3H), 2.18 (s, 3H), 1.99 (s, 3H), 1.58-1.40 (m, 6H).

Example 67

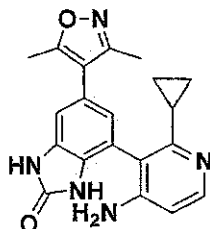
- 10 4-(2-cyclobutylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



- [00273] $C_{21}H_{20}N_4O_2$. 361.3 (M+1). ^1H NMR (400MHz, CD_3OD) δ 8.69 (d, $J = 4.8$ Hz, 1H), 8.31 (d, $J = 8.4$ Hz, 1H), 7.87-7.83 (m, 1H), 7.04 (s, 1H), 6.85 (s, 1H), 3.90-3.86 (m, 1H), 2.33 (s, 3H), 2.30 (bs, 1H), 2.14 (s, 3H), 2.11 (bs, 1H), 1.92 (bs, 2H), 1.78-1.71 (m, 2H).

Example 68

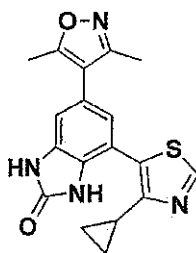
4-(4-amino-2-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



- 5 [00274] $C_{20}H_{19}N_5O_2$. 362.3 (M+1). ^1H NMR (400MHz, CD_3OD) δ 10.63 (s, 1H), 10.42 (s, 1H), 7.82 (s, 1H), 6.81 (s, 1H), 6.61 (s, 1H), 6.40 (s, 1H), 5.21 (s, 2H), 2.28 (s, 3H), 2.17 (s, 3H), 1.45-1.43 (m, 1H), 0.98-0.85 (m, 2H), 0.69-0.63 (m, 2H), 0.47-0.44 (m, 2H).

Example 69

- 10 4-(4-cyclopropylthiazol-5-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

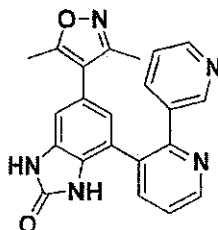


- [00275] $C_{18}H_{16}N_4O_2S$. 353.3 (M+1). ^1H NMR (400MHz, CD_3OD) δ 8.81 (s, 1H), 6.98 (s, 1H), 6.88 (s, 1H), 2.26 (s, 3H), 2.19 (s, 3H), 1.78 (bs, 1H), 0.86 (bs, 2H), 0.82 (bs, 2H).

15

Example 70

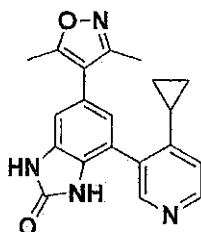
4-([2,3'-bipyridin]-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



[00276] $C_{22}H_{17}N_5O_2$. 384.3 (M+1). ^1H NMR (400MHz, CD_3OD) δ 8.83 (dd, $J = 1.2$,
 5 4.8 Hz, 1H), 8.75 (s, 1H), 8.63 (d, $J = 5.2$ Hz, 1H), 8.23 (d, $J = 7.2$ Hz, 1H), 8.08 (dd, $J = 1.2$,
 8.0 Hz, 1H), 7.72-7.67 (m, 2H), 6.99 (d, $J = 1.2$ Hz, 1H), 6.86 (s, 1H), 2.29 (s, 3H), 2.12 (s,
 3H).

Example 71

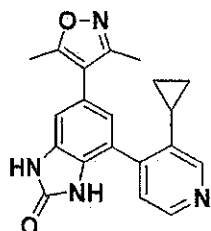
10 4-(4-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-
 one



[00277] $C_{20}H_{18}N_4O_2$. 347.3 (M+1). ^1H NMR (400MHz, CD_3OD) δ 8.34 (d, $J = 6.4$
 Hz, 1H), 8.28 (s, 1H), 6.98-6.97 (m, 1H), 6.93 (d, $J = 6.4$ Hz, 1H), 6.84 (d, $J = 1.2$ Hz, 1H),
 15 2.34 (s, 3H), 2.17 (s, 3H), 1.85-1.75 (m, 1H), 0.95 (bs, 2H), 0.78 (bs, 2H).

Example 72

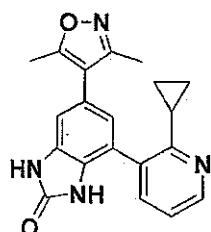
4-(3-cyclopropylpyridin-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



- 5 [00278] $C_{20}H_{18}N_4O_2$. 347.3 (M+1). ^1H NMR (400MHz, CD_3OD) δ 8.58 (d, J = 5.2 Hz, 1H), 8.43 (s, 1H), 7.82 (d, J = 6.4 Hz, 1H), 7.05 (d, J = 1.2 Hz, 1H), 6.94 (d, J = 1.6 Hz, 1H), 2.34 (s, 3H), 2.18 (s, 3H), 1.88-1.84 (m, 1H), 1.00-0.95 (m, 2H), 0.85-0.81 (m, 2H).

Example 73

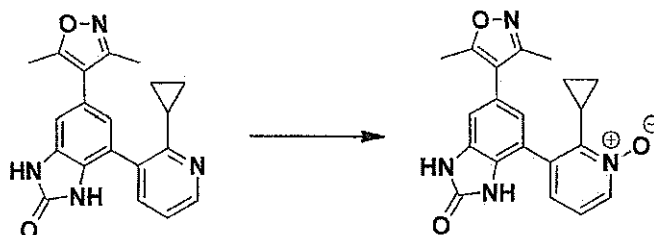
10 4-(2-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



- [00279] $C_{20}H_{18}N_4O_2$. 347.2 (M+1). ^1H NMR (400MHz, CD_3OD) δ 8.57 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 7.70-7.67 (m, 1H), 7.10 (s, 1H), 6.99 (s, 1H), 2.43 (s, 3H), 2.27 (s, 3H), 2.14-2.08 (m, 1H), 1.15 (bs, 4H).
- 15

Example 74

2-cyclopropyl-3-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)pyridine 1-oxide



[00280] 4-(2-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-

benzo[d]imidazol-2(3H)-one (35mg, 0.1 mmol) was dissolved in MeOH/DCM (1/1 mL). To the solution was added 3-Chloroperoxybenzoic acid (69.75 mg, 0.4 mol) and the mixture

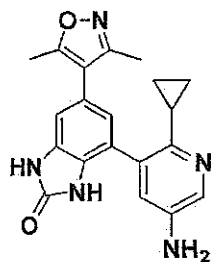
5 stirred at RT overnight. The organic solvent was evaporated and the residue was purified with Prep HPLC (0-100% CH₃CN/H₂O) to afford 2-cyclopropyl-3-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)pyridine 1-oxide.

[00281] C₂₀H₁₈N₄O₃. 363.2 (M+1). ¹H NMR (400MHz, CD₃OD) δ 8.47 (dd, *J* = 1.2, 6.4 Hz, 1H), 7.64 (dd, *J* = 1.2, 6.4 Hz, 1H), 7.54 (t, *J* = 6.4 Hz, 1H), 7.08 (d, *J* = 1.2 Hz, 1H),
 10 6.94 (d, *J* = 1.2 Hz, 1H), 2.42 (s, 3H), 2.25 (s, 3H), 2.04-1.99 (m, 1H), 0.96 (bs, 1H), 0.75 (bs, 1H), 0.61 (bs, 1H), 0.54 (bs, 1H).

Example 75

4-(5-amino-2-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

15



[00282] 6-(3,5-dimethylisoxazol-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one (150 mg, 0.42 mmol) and 5-bromo-6-cyclopropylpyridin-3-amine (180 mg, 0.84 mmol) were added to a solvent mixture of 1,2-dimethoxyethane (2 mL) and water (1 mL). To the mixture were added PEPPSI-Ipr (29 mg, 0.03 mmol) and Cs₂CO₃ (413 mg, 1 mmol). The reaction mixture was heated at 130°C in microwave reactor for 30

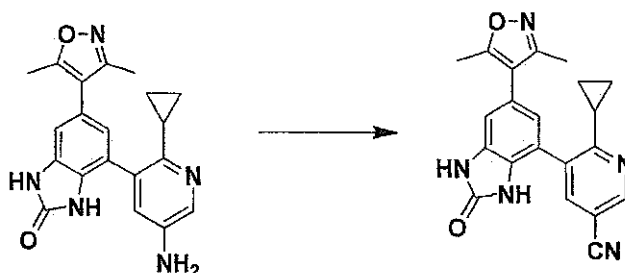
20

mins. The reaction mixture was then filtered and organic solvent was evaporated and the residue was purified with Prep HPLC (0-100% CH₃CN/H₂O) to afford 129 mg of 4-(5-amino-2-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one.

- 5 [00283] C₂₀H₁₉N₅O₂. 362.1 (M+1). ¹H NMR (400MHz, CD₃OD) δ 10.98 (s, 1H), 10.81 (s, 1H), 7.79 (s, 1H), 7.05 (s, 1H), 6.99 (s, 2H), 2.26 (s, 3H), 2.18 (s, 3H), 1.62 (bs, 1H), 0.82 (bs, 2H), 0.62 (bs, 2H).

Example 76

- 10 6-cyclopropyl-5-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)nicotinonitrile

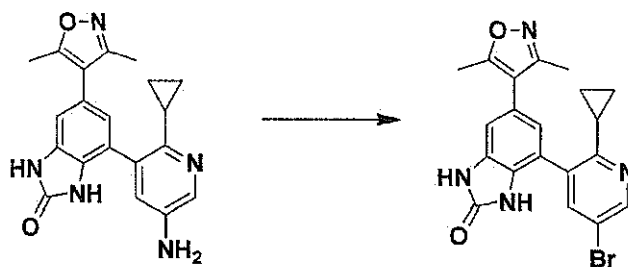


- [00284] 4-(5-amino-2-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one (21 mg, 0.058 mmol) was suspended in a mixture of water (1 mL) and con. HCl (1 mL), cooled suspension to 0°C, a solution of sodium nitrite (4 mg, 0.058 mmol) in water was added slowly. After 5 mins, the reaction mixture was neutralised by the addition of NaHCO₃ solution. Then the resultant suspension was added in aliquots to a solution of copper (I) cyanide (5 mg, 0.058 mmol) and sodium cyanide (6 mg, 0.11 mmol) in water at room temperature. Heated to 70°C for 30 mins. Extracted with EtOAc, evaporated organic solvent, the residue was purified with Prep HPLC. (0-100% CH₃CN/H₂O) to afford 1.2 mg of 6-cyclopropyl-5-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)nicotinonitrile.

- [00285] C₂₁H₁₇N₅O₂. 372.4 (M+1). ¹H NMR (400MHz, CD₃OD) δ 8.63 (s, 1H), 7.79 (s, 1H), 7.06 (s, 1H), 6.99 (s, 1H), 2.25 (s, 3H), 2.18 (s, 3H), 1.88-1.80 (m, 1H), 0.88-0.83 (m, 2H), 0.78-0.75 (m, 2H).

Example 77

4-(5-bromo-2-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



5

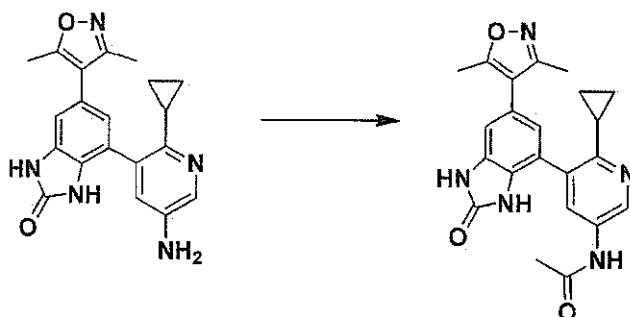
[00286] 4-(5-amino-2-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one (75 mg, 0.21 mmol) was dissolved in acetonitrile (2 ml), at room temperature added tert-butyl nitrite (32 mg, 0.31 mmol) and CuBr₂ (56 mg, 0.25 mmol), stirred at room temperature for 1h. The reaction mixture was diluted with EtOAc, washed with brine, evaporated organic solvent, purified with Prep HPLC. (0-100% CH₃CN/H₂O) to afford 6 mg of 4-(5-bromo-2-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one.

[00287] C₂₀H₁₇BrN₄O₂. 425.3 (M+1). ¹H NMR (400MHz, CD₃OD) δ 8.42 (s, 1H), 7.61 (s, 1H), 6.99 (s, 1H), 6.96 (s, 1H), 2.33 (s, 3H), 2.18 (s, 3H), 1.78-1.70 (m, 1H), 0.88-0.81 (m, 2H), 0.71-0.64 (m, 2H).

15

Example 78

N-(6-cyclopropyl-5-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)pyridin-3-yl)acetamide



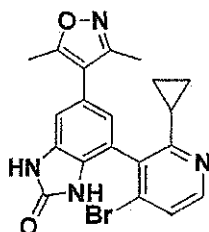
- 5 [00288] 4-(5-Amino-2-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one (75 mg, 0.21 mmol) was dissolved in acetonitrile (2 mL), at room temperature added tert-butyl nitrite (32 mg, 0.31 mmol) and CuBr₂ (56 mg, 0.25 mmol), stirred at room temperature for 1h. The reaction mixture was diluted with EtOAc, washed with brine, evaporated organic solvent, purified with Prep HPLC. (0-100%
 10 CH₃CN/H₂O) to afford 16 mg of N-(6-cyclopropyl-5-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)pyridin-3-yl)acetamide.

[00289] C₂₂H₂₁N₅O₃. 404.4 (M+1). ¹H NMR (400MHz, CD₃OD) δ 8.89 (s, 1H); 7.78 (s, 1H), 7.06 (s, 1H), 7.03 (s, 1H), 2.33 (s, 3H), 2.17 (s, 3H), 2.12 (s, 3H), 1.82-1.78 (m, 1H), 0.99-0.94 (m, 2H), 0.77-0.74 (m, 2H).

15

Example 79

4-(4-bromo-2-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

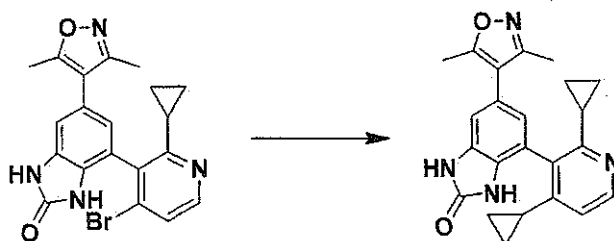


[00290] 4-(4-bromo-2-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one was made in similar fashion to 4-(5-bromo-2-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

[00291] $C_{20}H_{17}BrN_4O_2$. 425.3 (M+1). ^1H NMR (400MHz, CD_3OD) δ 8.18 (d, $J = 2.8$ Hz, 1H), 7.55 (d, $J = 2.8$ Hz, 1H), 6.98 (s, 1H), 6.78 (s, 1H), 2.35 (s, 3H), 2.20 (s, 3H), 1.75-1.65 (m, 1H), 1.03-0.88 (m, 2H), 0.82-0.68 (m, 2H).

Example 80

4-(2,4-dicyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



10

[00292] 4-(4-bromo-2-cyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one (17 mg, 0.04 mmol) and cyclopropyl boronic acid (100 mg, 1.2 mmol) were dissolved in dioxane (2 mL). To the reaction mixture were added K_3PO_4 (50 mg, 0.24 mol) and dichloro 1,1'-bis(diphenylphosphino)ferrocene palladium (II) dichloromethane (10 mg, 0.012 mmol). The reaction mixture was heated at 100°C for 3h. Solvent was evaporated, the residue was dissolved in EtOAc, washed with brine, evaporated organic solvent and the residue was purified with Prep HPLC (0-100% CH_3CN/H_2O) to afford 5.4 mg of 4-(2,4-dicyclopropylpyridin-3-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one.

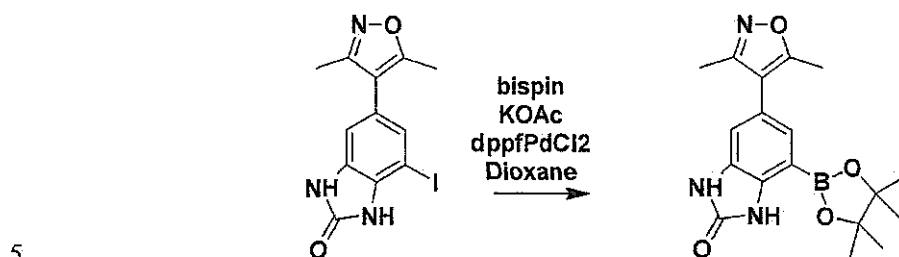
[00293] $C_{23}H_{22}N_4O_2$. 387.3 (M+1). ^1H NMR (400MHz, CD_3OD) δ 8.30 (d, $J = 6.4$ Hz, 1H), 7.19 (d, $J = 6.4$ Hz, 1H), 7.05 (s, 1H), 6.91 (s, 1H), 2.38 (s, 3H), 2.21 (s, 3H), 1.95-1.88 (m, 1H), 1.72-1.67 (m, 1H), 1.17-1.14 (m, 2H), 1.07-0.95 (m, 6H).

20

Example 81

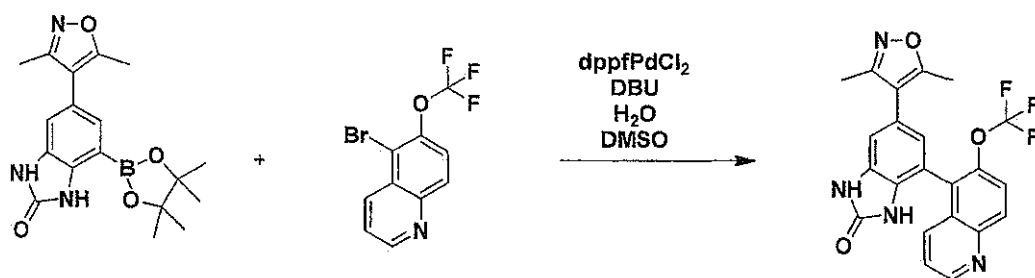
6-(3,5-dimethylisoxazol-4-yl)-4-(6-(trifluoromethoxy)quinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one

Step 1:



[00294] Degassed dioxane (120 mL) was added to a round-bottom flask containing 6-(3,5-dimethylisoxazol-4-yl)-4-iodo-1H-benzo[d]imidazol-2(3H)-one (6g, 16.9 mmol), dppfPdCl₂ (630 mg, 5%), KOAc, (3.3g, 2 equiv) and bispinacolato diboron (8.6g, 2 equiv). The reaction mixture was sonicated to eliminate lumps, and was then heated to 120 °C overnight. The reaction was complete via TLC and HPLC analysis. The reaction mixture was dry-loaded onto silica gel and purified by flash chromatography (rf 0.4 in ethyl acetate, eluting with ethyl acetate/methanol. 6-(3,5-dimethylisoxazol-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one was isolated and subjected to high-vacuum drying overnight, and contained an equivalent of pinacol side-products by NMR.

15 Step 2:



[00295] A solution of 5-bromo-6-(trifluoromethoxy)quinoline (obtained by bromination of 6-trifluoromethoxyquinoline) (50 mg, 0.17 mmol), 6-(3,5-dimethylisoxazol-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one (91 mg, 0.26 mmol), dichloro 1,1-bis(diphenylphosphino)ferrocene palladium(II)

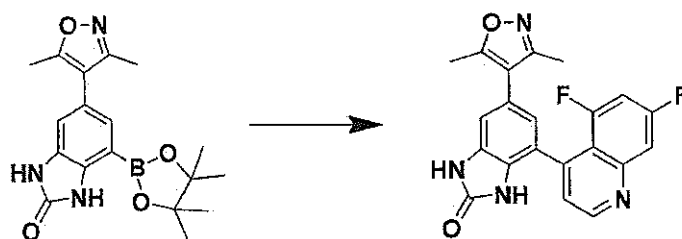
20

dichloromethane (12.7 mg, 0.02 mmol), 1,8-diazabicyclo[5.4.0]undec-7-ene (0.2 mL, 1.37 mmol), DMSO (0.2 mL) and water (0.2 mL) under nitrogen was heated at 120 °C for 1h. The reaction mixture was filtered and purified by reverse-phase HPLC to give 6-(3,5-dimethylisoxazol-4-yl)-4-(6-(trifluoromethoxy)quinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one.

[00296] $C_{22}H_{15}F_3N_4O_3$. 441.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.88 (s, 1H), 10.53 (d, J = 2.0 Hz, 1H), 9.00 (dd, J = 4.2, 1.7 Hz, 1H), 8.25 (d, J = 9.3 Hz, 1H), 7.94 – 7.82 (m, 2H), 7.58 (dd, J = 8.6, 4.2 Hz, 1H), 7.08 – 6.97 (m, 1H), 6.88 (d, J = 1.5 Hz, 1H), 2.39 (s, 3H), 2.21 (s, 3H).

Example 82

4-(5,7-difluoroquinolin-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

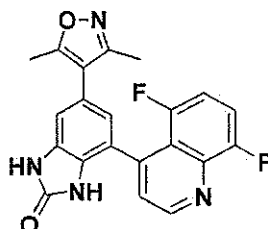


[00297] A mixture of 6-(3,5-dimethylisoxazol-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one (0.05g), commercially available 4-bromo-5,7-difluoroquinoline (0.137g), Peppsi catalyst (0.009g), and Cs_2CO_3 (0.183g) were stirred under N_2 in water/dioxane (1 mL each) at 140 °C for 30 min. After cooling to room temperature, brine (1 mL) was added, the organic layer separated and volatiles removed under vacuum. The residue was purified by preparative HPLC (5-95% MeCN in H_2O) to afford the title compound.

[00298] $C_{21}H_{14}F_2N_4O_2$; 393.20 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.85 (s, 1H), 10.59 (d, J = 1.7 Hz, 1H), 9.01 (d, J = 4.5 Hz, 1H), 7.78 (dt, J = 9.6, 1.7 Hz, 1H), 7.66 – 7.37 (m, 2H), 6.95 (dt, J = 18.3, 1.2 Hz, 2H), 2.38 (s, 3H), 2.32 (s, 3H).

Example 83

4-(5,8-difluoroquinolin-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



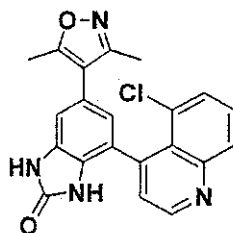
- 5 [00299] 4-(5,8-difluoroquinolin-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one was made in a similar fashion as that of Example 82.

[00300] C₂₁H₁₄F₂N₄O₂; 393.18 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 10.85 (d, J = 1.5 Hz, 1H), 10.57 (d, J = 1.8 Hz, 1H), 9.03 (d, J = 4.4 Hz, 1H), 7.76 – 7.60 (m, 1H), 7.35 (ddd, J = 12.3, 8.7, 3.9 Hz, 1H), 6.94 (dd, J = 13.6, 1.6 Hz, 2H), 2.39 (s, 3H), 2.21 (s, 3H).

10

Example 84

4-(5-chloroquinolin-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



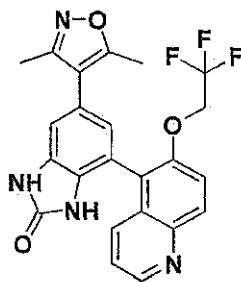
- 15 [00301] The boronic acid (0.05g), bromide (0.137g), Peppi catalyst (0.009g), Cs₂CO₃ (0.183g) was stirred under N₂ in water/dioxane (1 ml each) at 140 C for 30 min. After cooling to RT, brine (1 mL) was added, the organic layer separated and volatiles removed under vacuum. The residue was purified by preparative HPLC (5-95% MeCN in H₂O) to afford the title compound.

[00302] C₂₁H₁₅CIN₄O₂; 391.15 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 10.78 (d, J = 1.9 Hz, 1H), 10.52 (d, J = 1.9 Hz, 1H), 8.63 (d, J = 5.6 Hz, 1H), 8.11 (dd, J = 6.8, 2.6 Hz, 1H), 8.04 (d, J = 5.7 Hz, 0H), 7.83 – 7.72 (m, 1H), 2.36 (s, 3H), 2.18 (s, 3H).

[00303] The following compounds were prepared in a similar fashion to that of Example 82, using the appropriate bromo or chloro derivative:

Example 85

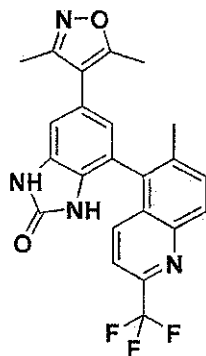
6-(3,5-dimethylisoxazol-4-yl)-4-(6-(2,2,2-trifluoroethoxy)quinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one



[00304] C₂₃H₁₇F₃N₄O₃. 455.1 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 10.77 (d, J = 2.0 Hz, 1H), 10.38 (d, J = 2.0 Hz, 1H), 8.87 (dd, J = 4.5, 1.6 Hz, 1H), 8.17 (d, J = 9.3 Hz, 1H), 7.89 (dd, J = 9.0, 5.4 Hz, 2H), 7.52 (dd, J = 8.6, 4.2 Hz, 1H), 6.97 (d, J = 1.5 Hz, 1H), 6.81 (d, J = 1.6 Hz, 1H), 4.86 (ddq, J = 56.9, 12.0, 8.9 Hz, 2H), 2.39 (s, 3H), 2.21 (s, 3H).

Example 86

6-(3,5-dimethylisoxazol-4-yl)-4-(6-methyl-2-(trifluoromethyl)quinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one



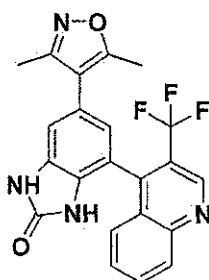
5

[00305] $C_{23}H_{17}F_3N_4O_2$. 439.2 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.89 (s, 1H), 10.39 (d, $J = 2.1$ Hz, 1H), 8.16 (d, $J = 8.7$ Hz, 1H), 7.98 (d, $J = 8.8$ Hz, 1H), 7.93 (d, $J = 8.8$ Hz, 1H), 7.86 (d, $J = 8.8$ Hz, 1H), 7.02 (d, $J = 1.4$ Hz, 1H), 6.84 (d, $J = 1.5$ Hz, 1H), 2.41 (s, 3H), 2.32 (s, 3H), 2.24 (s, 3H).

10

Example 87

6-(3,5-dimethylisoxazol-4-yl)-4-(3-(trifluoromethyl)quinolin-4-yl)-1H-benzo[d]imidazol-2(3H)-one

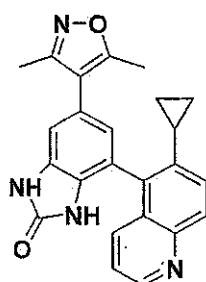


15 [00306] $C_{22}H_{15}F_3N_4O_2$. 425.2 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.95 (s, 1H), 10.54 (d, $J = 1.9$ Hz, 1H), 9.29 (s, 1H), 8.24 (d, $J = 8.4$ Hz, 1H), 7.96 (t, $J = 7.7$ Hz, 1H), 7.67

(t, $J = 7.6$ Hz, 1H), 7.47 – 7.37 (m, 1H), 7.06 (d, $J = 1.5$ Hz, 1H), 6.92 (d, $J = 1.6$ Hz, 1H), 2.40 (s, 3H), 2.22 (s, 3H).

Example 88

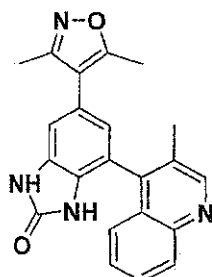
5 4-(6-cyclopropylquinolin-5-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



[00307] $C_{24}H_{20}N_4O_2$, 397.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.83 (d, $J = 1.9$ Hz, 1H), 10.39 (d, $J = 2.1$ Hz, 1H), 8.83 – 8.78 (m, 1H), 7.99 (d, $J = 8.9$ Hz, 1H), 7.64 (d, $J = 8.5$ Hz, 1H), 7.41 (dd, $J = 8.6, 4.2$ Hz, 1H), 7.34 (d, $J = 9.0$ Hz, 1H), 6.99 (d, $J = 1.5$ Hz, 1H), 6.82 (d, $J = 1.5$ Hz, 1H), 2.41 (s, 3H), 2.23 (s, 3H), 1.80 – 1.73 (m, 1H), 0.86 (t, $J = 6.8$ Hz, 4H).

Example 89

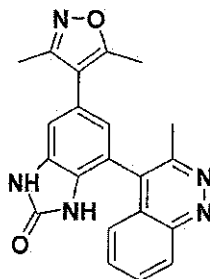
6-(3,5-dimethylisoxazol-4-yl)-4-(3-methylquinolin-4-yl)-1H-benzo[d]imidazol-2(3H)-one



[00308] $C_{22}H_{18}N_4O_2$. 371.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.95 (d, J = 1.9 Hz, 1H), 10.49 (d, J = 2.0 Hz, 1H), 9.09 (s, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.84 (t, J = 7.8 Hz, 1H), 7.62 (t, J = 7.5 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.05 (d, J = 1.5 Hz, 1H), 6.87 (d, J = 1.5 Hz, 1H), 2.41 (s, 3H), 2.29 (s, 3H), 2.24 (s, 3H).

Example 90

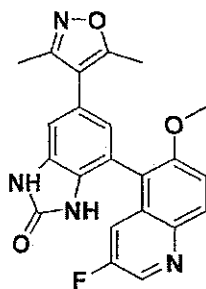
10 6-(3,5-dimethylisoxazol-4-yl)-4-(3-methylcinnolin-4-yl)-1H-benzo[d]imidazol-2(3H)-one



[00309] $C_{21}H_{17}N_5O_2$. 372.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.97 (s, 1H), 10.55 (d, J = 2.0 Hz, 1H), 8.62 – 8.41 (m, 1H), 7.97 – 7.85 (m, 1H), 7.78 (ddd, J = 8.4, 6.9, 1.4 Hz, 1H), 7.47 (d, J = 8.5 Hz, 1H), 7.15 – 7.02 (m, 1H), 6.95 (d, J = 1.5 Hz, 1H), 2.69 (s, 3H), 2.42 (s, 3H), 2.25 (s, 3H).

Example 91

6-(3,5-dimethylisoxazol-4-yl)-4-(3-fluoro-6-methoxyquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one

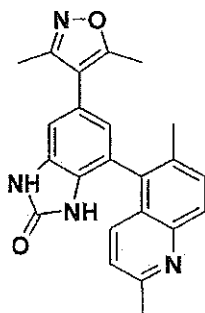


- 5 [00310] $C_{22}H_{17}FN_4O_3$. 405.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.80 (d, J = 2.0 Hz, 1H), 10.41 (s, 1H), 8.79 (d, J = 2.7 Hz, 1H), 8.17 (d, J = 9.4 Hz, 1H), 7.77 (d, J = 9.4 Hz, 1H), 7.50 – 7.41 (m, 1H), 7.00 – 6.90 (m, 1H), 6.88 – 6.76 (m, 1H), 3.89 (s, 3H), 2.41 (s, 3H), 2.24 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -128.19 (d, J = 10.8 Hz).

10

Example 92

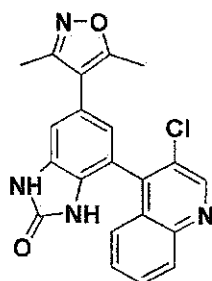
6-(3,5-dimethylisoxazol-4-yl)-4-(2,6-dimethylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one



- 15 [00311] $C_{23}H_{20}N_4O_2$. 385.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.94 (s, 1H), 10.40 (d, J = 1.9 Hz, 1H), 8.11 (d, J = 8.5 Hz, 2H), 7.99 (d, J = 8.8 Hz, 1H), 7.68 (d, J = 8.7 Hz, 1H), 7.03 (d, J = 1.6 Hz, 1H), 6.82 (d, J = 1.5 Hz, 1H), 2.85 (s, 3H), 2.41 (s, 3H), 2.31 (s, 3H), 2.24 (s, 3H).

Example 93

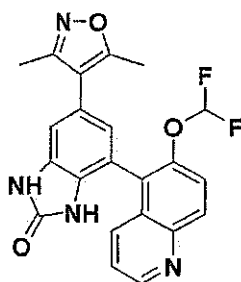
4-(3-chloroquinolin-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



[00312] $C_{21}H_{15}ClN_4O_2$. 391.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.95 (d, J = 1.9 Hz, 1H), 10.61 (s, 1H), 9.03 (s, 1H), 8.22 – 8.02 (m, 1H), 7.91 – 7.77 (m, 1H), 7.69 – 7.58 (m, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.06 (d, J = 1.5 Hz, 1H), 6.92 (d, J = 1.6 Hz, 1H), 2.42 (s, 3H), 2.24 (s, 3H).

Example 94

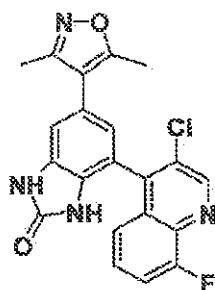
10 4-(6-(difluoromethoxy)quinolin-5-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



[00313] $C_{22}H_{16}F_2N_4O_3$. 423.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.86 (s, 1H), 10.50 (s, 1H), 8.98 – 8.92 (m, 1H), 8.22 (d, J = 9.3 Hz, 1H), 7.86 (d, J = 8.6 Hz, 1H), 7.80 (d, J = 9.2 Hz, 1H), 7.58 – 7.51 (m, 1H), 7.23 (dd, J = 74.5, 72.9 Hz, 1H), 7.04 – 6.98 (m, 1H), 6.87 (d, J = 1.6 Hz, 1H), 2.41 (s, 3H), 2.24 (s, 3H).

Example 95

4-(3-chloro-8-fluoroquinolin-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



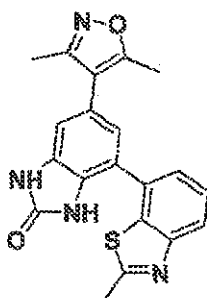
5

[00314] $C_{21}H_{14}ClFN_4O_2$. 409.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.95 (d, J = 2.0 Hz, 1H), 10.58 (d, J = 2.0 Hz, 1H), 9.08 (s, 1H), 7.73 – 7.47 (m, 2H), 7.34 – 7.21 (m, 1H), 7.15 – 7.00 (m, 1H), 6.94 (t, J = 1.3 Hz, 1H), 2.42 (s, 3H), 2.24 (s, 3H).

10

Example 96

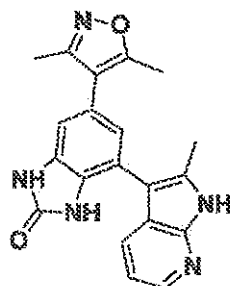
6-(3,5-dimethylisoxazol-4-yl)-4-(2-methylbenzo[d]thiazol-7-yl)-1H-benzo[d]imidazol-2(3H)-one



[00315] $C_{20}H_{16}N_4O_2S$. 377.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.91 (d, J = 2.2 Hz, 1H), 10.68 (d, J = 2.0 Hz, 1H), 7.95 (dd, J = 8.0, 1.1 Hz, 1H), 7.59 (t, J = 7.8 Hz, 1H), 7.50 (dd, J = 7.4, 1.1 Hz, 1H), 7.09 – 7.01 (m, 1H), 7.00 – 6.92 (m, 1H), 2.80 (s, 3H), 2.43 (s, 3H), 2.26 (s, 3H).

Example 97

6-(3,5-dimethylisoxazol-4-yl)-4-(2-methyl-1H-pyrrolo[2,3-b]pyridin-3-yl)-1H-benzo[d]imidazol-2(3H)-one



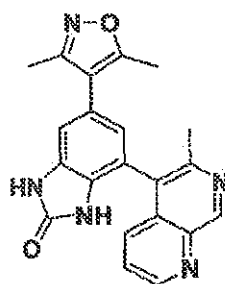
5

[00316] $C_{20}H_{17}N_5O_2$. 360.2 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 11.73 (s, 1H), 10.75 (d, J = 1.8 Hz, 1H), 10.40 (d, J = 1.8 Hz, 1H), 8.14 (dd, J = 4.7, 1.6 Hz, 1H), 7.64 (d, J = 7.8 Hz, 1H), 7.02 (dd, J = 7.8, 4.7 Hz, 1H), 6.86 (m, , 2H), 2.42 (s, 3H), 2.37 (s, 3H), 2.25 (s, 3H).

10

Example 98

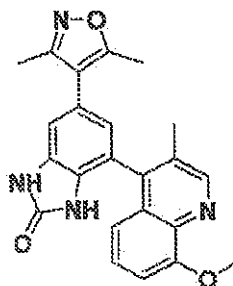
6-(3,5-dimethylisoxazol-4-yl)-4-(6-methyl-1,7-naphthyridin-5-yl)-1H-benzo[d]imidazol-2(3H)-one



15 [00317] $C_{21}H_{17}N_5O_2$. 372.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.93 (d, J = 1.9 Hz, 1H), 10.48 (d, J = 1.9 Hz, 1H), 9.52 (s, 1H), 9.06 (dd, J = 4.0, 1.7 Hz, 1H), 7.86 – 7.67 (m, 2H), 7.03 (d, J = 1.6 Hz, 1H), 6.89 (d, J = 1.6 Hz, 1H), 2.48 (s, 3H), 2.41 (s, 3H), 2.24 (s, 3H).

Example 99

6-(3,5-dimethylisoxazol-4-yl)-4-(8-methoxy-3-methylquinolin-4-yl)-1H-benzo[d]imidazol-2(3H)-one



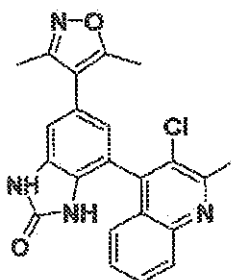
5

[00318] $C_{23}H_{20}N_4O_3$, 401.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.87 (s, 1H), 10.69 – 10.18 (m, 1H), 8.81 (s, 1H), 7.38 (s, 1H), 7.13 (s, 1H), 7.01 (d, J = 5.0 Hz, 1H), 6.90 (d, J = 7.4 Hz, 1H), 6.79 (d, J = 4.9 Hz, 1H), 3.97 (s, 3H), 2.41 (s, 3H), 2.23 (d, J = 4.8 Hz, 6H).

10

Example 100

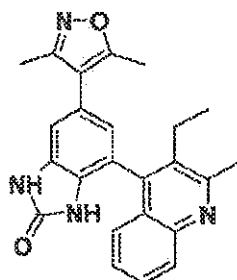
4-(3-chloro-2-methylquinolin-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



15 [00319] $C_{22}H_{17}ClN_4O_2$, 405.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.90 (s, 1H), 10.55 (s, 1H), 8.04 (s, 1H), 7.76 (s, 1H), 7.52 (s, 1H), 7.37 (s, 1H), 7.05 (s, 1H), 6.89 (s, 1H), 2.81 (s, 3H), 2.42 (s, 3H), 2.25 (d, J = 4.1 Hz, 3H).

Example 101

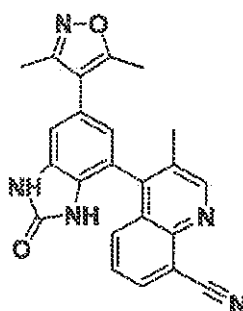
6-(3,5-dimethylisoxazol-4-yl)-4-(3-ethyl-2-methylquinolin-4-yl)-1H-benzo[d]imidazol-2(3H)-one



- 5 [00320] $C_{24}H_{22}N_4O_2$. 399.2 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.86 (s, 1H), 10.43 (s, 1H), 7.95 (s, 1H), 7.63 (s, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.17 (d, J = 8.2 Hz, 1H), 7.01 (s, 1H), 6.81 (s, 1H), 2.76 (s, 5H), 2.41 (s, 3H), 2.23 (s, 3H), 1.00 (d, J = 7.8 Hz, 3H).

Example 102

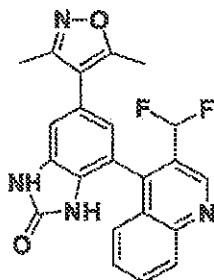
- 10 4-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-3-methylquinoline-8-carbonitrile



- [00321] $C_{23}H_{17}N_5O_2$. 396.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.93 (d, J = 1.8 Hz, 1H), 10.45 (d, J = 1.9 Hz, 1H), 9.10 (s, 1H), 8.31 (dd, J = 6.9, 1.6 Hz, 1H), 7.88 – 7.51 (m, 2H), 7.16 – 6.92 (m, 1H), 6.88 (d, J = 1.6 Hz, 1H), 2.41 (s, 3H), 2.30 (s, 3H), 2.24 (s, 3H).
- 15

Example 103

4-(3-(difluoromethyl)quinolin-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

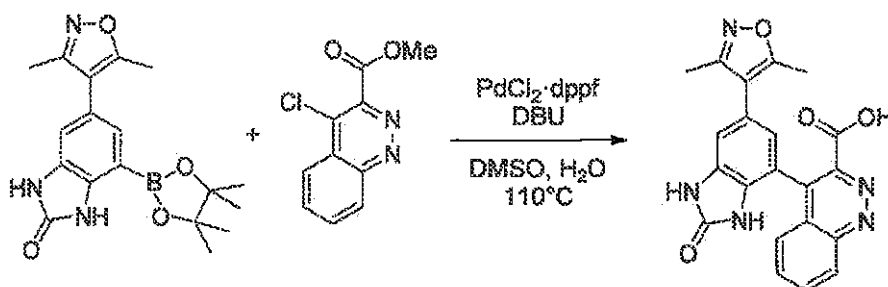


- 5 [00322] $C_{22}H_{16}F_2N_4O_2$, 407.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.96 (d, J = 1.8 Hz, 1H), 10.54 (d, J = 1.9 Hz, 1H), 9.22 (s, 1H), 8.19 (dd, J = 8.5, 1.2 Hz, 1H), 8.06 – 7.78 (m, 1H), 7.64 (ddd, J = 8.3, 6.8, 1.3 Hz, 1H), 7.54 – 7.35 (m, 1H), 7.08 (d, J = 1.6 Hz, 1H), 7.05 – 6.67 (m, 2H).

10

Example 104

4-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)cinnoline-3-carboxylic acid



- 15 [00323] A mixture of 6-(3,5-dimethylisoxazol-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one (100.0 mg, 0.282 mmol) and methyl 4-chlorocinnoline-3-carboxylate (94.0 mg, 0.422 mmol) was treated with $PdCl_2 \cdot dppf \cdot CH_2Cl_2$ (20.6 mg, 0.028 mmol) in the presence of 1,8-Diazabicycloundec-7-ene (DBU, 300.0 mg, 1.971 mmol, 7.0 equiv) in DMSO (1 mL) and water (1 mL). The reaction mixture was heated at 110 °C for 12 min in oil bath. The reaction mixture was purified by HPLC to give 4-(6-

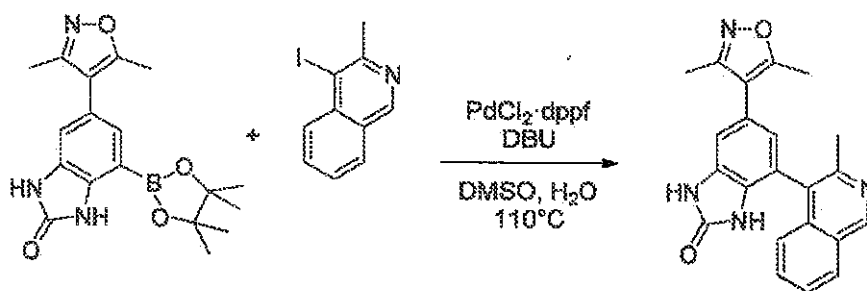
(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)cinnoline-3-carboxylic acid.

[00324] $C_{21}H_{15}N_5O_4$. MS. m/z 402.0 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 8.67 (d, $J = 8.8$ Hz, 1H), 8.09 (t, $J = 8.8$ Hz, 1H), 7.92 (d, $J = 8.8$ Hz, 1H), 7.70 (d, $J = 8.8$ Hz, 1H), 7.17 (s, 1H), 6.96 (s, 1H), 2.44 (s, 3H), 2.29 (s, 3H).

Example 105

6-(3,5-dimethylisoxazol-4-yl)-4-(3-methylisoquinolin-4-yl)-1H-benzo[d]imidazol-2(3H)-one

10

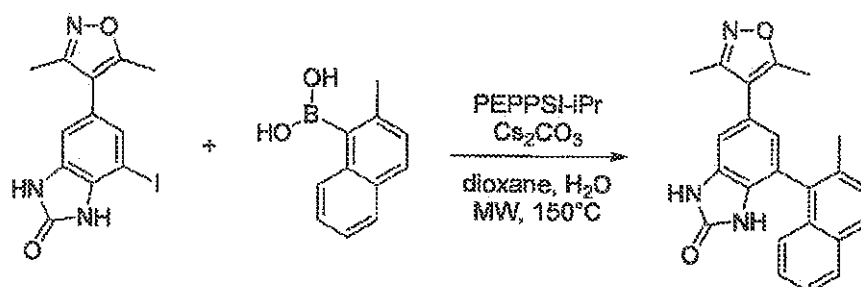


[00325] 6-(3,5-Dimethylisoxazol-4-yl)-4-(3-methylisoquinolin-4-yl)-1H-benzo[d]imidazol-2(3H)-one was prepared from 4-iodo-3-methylisoquinoline in a similar fashion as Example 104.

15 [00326] $C_{22}H_{18}N_4O_2$. MS. m/z 371.1 (M+1). ^1H NMR (400 MHz, Methanol- d_4) 9.26 (s, 1H), 8.16 (d, $J = 7.7$ Hz, 1H), 7.67 (m, 2H), 7.42 (d, $J = 8.2$ Hz, 1H), 7.15 (s, 1H), 6.91 (s, 1H), 2.50 (s, 3H), 2.45 (s, 3H), 2.29 (s, 3H).

Example 106

6-(3,5-dimethylisoxazol-4-yl)-4-(2-methylnaphthalen-1-yl)-1H-benzo[d]imidazol-2(3H)-one

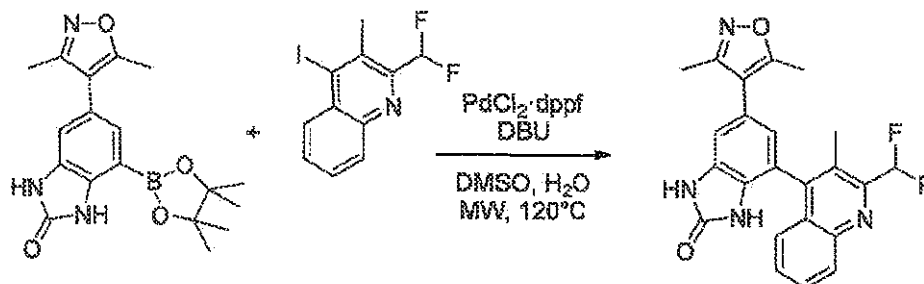


- 5 [00327] In a 2-5 mL Smith Process Vial, 6-(3,5-dimethylisoxazol-4-yl)-4-iodo-1H-benzo[d]imidazol-2(3H)-one (100.0 mg 0.282 mmol), (2-methylnaphthalen-1-yl)boronic acid (176.0 mg, 0.946 mmol, 3.36 equiv), PEPPSI-iPr (19.2 mg, 0.028 mmol, 0.1 equiv) and Cs₂CO₃ (337.0 mg, 1.126 mmol, 4 equiv) were placed. The mixture was suspended in 1,4-dioxane (1.5 mL) and water (0.5 mL) under N₂. The mixture was heated at 150°C for 75 min
- 10 using microwave reactor (Biotage Optimizer). After an aqueous work up, the crude product was purified by a silica-gel column chromatography (hexane / EtOAc 20:80) to give 6-(3,5-dimethylisoxazol-4-yl)-4-(2-methylnaphthalen-1-yl)-1H-benzo[d]imidazol-2(3H)-one.

- [00328] C₂₃H₁₉N₃O₂. MS. m/z 370.1 (M+1). ¹H NMR (400 MHz, Methanol-d₄) δ 7.88 (d, J = 8.6 Hz, 2H), 7.50 (d, J = 8.6 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.38 – 7.33 (m, 2H),
- 15 7.10 (s, 1H), 6.82 (s, 1H), 2.43 (s, 3H), 2.28 (s, 6H).

Example 107

4-(2-(difluoromethyl)-3-methylquinolin-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



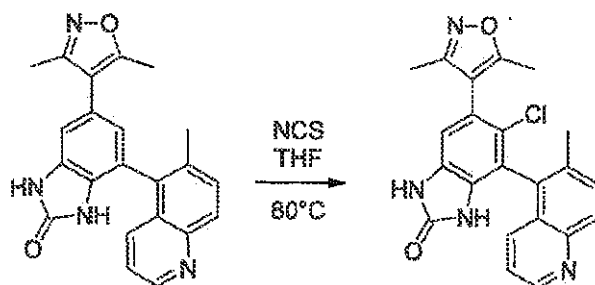
5 [00329] 4-(2-(Difluoromethyl)-3-methylquinolin-4-yl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one was prepared from 2-(difluoromethyl)-4-iodo-3-methylquinoline in a similar fashion as Example 104.

[00330] $C_{23}H_{18}F_2N_4O_2$. MS. m/z 421.1 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 8.18 (d, $J = 9.0$ Hz, 1H), 7.83 – 7.74 (m, 1H), 7.63 – 7.57 (m, 1H), 7.45 (d, $J = 9.4$ Hz, 1H),
 10 7.23 – 6.87 (m, 2H), 2.44 (s, 6H), 2.30 (s, 3H).

Example 108

4-chloro-5-(3,5-dimethylisoxazol-4-yl)-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one

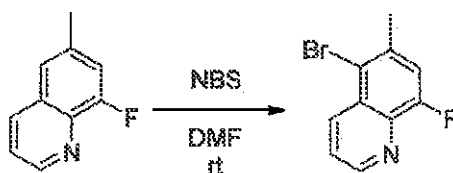
15 [00331] In 0.5 -2 mL Smith Process Vial, the substrate (25.0 mg, 0.067 mmol) and NCS (36.3 mg, 0.135 mmol) were dissolved into THF (2 mL). The mixture was heated at 80°C for 2 h in an oil bath. The reaction mixture was purified by HPLC (5-95% acetonitrile: water with 0.05% trifluoroacetic acid, on a Phenomenex Luna C18 column) to give the desired product.



[00332] $C_{22}H_{17}ClN_4O_2$. MS. m/z 405.1 (M+1), 407.1 (M+2+1). ^1H NMR (400 MHz, Methanol- d_4) δ 9.25 – 9.05 (d, J = 5.8 Hz, 1H), 8.47 – 8.40 (m, 1H), 8.30 (d, J = 9.0 Hz, 1H), 8.20 (d, J = 9.0 Hz, 1H), 7.96 – 7.90 (m, 1H), 7.19 (s, 1H), 2.40 (s, 3/2H), 2.39 (s, 3/2H), 2.38 (s, 3/2H), 2.34 (s, 3/2H), 2.21 (s, 3/2H), 2.19 (s, 3/2H).

Example 109

6-(3,5-dimethylisoxazol-4-yl)-4-(8-fluoro-6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one

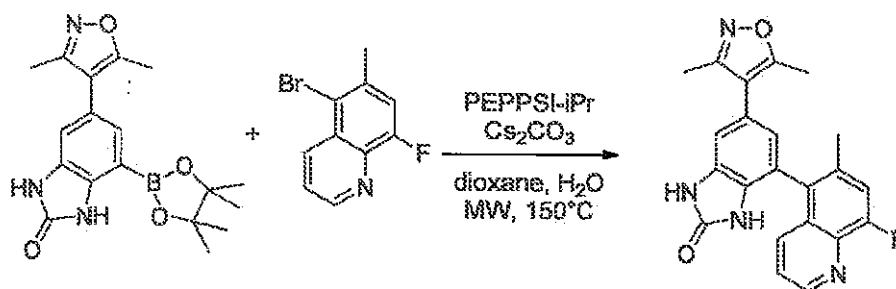


Step 1:

[00333] 3,5-Dicyclopropylisoxazole (70.0 mg, 0.469 mmol) was treated with NBS (167.0 mg, 0.938 mmol, 2 equiv) in CH_2Cl_2 at room temperature for 12 h. The solvent was removed under a reduced pressure and the residue was directly loaded onto a silica gel column chromatography (hexane EtOAc 87:13) to give 5-bromo-8-fluoro-6-methylquinoline.

[00334] $C_9H_{10}BrON$. MS. m/z 239.9 (M-1+1), 241.9 (M+1+1).

Step 2:



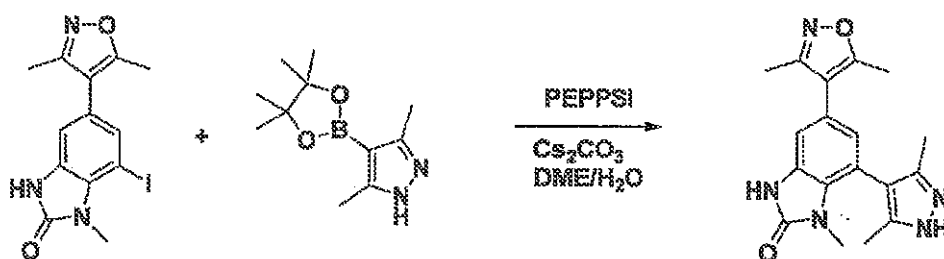
[00335] $C_{22}H_{17}FN_4O_2$. MS. m/z 398.1 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ
 8.93 (d, 1H, $J = 4.0$ Hz), 8.08 (d, 1H, $J = 8.0$ Hz), 7.70 (d, 1H, $J = 11.2$ Hz), 7.67 (dd, 1H, J
 = 8.0, 4.0 Hz), 7.15 (d, 1H, $J = 1.0$ Hz), 6.88 (d, 1H, $J = 1.0$ Hz), 2.43 (s, 3H), 2.38 (s, 3H),
 5 2.28 (s, 3H).

Example 110,

Example 111, and

Example 112

10 7-(3,5-dimethyl-1H-pyrazol-4-yl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-
 benzo[d]imidazol-2(3H)-one



[00336] 5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1-methyl-1H-benzo[d]imidazol-2(3H)-
 one (60 mg, 0.16 mmol) was placed in a microwave vial followed by the addition of PEPPSI
 15 (11 mg, 0.016 mmol) and cesium carbonate (158.9 mg, 4.9 mmol). The material was then
 dissolved in 1.5 mL of DME and 1.5 mL of water. The vial was then placed in the microwave
 where it was heated to 165°C for one hour. The crude solution was then diluted with water
 and extracted 3 times with ethyl acetate. Combined organic layers were washed with brine,
 dried over sodium sulphate, filtered, concentrated *in vacuo*, and purified via HPLC to afford

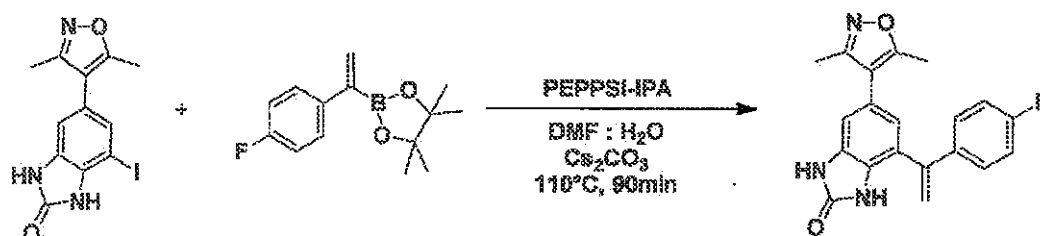
7-(3,5-dimethyl-1H-pyrazol-4-yl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one.

[00337] $C_{18}H_{19}N_5O_2$; 338.2 ($m/z + 1$). ^1H NMR (400 MHz, cd_3od) δ 7.03 (d, $J = 1.6$ Hz, 1H), 6.75 (d, $J = 1.6$ Hz, 1H), 3.01 (s, 3H), 2.41 (s, 3H), 2.26 (s, 3H), 2.12 (s, 6H).

5

Example 113

6-(3,5-dimethylisoxazol-4-yl)-4-(1-(4-fluorophenyl)vinyl)-1H-benzo[d]imidazol-2(3H)-one



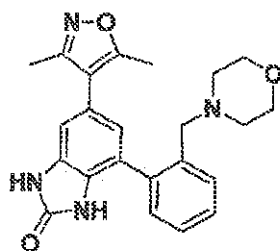
10 [00338] 6-(3,5-Dimethylisoxazol-4-yl)-4-iodo-1H-benzo[d]imidazol-2(3H)-one (100 mg, 0.28 mmol), 1-(4-Fluorophenyl)vinylboronic acid, pinacol ester (209.59 mg, 0.84 mmol), PEPPSI[®]-IPr catalyst (19.19 mg, 0.03 mmol), 1,8-Diazabicyclo[5.4.0]undec-7-ene solution (0.25 ml, 1.69 mmol) were mixed in 1-Methyl-2-pyrrolidinone (6 ml) and Water (3 ml) in sealed in a microwave vial and heated to 110°C for 30 minutes in a microwave reactor. The
15 reaction mixture was then cooled and partitioned between water and ethyl acetate. The organic layer was washed with water then brine and dried over sodium sulfate. Purification on silica gel (Hexane/EtOAc) followed by preparative HPLC afforded 6-(3,5-dimethylisoxazol-4-yl)-4-(1-(4-fluorophenyl)vinyl)-1H-benzo[d]imidazol-2(3H)-one.

[00339] $C_{20}H_{16}FN_3O_2$; 350.2 ($M+1$). ^1H NMR (400 MHz, DMSO- d_6) δ 7.35 (dd, $J = 8.7, 5.6$ Hz, 2H), 7.16 (t, $J = 8.8$ Hz, 2H), 6.86 (d, $J = 1.6$ Hz, 1H), 6.59 (d, $J = 1.6$ Hz, 1H), 5.81 (s, 1H), 5.44 (s, 1H), 2.32 (s, 3H), 2.14 (s, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -114.96 (ddd, $J = 14.4, 9.1, 5.5$ Hz).

20 [00340] The following compound(s) were made in a similar fashion using appropriately substituted boronic acids or esters.

Example 114

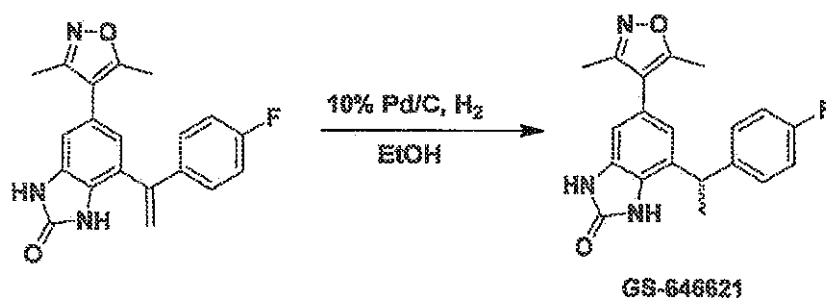
6-(3,5-dimethylisoxazol-4-yl)-4-(2-(morpholinomethyl)phenyl)-1H-benzo[d]imidazol-2(3H)-one



[00341] $C_{23}H_{24}N_4O_3$; 405.2 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 7.52 (dd, J = 7.4, 1.7 Hz, 1H), 7.40 (ddd, J = 14.7, 7.3, 1.7 Hz, 2H), 7.30 (dd, J = 7.2, 1.8 Hz, 1H), 6.90 (d, J = 1.6 Hz, 1H), 6.78 (d, J = 1.6 Hz, 1H), 3.47 (t, J = 4.4 Hz, 3H), 2.41 (s, 3H), 2.24 (s, 5H), 1.66 (d, J = 5.6 Hz, 1H), 1.54 (dq, J = 13.7, 6.9, 6.3 Hz, 2H).

Example 115

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



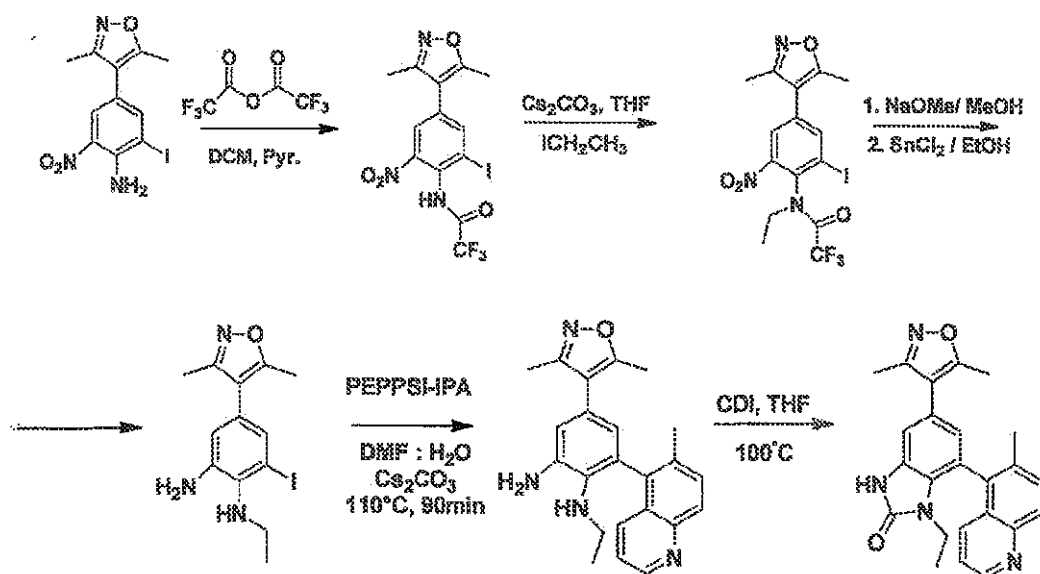
[00342] A suspension of 6-(3,5-dimethylisoxazol-4-yl)-4-(1-(4-fluorophenyl)vinyl)-1H-benzo[d]imidazol-2(3H)-one (60 mg, 0.172 mmol) and 10% palladium on carbon (20 mg) in 5 mL ethanol was purged with hydrogen gas and allowed to stir for 2 hours. The reaction

mixture was then filtered and the solvents evaporated. Residue was purified by preparative HPLC which afforded 6-(3,5-dimethylisoxazol-4-yl)-4-(1-(4-fluorophenyl)ethyl)-1H-benzo[d]imidazol-2(3H)-one.

- [00343] $C_{20}H_{18}FN_3O_2$; 352.2 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.92 (s, 1H), 10.71 (s, 1H), 7.45 (dd, $J = 8.6, 5.7$ Hz, 2H), 7.12 (t, $J = 8.9$ Hz, 2H), 6.84 (d, $J = 1.5$ Hz, 1H), 6.73 (d, $J = 1.5$ Hz, 1H), 4.43 (q, $J = 7.2$ Hz, 1H), 2.35 (s, 3H), 2.17 (s, 3H), 1.61 (d, $J = 7.2$ Hz, 3H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -117.55 (tt, $J = 9.1, 5.6$ Hz).

Example 116

- 10 5-(3,5-dimethylisoxazol-4-yl)-1-ethyl-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one



Step 1:

- 15 [00344] 4-(3,5-Dimethylisoxazol-4-yl)-2-iodo-6-nitroaniline (4g, 11.1 mmol) was dissolved in 100 mL DCM and to the solution was added pyridine (2.7 mL, 33.3 mmol) before cooling to 0°C under argon. To the solution was then added dropwise triflic anhydride (3g, 14.5 mmol) before allowing the reaction to slowly warm to room temperature overnight. The reaction mixture was suspended slowly into stirring DCM / water before extracting 3
20 times with DCM. Organics were then washed with water, brine then dried over sodium

sulfate. Solvent was removed under reduced pressure to yield crude N-(4-(3,5-dimethylisoxazol-4-yl)-2-iodo-6-nitrophenyl)-2,2,2-trifluoroacetamide as a brown oil.

Step 2:

[00345] A mixture of N-(4-(3,5-dimethylisoxazol-4-yl)-2-iodo-6-nitrophenyl)-2,2,2-trifluoroacetamide (2.2 g, 4.83 mmol), cesium carbonate (3.94 g, 12.08 mmol) and N,N-Dimethylformamide (100 ml) was stirred at room temperature under argon. To the mixture was added iodoethane (3.77 g, 24.17 mmol) and reaction was heated to 45°C overnight. Crude mixture was diluted in EtOAc and water and extracted 3 times with EtOAc. Organics were washed with water, aq LiCl, then brine, dried over sodium sulfate and evaporated to dryness under reduced pressure to afford crude N-(4-(3,5-dimethylisoxazol-4-yl)-2-iodo-6-nitrophenyl)-N-ethyl-2,2,2-trifluoroacetamide as a dark oil.

Step 3:

[00346] Crude N-(4-(3,5-dimethylisoxazol-4-yl)-2-iodo-6-nitrophenyl)-N-ethyl-2,2,2-trifluoroacetamide (1.5g, 3.1 mmol) was dissolved in 100 mL of methanol. To the mixture was added 1M sodium methoxide in methanol (15.5 mL, 15.5 mmol) and reaction stirred at room temperature until complete. Reaction was then quenched with 15 mL of 1M HCl or until pH is approximately neutral then diluted with aqueous ammonium chloride. Methanol was removed under reduced pressure and then remaining suspension was extracted with EtOAc. The solution was washed with water, brine then dried over sodium sulfate. Solvents were removed under reduced pressure the residue was then dissolved in 20 mL of ethanol and placed in a sealed pressure tube with stannous chloride (2.2 g, 11.62 mmol). The mixture was heated at 120°C for 1 hour. Reaction mixture was cooled to room temperature. To the mixture was added 1M NaOH (10 mL) and the mixture was stirred at room temperature for 30 minutes. At this point the reaction mixture was diluted with water and extracted with EtOAc (3 times). The solution was washed with water, brine and dried over sodium sulfate. Solvents were removed under reduced pressure and crude product was purified by silica gel chromatography (Hexanes / EtOAc as the eluent) to provide 4-(3,5-dimethylisoxazol-4-yl)-N1-ethyl-6-iodobenzene-1,2-diamine (310 mg, 22%).

Step 4:

[00347] 4-(3,5-Dimethylisoxazol-4-yl)-N1-ethyl-6-iodobenzene-1,2-diamine (105 mg, 0.29 mmol), 6-methylquinolin-5-ylboronic acid (274.86 mg, 1.47 mmol), 1,8-Diazabicyclo[5.4.0]undec-7-ene (0.26 mL, 1.76 mmol), 1-Methyl-2-pyrrolidinone (5 mL), and water (2 mL) were placed in microwave vial, pre-stirred for 2 minutes, then heated to 110°C for 15 minutes. Reaction mixture was diluted with EtOAc and aqueous ammonium chloride and extracted with EtOAc (3 times). Organics were washed with ammonium chloride, water and brine and dried over sodium sulfate. Solvent was evaporated to dryness. Crude material was purified by silica gel chromatography (DCM / MeOH as eluent) to afford 4-(3,5-dimethylisoxazol-4-yl)-N1-ethyl-6-(6-methylquinolin-5-yl)benzene-1,2-diamine.

10 Step 5:

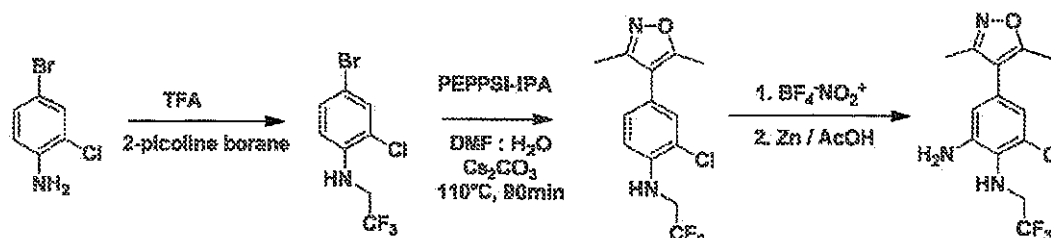
[00348] 4-(3,5-Dimethylisoxazol-4-yl)-N1-ethyl-6-(6-methylquinolin-5-yl)benzene-1,2-diamine (90 mg, 0.24 mmol) and 1,1'-carbonyldiimidazole (86.2 mg, 0.53 mmol) were added to tetrahydrofuran (10 ml) in a sealed vessel and heated to 105°C overnight. The reaction mixture was diluted in EtOAc and aqueous ammonium chloride and extracted with EtOAc (3 times). Organics were washed with ammonium chloride, water and brine and dried over sodium sulfate. Solvent was evaporated to dryness. Crude material was purified by silica gel chromatography (DCM / MeOH as eluent) then by preparative HPLC to afford 5-(3,5-dimethylisoxazol-4-yl)-1-ethyl-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one.

20 [00349] $C_{24}H_{22}N_4O_2$. 399.2 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 8.86 (d, J = 4.2 Hz, 1H), 8.12 (d, J = 8.7 Hz, 1H), 7.97 – 7.89 (m, 1H), 7.85 (d, J = 8.7 Hz, 1H), 7.51 (dd, J = 8.6, 4.3 Hz, 1H), 7.19 (d, J = 1.6 Hz, 1H), 6.82 (d, J = 1.6 Hz, 1H), 3.19 – 3.00 (m, J = 7.1 Hz, 2H), 2.43 (s, 3H), 2.36 (s, 3H), 2.27 (s, 3H), 0.52 (t, J = 7.1 Hz, 3H).

25

Example 117

5-(3,5-dimethylisoxazol-4-yl)-7-(6-methylquinolin-5-yl)-1-(2,2,2-trifluoroethyl)-1H-benzo[d]imidazol-2(3H)-one

5 Step 1:

[00350] 4-Bromo-2-chloroaniline (5000 mg, 24.22 mmol) was dissolved in trifluoroacetic acid (40 ml) and 1,2-dimethoxyethane (50 ml) then cooled under argon to 0°C. To the mixture was added 2-picoline borane complex (12951.34 mg, 121.08 mmol) and then the reaction mixture was heated 110°C for 90 minutes. Solvents were removed under reduced pressure and crude material was taken up in 1N HCl and stirred at 110°C 30 minutes. Crude mixture was then diluted with EtOAc and water and extracted EtOAc (3 times). Organics were washed with water then brine, dried over sodium sulfate and evaporated to dryness under reduced pressure. Crude material was purified by silica gel chromatography using EtOAc/Hexanes as the eluent to afford 4-bromo-2-chloro-N-(2,2,2-trifluoroethyl)aniline.

Step 2:

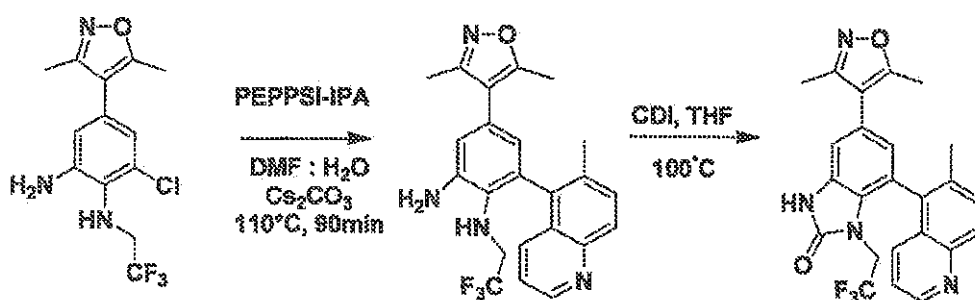
[00351] A mixture of 4-Bromo-2-chloro-N-(2,2,2-trifluoroethyl)aniline (5280 mg, 18.3 mmol), 3,5-dimethylisoxazole-4-boronic acid, pinacol ester (4082.76 mg, 18.3 mmol), PEPPSI[®]-IPr catalyst (1247.24 mg, 1.83 mmol), Cesium carbonate (17889.52 mg, 54.91 mmol) in 120 mL DME:H₂O (2:1) was heated to 90°C under argon. The reaction mixture was then cooled and partitioned between water and ethyl acetate. The organic layer was washed with water then brine and dried over sodium sulfate. Purification on silica gel (Hexanes/EtOAc) afforded 2-chloro-4-(3,5-dimethylisoxazol-4-yl)-N-(2,2,2-trifluoroethyl)aniline.

25 Step 3:

[00352] 2-Chloro-4-(3,5-dimethylisoxazol-4-yl)-N-(2,2,2-trifluoroethyl)aniline (200 mg, 0.66 mmol) was dissolved in dichloromethane (10 mL) and acetonitrile (10 mL) and cooled to 0°C under argon. To reaction mixture was added 0.5M nitronium tetrafluoroborate (1.84 mL) slowly over 20 minutes. Reaction mixture was stirred at 0°C, for 1 hour and
 5 allowed to warm to room temperature. After 3 hours, the reaction mixture was cooled to 0°C again and 0.5M nitronium tetrafluoroborate in sulfolane (1.84 mL) was added and the reaction solution was stirred at room temperature overnight. Reaction solvents were removed under reduced pressure and the residue taken up in EtOAc and the solution was washed with aq. NaHCO₃, then water, brine and dried over sodium sulfate. Solvents were removed under
 10 reduced pressure to yield a dark red oil/liquid. This material was dissolved in 2 mL of ethanol and 2 mL of acetic acid. To the solution was added Zinc dust and suspension was stirred. After 30 minutes of stirring the zinc dust was filtered off and the solvents were removed under reduced pressure. The residue was dissolved in EtOAc and the solution was washed with aq. NaHCO₃, then water, brine and dried over sodium sulfate. Solvent was
 15 removed and the crude residue was purified by silica gel chromatography (Hexanes/EtOAc as the eluent) to afford 6-chloro-4-(3,5-dimethylisoxazol-4-yl)-N1-(2,2,2-trifluoroethyl)benzene-1,2-diamine as a light colored oil.

Example 118

20 The following compound was synthesized in a similar fashion as that of Example 117.



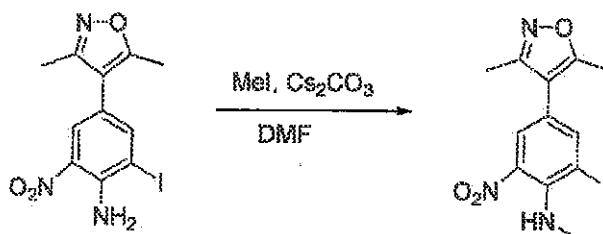
[00353] C₂₄H₁₉F₃N₄O₂; 453.3 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 11.51 (s, 1H), 8.86 (dd, J = 4.2, 1.6 Hz, 1H), 8.16 – 7.97 (m, 1H), 7.78 (d, J = 8.7 Hz, 1H), 7.73 – 7.61 (m, 1H), 7.44 (dd, J = 8.6, 4.2 Hz, 1H), 7.14 (d, J = 1.7 Hz, 1H), 6.81 (d, J = 1.7 Hz, 1H),

3.89 – 3.58 (m, 2H), 2.39 (s, 3H), 2.22 (d, $J = 4.6$ Hz, 6H). ^{19}F NMR (376 MHz, DMSO- d_6) δ -69.65 (t, $J = 8.9$ Hz).

Example 119

5 5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one

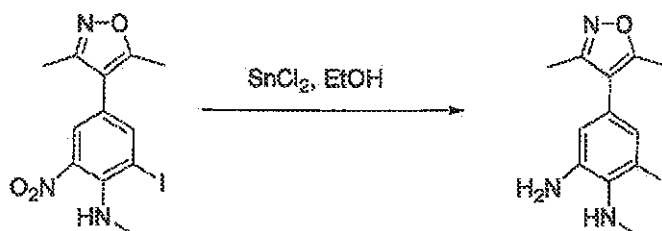
Step 1: 4-(3,5-dimethylisoxazol-4-yl)-2-iodo-N-methyl-6-nitroaniline



[00354] To a flask containing 4-(3,5-dimethylisoxazol-4-yl)-2-iodo-6-nitroaniline
 10 (1000 mg, 2.78 mmol, 1 equiv) was added DMF (15 mL, 0.2 M), cesium carbonate (1.4 gm, 4.17 mmol, 1.5 equiv.) and idomethane (260 μL , 4.17 mmol, 1.5 equiv). After an hour, the reaction was quenched with water and partitioned between water and ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. Purification was carried out by flash column chromatography to furnish 4-(3,5-dimethylisoxazol-4-yl)-2-iodo-N-methyl-6-nitroaniline (615 mg, 60 %). ^1H NMR (400 MHz, CDCl_3) δ 7.81 (t, $J = 3.0$ Hz, 1H), 7.70 (d, $J = 2.1$ Hz, 1H), 2.97 (s, 3H), 2.40 (d, $J = 16.8$ Hz, 3 H), 2.26 (d, $J = 14.2$ Hz, 3H).

[00355] LCMS ($m/z + 1$) 373.

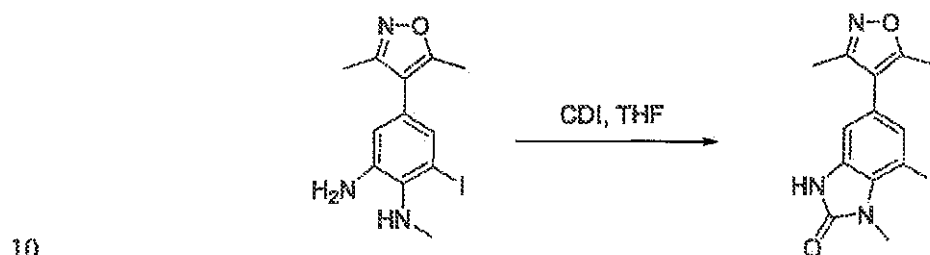
Step 2: 5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(6-methylquinolin-5-yl)-1H-benzof[d]imidazol-2(3H)-one



[00356] To a microwave vial containing 4-(3,5-dimethylisoxazol-4-yl)-2-iodo-N-methyl-6-nitroaniline (610 mg, 1.64 mmol, 1 equiv) was added EtOH (12 mL, 0.25M) and tin (II) chloride (622 mg, 3.28 mmol, 2 equiv). The reaction mixture was heated for 30 min at 110 °C. The reaction was then stirred in 2N NaOH solution for 20 minutes and partitioned
 5 between water and ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. Purification was carried out by flash column chromatography to furnish 4-(3,5-dimethylisoxazol-4-yl)-6-iodo-N1-methylbenzene-1,2-diamine.

[00357] LCMS (m/z +1) 344.02

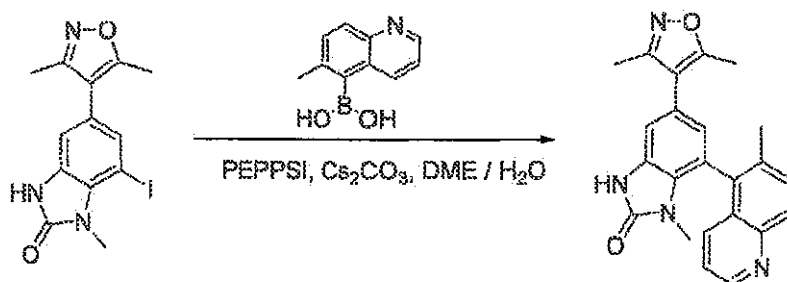
Step 3: 5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1-methyl-1H-benzo[d]imidazol-2(3H)-one



To a flask containing 4-(3,5-dimethylisoxazol-4-yl)-6-iodo-N1-methylbenzene-1,2-diamine (299 mg, 0.87mmol, 1 equiv) was added THF (8 mL) and CDI (282 mg, 1.74 mmol, 2 equiv). The reaction mixture was heated for 2 hr at 120 °C. The reaction mixture was then concentrated *in vacuo* and the solid triturated with diethyl ether to furnish 5-(3,5-
 15 dimethylisoxazol-4-yl)-7-iodo-1-methyl-1H-benzo[d]imidazol-2(3H)-one as a light yellow solid.

LCMS (m/z +1) 370.00.

Step 4:

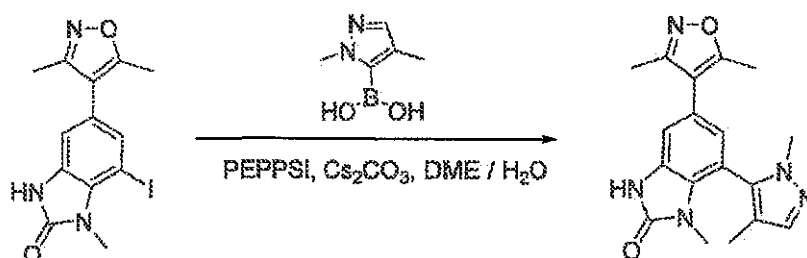


[00358] To a microwave vial containing 5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1-methyl-1H-benzo[d]imidazol-2(3H)-one (40 mg, 0.11 mmol, 1 equiv.) were added 3,5-6-methylquinolin-5-ylboronic acid (51 mg, 0.27 mmol, 2.5 equiv.), Cs₂CO₃ (141 mg, 0.43 mmol, 4 equiv.) and PEPPSI™-IPr catalyst (8 mg, 0.02 mmol, 0.1 equiv.) in DME-H₂O (20 mL, 0.2 M, 2/1, v/v). The mixture was heated to 140 °C. After 2 hr, the reaction was complete. Following cooling, the reaction mixture was extracted with EtOAc and washed with water, saturated NH₄Cl. After drying with MgSO₄, it was filtered and concentrated to dryness under reduced pressure. Purification was carried out by reverse phase HPLC to furnish the title compound.

10 [00359] ¹H NMR (400 MHz, cd₃od) δ 8.82 (d, *J* = 4.3 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 7.82 (t, *J* = 7.1 Hz, 2H), 7.47 (dd, *J* = 8.5, 4.3 Hz, 1H), 7.17 (d, *J* = 1.6 Hz, 1H), 6.82 (d, *J* = 1.6 Hz, 1H), 2.53 (s, 3H), 2.42 (s, 3H), 2.33 (s, 3H), 2.27 (s, 3H). LCMS (*m/z* +1) 385.23.

Example 120

15 7-(1,4-dimethyl-1H-pyrazol-5-yl)-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one



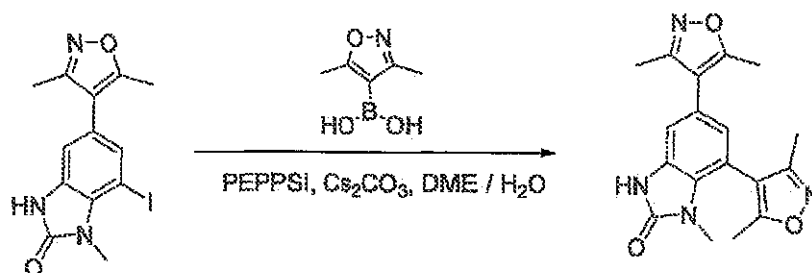
[00360] To a microwave vial containing 5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1-methyl-1H-benzo[d]imidazol-2(3H)-one (40 mg, 0.11 mmol, 1 equiv.) were added 1,4-dimethyl-1H-pyrazol-5-ylboronic acid (72 mg, 0.32 mmol, 3 equiv.), Cs₂CO₃ (141 mg, 0.43 mmol, 4 equiv.) and PEPPSI™-IPr catalyst (8 mg, 0.02 mmol, 0.1 equiv.) and DME-H₂O (20 mL, 0.2 M, 2/1, v/v). The mixture was heated to 140°C. After 1 hr, the reaction was complete. Following cooling, the reaction was extracted with EtOAc and the organic solution was washed with water, saturated NH₄Cl. After drying with MgSO₄, it was filtered and concentrated to dryness under reduced pressure. Purification of the residue was carried out by reverse phase HPLC to furnish the desired product.

[00361] ^1H NMR (400 MHz, cd_3od) δ 7.44 (s, 1H), 7.15 (d, $J = 1.6$ Hz, 1H), 6.88 (d, $J = 1.6$ Hz, 1H), 3.65 (s, 3H), .90 (s, 3H), 2.42 (s, 3H), 2.27 (s, 7H), 1.95 (s, 3H). LCMS (m/z +1) 338.19.

5

Example 121

5,7-bis(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one



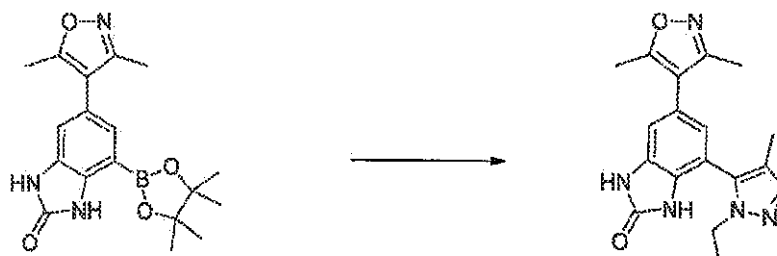
[00362] To a microwave vial containing 5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1-methyl-1H-benzo[d]imidazol-2(3H)-one (40 mg, 0.11 mmol, 1 equiv.) were added 3,5-dimethylisoxazole-4-boronic acid pinacol ester (72 mg, 0.32 mmol, 3 equiv.), Cs_2CO_3 (141 mg, 0.43 mmol, 4 equiv.), PEPPSITM-IPr catalyst (8 mg, 0.02 mmol, 0.1 equiv.) and DME- H_2O (20 mL, 0.2 M, 2/1, v/v). The mixture was heated to 140°C. After 1 hr, the reaction was complete. Following cooling, the reaction mixture was extracted with EtOAc and the organic solution was washed with water, saturated NH_4Cl . After drying with MgSO_4 , it was filtered and concentrated to dryness. The resulting solid was washed with EtOAc. Purification of the residue was carried out by reverse phase HPLC to furnish the title compound.

20

[00363] ^1H NMR (400 MHz, cd_3od) δ 7.09 (d, $J = 1.6$ Hz, 1H), 6.81 (d, $J = 1.6$ Hz, 1H) 3.11 (d, $J = 14.5$ Hz, 3H), 2.41 (s, 3H), 2.35 – 2.23 (m, 6H), 2.15 (s, 3H). LCMS (m/z +1) 339.15.

Example 122

6-(3,5-dimethylisoxazol-4-yl)-4-(1-ethyl-4-methyl-1H-pyrazol-5-yl)-1H-benzo[d]imidazol-2(3H)-one



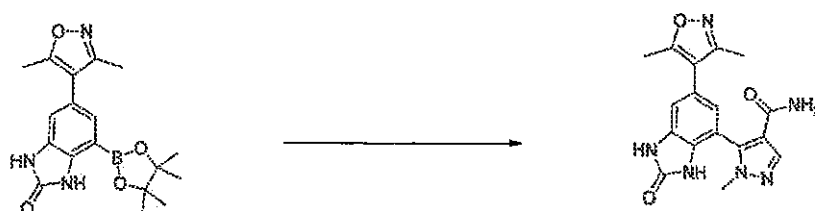
- 5 [00364] To a microwave vial containing 6-(3,5-dimethylisoxazol-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one (40 mg, 0.11 mmol, 1 equiv.) were added 5-bromo-1-ethyl-4-methyl-1H-pyrazole 11 (64 mg, 0.34 mmol, 3 equiv.), Pd(dppf)Cl₂·CH₂Cl₂ (9 mg, 0.011 mmol, 0.1 equiv.), DBU (101 μL, 6 equiv.) and DMSO-H₂O (4 mL, 0.2 M, 2/1, v/v). The mixture was heated to 120°C for 30 min in microwave. The
- 10 reaction was concentrated under reduced pressure and purification was carried out by reverse phase HPLC.

[00365] ¹H NMR (400 MHz, Methanol-d₄) δ 7.45 (d, J = 0.8 Hz, 1H), 7.09 (d, J = 1.6 Hz, 1H), 6.88 (d, J = 1.6 Hz, 1H), 4.02 (dd, J = 28.3, 7.2 Hz, 1H), 2.43 (s, 4H), 2.27 (s, 4H), 1.96 (d, J = 0.7 Hz, 3H), 1.25 (t, J = 7.2 Hz, 4H). LCMS (m/z +1) 338.22.

15

Example 123

5-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-1-methyl-1H-pyrazole-4-carboxamide



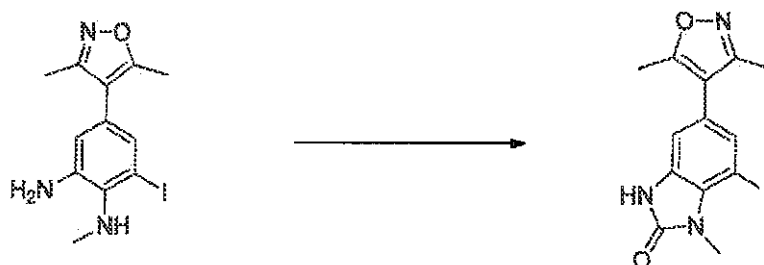
[00366] To a microwave vial containing 6-(3,5-dimethylisoxazol-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one (100 mg, 0.28 mmol, 1 equiv.) was added 5-bromo-1-methyl-1H-pyrazole-4-carbonitrile (130 mg, 0.30 mmol, 2.5 equiv.), Pd(dppf)Cl₂.CH₂Cl₂ (23 mg, 0.03 mmol, 0.1 equiv.) and DBU (253 μ L, 1.69 mmol, 6 equiv.) and dissolved in DMSO-H₂O (4 mL, 0.2 M, 2/1, v/v). The mixture was heated to 120°C for 30 min in microwave. The reaction was concentrated in vacuo and purification was then carried out by reverse phase HPLC.

[00367] LCMS (m/z +1) 352.99. ¹H NMR (400 MHz, Methanol-d₄) δ 8.04 (s, 1H), 7.10 (d, J = 1.6 Hz, 1H), 6.95 (d, J = 1.6 Hz, 1H), 3.72 (s, 4H), 2.40 (d, J = 15.8 Hz, 4H), 2.25 (d, J = 16.4 Hz, 4H).

Example 124

1-cyclopropyl-5-(3,5-dimethylisoxazol-4-yl)-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one

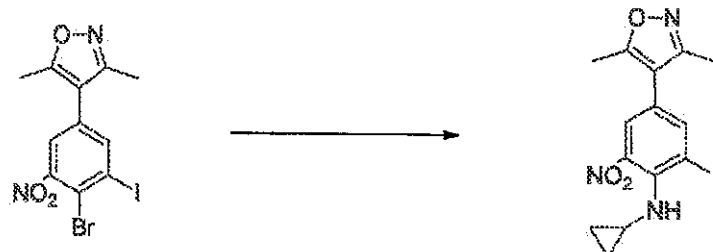
15 Step 1: 5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1-methyl-1H-benzo[d]imidazol-2(3H)-one



[00368] To a mixture of 4-(3,5-dimethylisoxazol-4-yl)-6-iodo-N1-methylbenzene-1,2-diamine (1.89 g, 5.5 mmol, 1 equiv.) in a pressure tube was added THF (5 mL) and CDI (2.67 g, 18.5 mmol, 3 equiv.). The mixture was heated to 120°C for 30 minutes in a microwave reactor. The reaction was concentrated in vacuo and purified by HPLC to provide 5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1-methyl-1H-benzo[d]imidazol-2(3H)-one.

[00369] LCMS (m/z +1) 370.16.

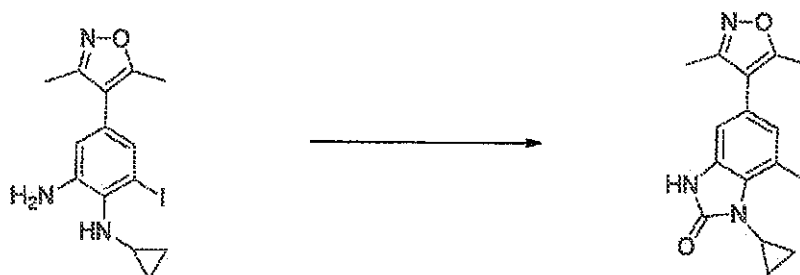
Step 2: N-cyclopropyl-4-(3,5-dimethylisoxazol-4-yl)-2-iodo-6-nitroaniline



[00370] To a mixture of 4-(4-bromo-3-iodo-5-nitrophenyl)-3,5-dimethylisoxazole (1 g, 2.36 mmol, 1 equiv.) in a pressure tube was added NMP (10 mL) and cyclopropylamine (982 μ L, 14.2 mmol, 6 equiv.). The mixture was heated to 130°C for 60 minutes in a microwave reactor. The reaction was concentrated under reduced pressure and purified by flash column chromatography to provide N-cyclopropyl-4-(3,5-dimethylisoxazol-4-yl)-2-iodo-6-nitroaniline.

[00371] LCMS (m/z +1) 400.02

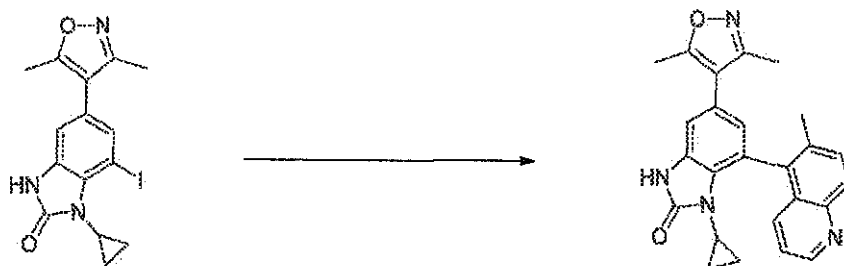
Step 3: 1-cyclopropyl-5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1H-benzo[d]imidazol-2(3H)-one



10

[00372] To a mixture of N1-cyclopropyl-4-(3,5-dimethylisoxazol-4-yl)-6-iodobenzene-1,2-diamine (170 mg, 0.46 mmol, 1 equiv.) in a pressure tube was added THF (5 mL) and CDI (223 mg, 1.38 mmol, 3 equiv.). The mixture was heated to 120°C for 30 minutes in a microwave reactor. The reaction was concentrated in vacuo and purified by HPLC to provide 1-cyclopropyl-5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1H-benzo[d]imidazol-2(3H)-one. LCMS (m/z +1) 396.3.

Step 4:



[00373] To a microwave vial containing 1-cyclopropyl-5-(3,5-dimethylisoxazol-4-yl)-7-iodo-1H-benzo[d]imidazol-2(3H)-one (25 mg, 0.063 mmol, 1 equiv.) was added 3,5-6-methylquinolin-5-ylboronic acid (71 mg, 0.38 mmol, 6 equiv.), Pd(dppf)Cl₂.CH₂Cl₂ (11 mg, 0.013 mmol, 0.1 equiv.) and DBU (76 μ L, 0.51 mmol, 8 equiv.) and dissolved in DMSO-H₂O (4 mL, 0.2 M, 2/1, v/v). The mixture was heated to 140 °C for 30 minutes in the microwave reactor.. Purification was carried out by reverse phase HPLC.

[00374] ¹H NMR (400 MHz, Methanol-d₄) δ 8.80 (dd, *J* = 4.4, 1.6 Hz, 1H), 8.10 – 7.98 (m, 1H), 7.93 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.79 (d, *J* = 8.7 Hz, 1H), 7.47 (dd, *J* = 8.6, 4.3 Hz, 1H), 7.13 (d, *J* = 1.7 Hz, 1H), 6.85 (d, *J* = 1.7 Hz, 1H), 4.57 (s, 0H), 2.42 (s, 3H), 2.39 (s, 3H), 2.27 (s, 3H), 1.93 (dt, *J* = 7.0, 3.4 Hz, 1H). LCMS (*m/z* +1) 411.24.

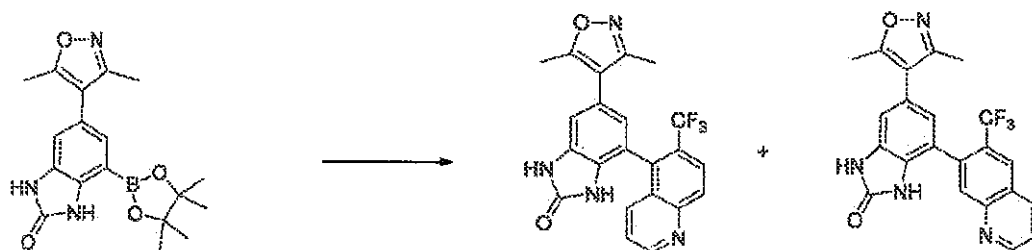
Example 125, and

Example 126

15 6-(3,5-dimethylisoxazol-4-yl)-4-(6-(trifluoromethyl)quinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one

and

6-(3,5-dimethylisoxazol-4-yl)-4-(6-(trifluoromethyl)quinolin-7-yl)-1H-benzo[d]imidazol-2(3H)-one



[00375] To a microwave vial containing 6-(3,5-dimethylisoxazol-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one (100 mg, 0.28 mmol, 1 equiv.) was added 5-chloro-6-(trifluoromethyl)quinolone (140 mg, 0.56 mmol, 2 equiv.),
 5 Cs₂CO₃ (450 mg, 1.41 mmol, 5 equiv.) and PEPPSI™-IPr catalyst (45 mg, 0.056 mmol, 0.2 equiv.) and dissolved in DME-H₂O (4 mL, 0.2 M, 2/1, v/v). The mixture was heated to 120°C for 30 min in microwave. The reaction was concentrated in vacuo and purification was carried out by reverse phase HPLC.

[00376] ¹H NMR (400 MHz, Methanol-d₄) δ 9.00 (dd, J = 4.2, 1.6 Hz, 1H), 8.32 (d, J = 9.1 Hz, 1H), 8.19 (d, J = 9.0 Hz, 1H), 7.97 – 7.76 (m, 1H), 7.56 (dd, J = 8.6, 4.3 Hz, 1H), 7.16 (d, J = 1.5 Hz, 1H), 6.91 (d, J = 1.4 Hz, 1H), 2.42 (s, 3H), 2.27 (s, 3H). LCMS (m/z +1) 425.38

[00377] ¹H NMR (400 MHz, Methanol-d₄) δ 9.03 (ddd, J = 20.6, 4.3, 1.6 Hz, 1H), 8.69 – 8.48 (m, 1H), 8.32 (d, J = 9.0 Hz, 0H), 8.19 (d, J = 9.0 Hz, 0H), 8.09 (s, 1H), 7.86 (d, J = 8.7 Hz, 0H), 7.72 (dd, J = 8.4, 4.4 Hz, 1H), 7.56 (dd, J = 8.6, 4.3 Hz, 0H), 7.12 (dd, J = 32.1, 1.5 Hz, 1H), 6.93 (d, J = 10.3 Hz, 1H), 2.42 (s, 3H), 2.27 (s, 3H). LCMS (m/z +1) 425.38.

Example 127 and

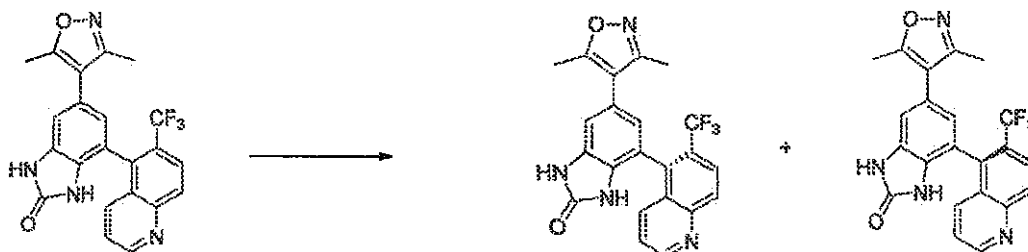
20

Example 128

(S)-6-(3,5-dimethylisoxazol-4-yl)-4-(6-(trifluoromethyl)quinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one

and

(R)-6-(3,5-dimethylisoxazol-4-yl)-4-(6-(trifluoromethyl)quinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one

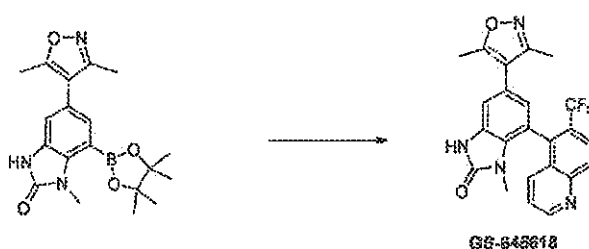


[00378] The crude was separated to provide the two atropisomers using HPLC chiral separation.

[00379] ^1H NMR (400 MHz, Methanol- d_4) δ 9.00 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.32 (d, $J = 9.1$ Hz, 1H), 8.19 (d, $J = 9.0$ Hz, 1H), 7.97 – 7.76 (m, 1H), 7.56 (dd, $J = 8.6, 4.3$ Hz, 1H), 7.16 (d, $J = 1.5$ Hz, 1H), 6.91 (d, $J = 1.4$ Hz, 1H), 2.42 (s, 3H), 2.27 (s, 3H). LCMS ($m/z + 1$) 425.38.

Example 129

5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(6-(trifluoromethyl)quinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one



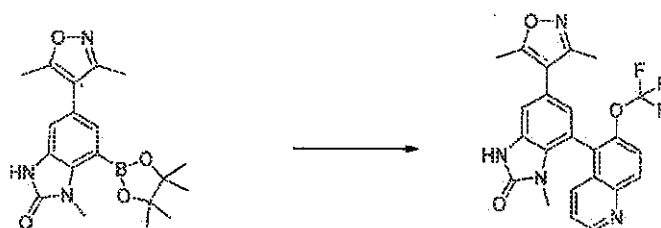
[00380] To a microwave vial containing 5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one (30 mg, 0.08 mmol, 1 equiv.) was added 5-bromo-6-(trifluoromethyl)quinoline (68 mg, 0.24 mmol, 3 equiv.), Cs_2CO_3 (105 mg, 0.33 mmol, 4 equiv.) and PEPPSITM-IPr catalyst (11 mg, 0.016 mmol, 0.2 equiv.) and dissolved in DME- H_2O (4 mL, 0.2 M, 2/1, v/v). The mixture was

heated to 120°C for 30 min in microwave. The reaction was concentrated in vacuo and purification was then carried out by reverse phase HPLC.

[00381] ¹H NMR (400 MHz, Methanol-*d*₄) δ 9.28 (s, 1H), 8.30 – 8.19 (m, 1H), 7.98 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.70 (ddd, *J* = 8.3, 6.9, 1.2 Hz, 1H), 7.59 – 7.44 (m, 1H), 7.23 (d, *J* = 1.6 Hz, 1H), 6.92 (d, *J* = 1.5 Hz, 1H), 2.54 (s, 4H), 2.41 (s, 3H), 2.25 (s, 4H). LCMS (*m/z* + 1) 385.22

Example 130

5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(6-(trifluoromethoxy)quinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one

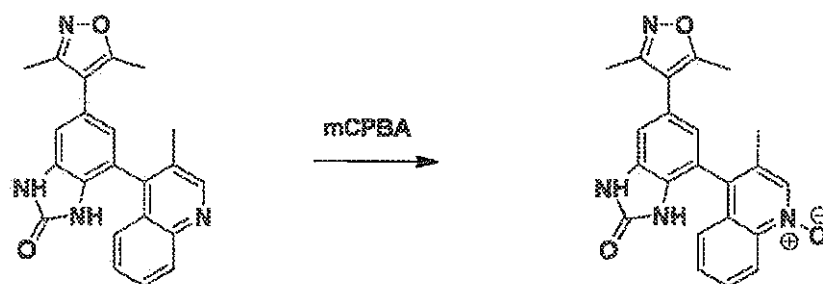


[00382] To a microwave vial containing 5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one (52 mg, 0.14 mmol, 1 equiv.) was added 5-bromo-6-(trifluoromethoxy)quinoline (124 mg, 0.42 mmol, 3 equiv.), Cs₂CO₃ (230 mg, 0.70 mmol, 5 equiv.) and PEPPSI™-IPr catalyst (9.5 mg, 0.014 mmol, 0.1 equiv.) and dissolved in DME-H₂O (4 mL, 0.2 M, 2/1, v/v). The mixture was heated to 120°C for 30 min in microwave. The reaction was concentrated in vacuo and purification was then carried out by reverse phase HPLC.

[00383] ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.97 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.31 (d, *J* = 9.4 Hz, 1H), 8.11 – 7.83 (m, 2H), 7.59 (dd, *J* = 8.6, 4.3 Hz, 1H), 7.20 (d, *J* = 1.6 Hz, 1H), 6.89 (s, 1H), 2.61 (s, 3H), 2.41 (s, 3H), 2.26 (s, 3H). ¹⁹F NMR (376 MHz, Methanol-*d*₄) δ -58.53. LCMS (*m/z* + 1) 455.29

Example 131

4-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-3-methylquinoline 1-oxide



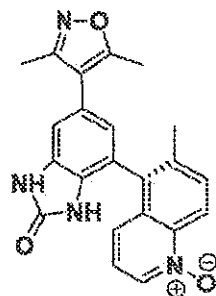
- 5 [00384] A solution of 6-(3,5-dimethylisoxazol-4-yl)-4-(3-methylquinolin-4-yl)-1H-benzo[d]imidazol-2(3H)-one (30 mg, 0.08 mmol) and mCPBA (100 mg, 0.58 mmol) in dichloromethane (0.5 mL) and methanol (0.5 mL) was stirred for 1 hour at room temperature. The reaction was quenched with sodium sulfite solution, extracted with ethyl acetate and purified by reverse-phase HPLC.

- 10 [00385] C₂₂H₁₈N₄O₃. 387.1 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.90 (d, *J* = 1.9 Hz, 1H), 10.48 (d, *J* = 2.0 Hz, 1H), 8.73 (s, 1H), 8.62 – 8.56 (m, 1H), 7.81 – 7.75 (m, 1H), 7.63 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.41 (dd, *J* = 8.6, 1.3 Hz, 1H), 7.10 – 7.02 (m, 1H), 6.88 (d, *J* = 1.6 Hz, 1H), 2.43 (s, 3H), 2.25 (s, 3H), 2.17 (s, 3H).

15

Example 132

(R)-5-(6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-6-methylquinoline 1-oxide

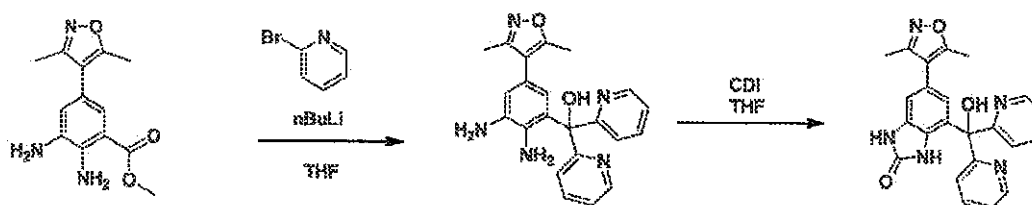


[00386] $C_{22}H_{18}N_4O_3$. 387.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.86 (d, J = 2.2 Hz, 1H), 10.40 (s, 1H), 8.63 – 8.48 (m, 2H), 7.80 (d, J = 9.0 Hz, 1H), 7.34 (dd, J = 8.8, 6.0 Hz, 1H), 7.26 – 7.15 (m, 1H), 7.05 – 6.96 (m, 1H), 6.81 (t, J = 1.2 Hz, 1H), 2.40 (s, 3H), 2.24 (d, J = 7.9 Hz, 6H).

5

Example 133

6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxydi(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one



10 [00387] Butyllithium (1.6M solution in hexanes, 24 mL, 38 mmol) was added dropwise over 20 minutes to a solution of 2-bromopyridine (3.7 mL, 38 mmol in methyl-THF (100 mL) at -78 °C. The reaction mixture was stirred for 1 hour and a solution of methyl 2,3-diamino-5-(3,5-dimethylisoxazol-4-yl)benzoate (2.0 g, 7.7 mmol) in 20 mL of methyl-THF was added. The reaction mixture was warmed to room temperature, stirred for
15 30 minutes and quenched with water. The reaction mixture was extracted with ethyl acetate and purified by silica gel chromatography (90:9:1 ethyl acetate/methanol/ammonium hydroxide) to give (2,3-diamino-5-(3,5-dimethylisoxazol-4-yl)phenyl)di(pyridin-2-yl)methanol as an orange powder..

[00388] CDI (1.1 g, 6 mmol) was added to a solution of (2,3-diamino-5-(3,5-dimethylisoxazol-4-yl)phenyl)di(pyridin-2-yl)methanol (1.43 g, 3.7 mmol) in THF (10 mL) and the reaction mixture was stirred for 3 days. The reaction mixture was diluted with 100 mL water and 100 mL ethyl acetate and sonicated and filtered to yield the desired product.

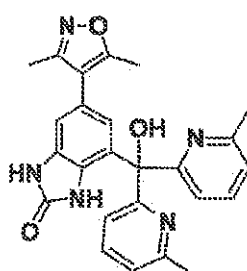
[00389] $C_{23}H_{19}N_5O_3$. 414.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.69 (d, J = 1.6 Hz, 1H), 9.79 (s, 1H), 8.49 (ddd, J = 4.9, 1.8, 0.9 Hz, 2H), 7.80 (td, J = 7.7, 1.8 Hz, 2H),
25 7.58 (dt, J = 8.0, 1.1 Hz, 2H), 7.30 (ddd, J = 7.5, 4.8, 1.1 Hz, 2H), 6.86 (s, 1H), 6.81 (d, J = 1.5 Hz, 1H), 6.56 (d, J = 1.6 Hz, 1H), 2.26 (s, 3H), 2.06 (s, 3H).

[00390] The following compound was made similarly to 6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxydi(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one using 2-pyridyl-6-magnesiumbromide:

5

Example 134

6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxybis(6-methylpyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one



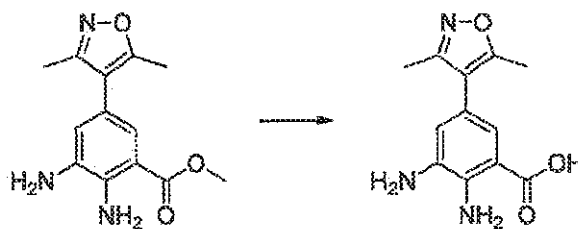
[00391] GS-694472 $C_{25}H_{23}N_5O_3$, 442.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ
 10.77 (s, 1H), 10.07 (s, 1H), 7.89 (d, J = 17.5 Hz, 2H), 7.51 (t, J = 8.0 Hz, 2H), 7.39 (d, J =
 37.6 Hz, 2H), 6.86 (d, J = 1.3 Hz, 1H), 2.50 (s, 6H), 2.27 (s, 3H), 2.08 (s, 3H).

15

Example 135

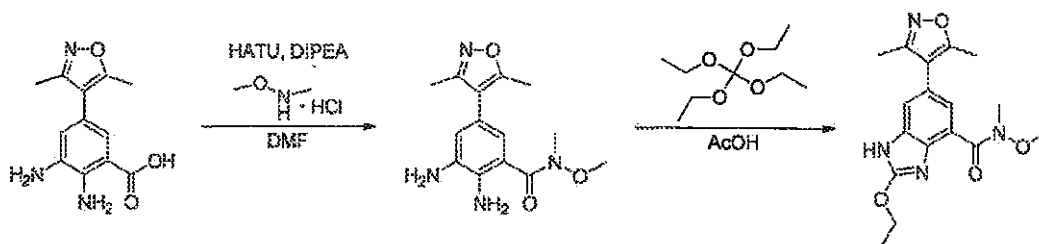
6-(3,5-dimethylisoxazol-4-yl)-4-(1-hydroxy-2-methyl-1-(pyridin-2-yl)butyl)-1H-benzo[d]imidazol-2(3H)-one

Step 1:



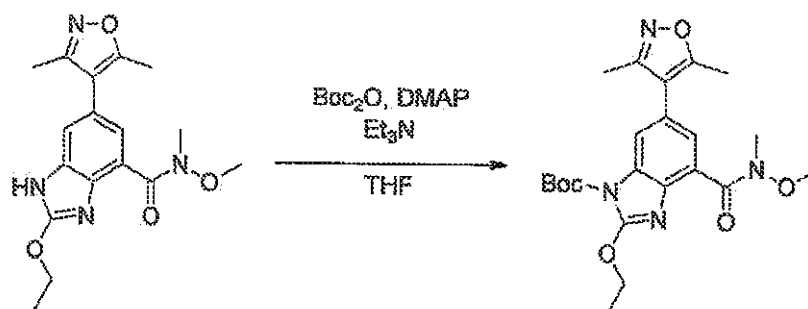
[00392] Methyl ester (25 g, 0.096 mol) was dissolved in a mixture of MeOH (400 mL) and 1 M NaOH (200 mL), an air condenser was attached and the reaction was heated to 60 °C for 1.5 hours. Reaction was allowed to cool to room temperature and concentrated in vacuo. The residue was then diluted in a minimal amount of water and neutralized with 1 M HCl until pH 6-7. The precipitate was collected by vacuum filtration, taken up in MeOH, and concentrated in vacuo to give 2,3-diamino-5-(3,5-dimethylisoxazol-4-yl)benzoic acid as a brown powder. Material was used without further purification.

[00393] C₁₂H₁₃N₃O₃ 248.1 (M + 1)

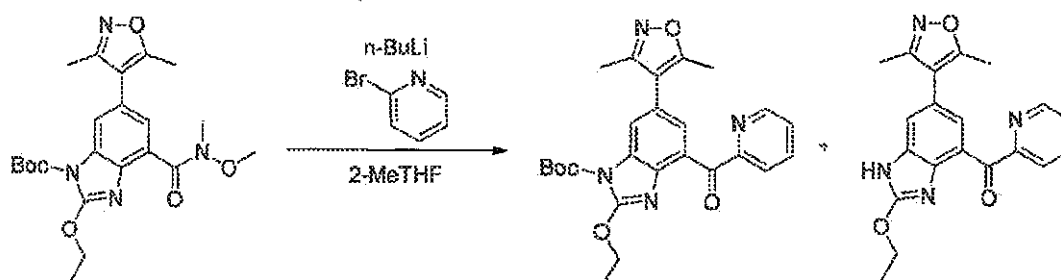


[00394] 2,3-diamino-5-(3,5-dimethylisoxazol-4-yl)benzoic acid (22 g, 0.089 mol) was dissolved in DMF (C=3.0 M) and HATU (1.3 eq), DIPEA (7 eq), and N,O-dimethylhydroxylamine hydrochloride (2.5 eq) were added in one portion and the reaction was allowed to stir under air at room temperature for 1 hr. The reaction was concentrated in vacuo and the residue was dissolved in ethyl acetate. The solution was washed once with NaHCO₃ and three times with brine. The crude was concentrated in vacuo and purified via silica gel chromatography to give 2,3-diamino-5-(3,5-dimethylisoxazol-4-yl)-N-methoxy-N-methylbenzamide as a light brown powder.

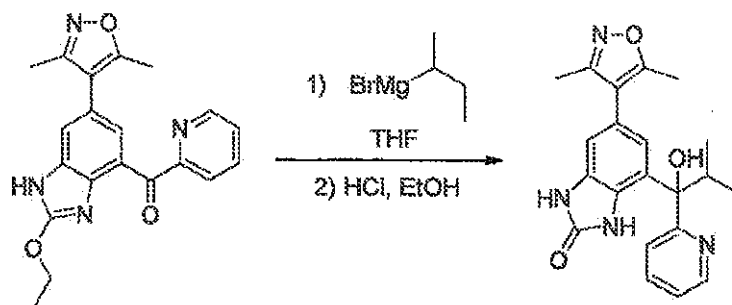
[00395] 2,3-diamino-5-(3,5-dimethylisoxazol-4-yl)-N-methoxy-N-methylbenzamide (25 g, 0.086 mol) was dissolved in a 1:1 mixture (32 mL total) of tetraethylorthocarbonate and AcOH and allowed to stir under air at room temperature for 1.5 hr. The reaction mixture was concentrated in vacuo at room temperature and the crude residue was dissolved in EtOAc. The solution was washed three times with bicarb, once with water, and organic layer was concentrated in vacuo to give 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-N-methoxy-N-methyl-1H-benzo[d]imidazole-4-carboxamide as a dark oil. Crude material was used without further purification.



- [00396] 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-N-methoxy-N-methyl-1H-benzo[d]imidazole-4-carboxamide (23 g, 0.067 mol) was dissolved in THF (80 mL, 1.0 M) and Boc_2O (2 eq), DMAP (0.4 eq), and triethylamine (3.5 eq) were added to the reaction mixture and allowed to stir under air at room temperature for 1 hr. Reaction mixture was then concentrated in vacuo and purified by silica gel chromatography (80-100 % EtOAc/hex) to give tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(methoxy(methyl)carbamoyl)-1H-benzo[d]imidazole-1-carboxylate (5) as a white powder.



- [00397] 2-bromopyridine (4.5 mmol, 2 eq) was dissolved in 2-MeTHF ($C=0.15$ M) and cooled to -78°C under Ar. $n\text{-BuLi}$ (1.6 M, 2 eq) was added dropwise to the solution over 15 minutes and the reaction was allowed to stir at -78°C for 1 hour. tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(methoxy(methyl)carbamoyl)-1H-benzo[d]imidazole-1-carboxylate (1 g, 2.25 mmol) was dissolved in a minimal amount of 2-MeTHF and added to the reaction via syringe in one portion and the reaction was then allowed to slowly warm to room temperature. The reaction was quenched with water, diluted with EtOAc, washed twice with brine, and concentrated in vacuo. The crude material was purified by silica gel chromatography to give tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-picolinoyl-1H-benzo[d]imidazole-1-carboxylate (300 mg, 29%) as a yellow powder and 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl(pyridin-2-yl)methanone (460 mg, 56%) as a pale yellow powder.



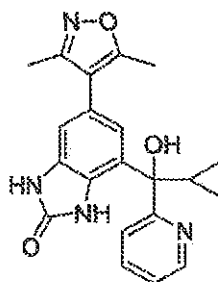
[00398] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanone (20 mg, 0.055 mmol) was dissolved in dry THF (0.55 mL) under argon. Sec-butylmagnesium bromide (1.0 M in THF, 0.27 mL, 0.28 mmol) was added dropwise and the reaction was allowed to stir for 10 minutes. The reaction was quenched with water, concentrated and purified by reverse-phase HPLC to give 1-(6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)-2-methyl-1-(pyridin-2-yl)butan-1-ol intermediate. Intermediate was taken up in 0.5 mL EtOH and 0.3 mL 4.0M HCl/dioxane and heated to 65°C for 1 hr. Reaction was concentrated and purified by reverse phase HPLC to afford the desired product

[00399] $C_{22}H_{24}N_4O_3$ 393.5 (M + 1). ^1H NMR (400 MHz, DMSO- d_6) δ 10.64 (s, 1H), 9.99 (s, 1H), 8.54 (s, 1H), 7.84 (s, 2H), 7.27 (s, 1H), 7.11 (t, J = 1.8 Hz, 1H), 6.71 (d, J = 3.1 Hz, 1H), 2.36 (d, J = 5.7 Hz, 3H), 2.18 (d, J = 5.8 Hz, 3H), 0.87 (t, J = 7.3 Hz, 5H), 0.80 (d, J = 7.2 Hz, 3H), 0.62 (d, J = 6.5 Hz, 2H).

15

Example 136

4-(cyclopropyl(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



[00400] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanone (40 mg, 0.11 mmol) was dissolved in dry THF (1.1 mL) and cyclopropylmagnesium bromide (0.5 M in diethylether, 1.1 mL, 0.55 mmol) was added dropwise at rt and the reaction was allowed to stir for 10 minutes. The reaction was
 5 quenched with water, concentrated, and purified by reverse-phase HPLC to give cyclopropyl(6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanol intermediate which was taken up in 1.0 mL EtOH and 0.7 mL 4.0M HCl/dioxane and heated for 2 hours at 65°C. Reaction was then concentrated down and purified by reverse-phase HPLC to afford the desired product as a white powder.

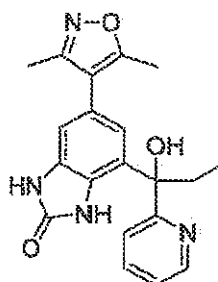
10 [00401] C₂₁H₂₀N₄O₃ 377.3 (M+1)

[00402] ¹H NMR (400 MHz, DMSO-d₆) δ 10.66 (s, 1H), 9.73 (s, 1H), 8.54 (s, 1H), 7.92 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.40 (s, 1H), 7.27 (s, 1H), 6.81 (s, 1H), 2.39 (s, 3H), 2.21 (s, 3H), 2.01 (s, 1H), 0.54 (d, J = 5.6 Hz, 3H), 0.29 (d, J = 10.3 Hz, 1H).

15

Example 137

6-(3,5-dimethylisoxazol-4-yl)-4-(1-hydroxy-1-(pyridin-2-yl)propyl)-1H-benzo[d]imidazol-2(3H)-one



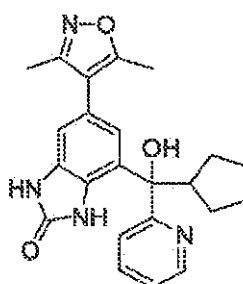
[00403] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanone (20 mg, 0.055 mmol) was dissolved in dry THF (0.5 mL) and ethylmagnesium bromide (1.0 M, 0.27 mL, 0.27 mmol) was added dropwise. The reaction was allowed to stir at r.t. for 10 minutes and then a mixture of EtOH (1 mL) and 4.0M HCl/dioxane (0.5 mL) was added and the reaction was heated to 65 °C for 3 hours. The reaction was concentrated and purified by reverse-phase HPLC to afford the desired product
 20 as a white powder.
 25

[00404] C₂₀H₂₀N₄O₃ 365.1 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 10.67 (s, 1H), 9.89 (s, 1H), 8.57 (s, 1H), 7.88 (s, 2H), 7.35 (s, 1H), 6.97 (s, 1H), 6.75 (s, 1H), 2.42 (d, J = 9.1 Hz, 2H), 2.35 (s, 3H), 2.17 (s, 3H), 0.79 (t, J = 7.2 Hz, 3H).

5

Example 138

4-(cyclopentyl(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



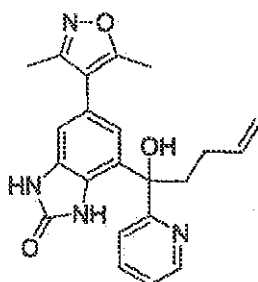
[00405] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanone (50 mg, 0.14 mmol) was dissolved in dry THF (1.4 mL) under argon and cooled to 0 °C. Cyclopentylmagnesium chloride (2.0 M, 0.14 mL, 0.28 mmol) was added dropwise and reaction was allowed to stir for 10 minutes then quenched with water. Reaction mixture was extracted three times with EtOAc and combined organic layers were washed once with water and concentrated. Residue was taken up in EtOH (1.5 mL) and 4.0M HCl/dioxane (0.75 mL) and heated to 65 °C for 2 hours. Reaction was concentrated and purified by reverse-phase HPLC to afford the desired product as a white powder.

[00406] C₂₃H₂₄N₄O₃ . 405.2 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 10.77 (d, J = 5.3 Hz, 1H), 10.03 (s, 1H), 8.67 (s, 1H), 8.14 (s, 1H), 7.94 (s, 1H), 7.61 (s, 1H), 7.19 (s, 1H), 6.80 (s, 1H), 3.55 – 3.45 (m, 1H), 2.39 (s, 3H), 2.22 (s, 3H), 1.69 – 1.60 (m, 2H), 1.55 (dd, J = 11.5, 5.4 Hz, 3H), 1.46 (d, J = 7.7 Hz, 1H), 1.31 (d, J = 11.1 Hz, 1H), 1.12 (s, 1H).

20

Example 139

6-(3,5-dimethylisoxazol-4-yl)-4-(1-hydroxy-1-(pyridin-2-yl)pent-4-en-1-yl)-1H-benzo[d]imidazol-2(3H)-one

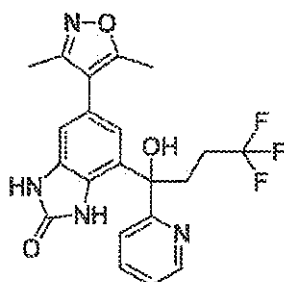


[00407] Magnesium metal (20 mg, 0.82 mmol) was taken up in THF (1.5 mL) and (bromomethyl) cyclopropane (100 mg, 0.71 mmol) was added dropwise and the reaction was heated to 65 °C for 1 hr. (Cyclopropylmethyl)magnesium bromide (0.5 M, 0.83 mL, 0.41 mmol) was then added dropwise to a solution of 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl(pyridin-2-yl)methanone (50 mg, 0.14 mmol) in dry THF (1.4 mL) which was cooled to 0 °C. Reaction mixture was allowed to stir for 10 mins, quenched with water and extracted three times with EtOAc. Combined organic layers were washed once with water and concentrated. Residue was dissolved in a mixture of EtOH (1.5 mL) and 4.0M HCl/dioxane (0.75 mL) and heated for 2 hours at 65 °C. Reaction was then concentrated and purified by reverse-phase HPLC to afford the desired product as a white powder.

[00408] C₂₂H₂₂N₄O₃. 391.5 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 10.68 (s, 1H), 9.93 (s, 1H), 8.55 (s, 1H), 7.88 (s, 2H), 7.32 (s, 1H), 6.95 (s, 1H), 6.75 (s, 1H), 5.82 (dd, J = 9.8, 7.0 Hz, 1H), 5.00 – 4.85 (m, 3H), 2.35 (s, 3H), 2.16 (s, 3H), 2.10-1.90 (m, 4H).

Example 140

6-(3,5-dimethylisoxazol-4-yl)-4-(4,4,4-trifluoro-1-hydroxy-1-(pyridin-2-yl)butyl)-1H-benzo[d]imidazol-2(3H)-one

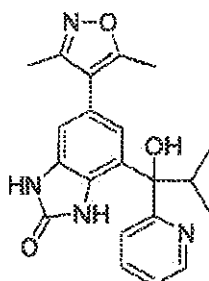


[00409] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanone (50 mg, 0.14 mmol) was dissolved in dry THF (1.4 mL) and cooled to 0 °C. (3,3,3-trifluoropropyl)magnesium bromide (0.5 M, 0.55 mL, 0.28 mmol) was added dropwise and the reaction was allowed to stir for 10 mins and then quenched with water. Reaction was
 5 extracted three times with EtOAc and combined organic layers were washed once with water and concentrated. Residue was taken up in EtOH (1.5 mL) and 4.0M HCl/dioxane (0.75 mL), heated to 65 °C for two hours, concentrated, then purified by reverse-phase HPLC to afford the desired product as a white powder.

[00410] C₂₁H₁₉F₃N₄O₃ 433.4 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 10.72 (s, 1H), 10.05 (s, 1H), 8.56 (d, J = 4.6 Hz, 1H), 7.88 (s, 2H), 7.31 (s, 1H), 6.82 (s, 1H), 6.76 (s, 1H), 2.67 (s, 1H), 2.60 (d, J = 4.0 Hz, 1H), 2.32 (s, 4H), 2.16 (s, 2H), 2.13 (s, 3H).

Example 141

15 6-(3,5-dimethylisoxazol-4-yl)-4-(1-hydroxy-2-methyl-1-(pyridin-2-yl)propyl)-1H-benzo[d]imidazol-2(3H)-one



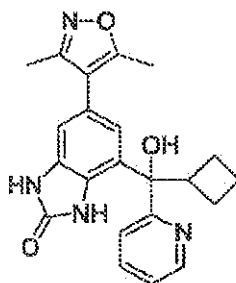
[00411] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanone (50 mg, 0.14 mmol) was dissolved in dry THF (1.4 mL) and cooled to 0 °C. Isopropylmagnesium bromide (2.0 M, 0.14 mL, 0.28 mmol) was added dropwise and the
 20 reaction was allowed to stir for 10 mins and then quenched with water. Reaction was extracted three times with EtOAc and combined organic layers were washed once with water and concentrated. Residue was taken up in EtOH (1.5 mL) and 4.0M HCl/dioxane (0.75 mL), heated to 65 °C for two hours, concentrated, then purified by reverse-phase HPLC to afford the desired product as a white powder.

[00412] C₂₁H₂₂N₄O₃ 379.3 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 10.70 (s, 1H), 10.01 (d, J = 2.1 Hz, 1H), 8.60 (s, 1H), 7.91 (s, 2H), 7.41 (s, 1H), 7.15 (s, 1H), 6.74 (s, 1H), 3.17 (s, 1H), 2.37 (s, 3H), 2.33 (d, J = 1.7 Hz, 0H), 2.20 (s, 3H), 2.15 (s, 0H), 1.23 (d, J = 6.7 Hz, 1H), 0.93 (d, J = 6.0 Hz, 3H), 0.65 (d, J = 6.9 Hz, 3H).

5

Example 142

4-(cyclobutyl(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



10 [00413] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanone (50 mg, 0.14 mmol) was dissolved in dry THF (1.4 mL) and cooled to 0 °C. Cyclobutylmagnesium chloride (0.5 M, 1.1 mL, 0.55 mmol) was added dropwise and the reaction was allowed to stir for 10 mins and then quenched with water. Reaction was extracted three times with EtOAc and combined organic layers were washed once with water, concentrated, and purified by reverse-phase HPLC to give cyclobutyl(6-(3,5-

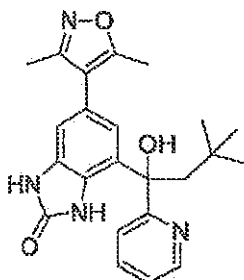
15 dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanol intermediate. The intermediate was taken up in EtOH (1.5 mL) and 4.0 M HCl/dioxane and heated to 65 °C for 2 hours, concentrated and purified by reverse-phase HPLC to afford the desired product as a white powder.

20 [00414] C₂₂H₂₂N₄O₃ 391.5 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 10.70 (s, 1H), 9.93 (d, J = 2.6 Hz, 1H), 8.58 (s, 1H), 7.96 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.43 (s, 1H), 7.00 (s, 1H), 6.79 (d, J = 2.1 Hz, 1H), 3.82 – 3.71 (m, 1H), 2.39 (s, 3H), 2.21 (s, 3H), 2.19 – 2.10 (m, 1H), 2.02 – 1.94 (m, 1H), 1.91 (s, 1H), 1.80 (q, J = 9.1 Hz, 1H), 1.67 (t, J = 9.7 Hz, 1H), 1.44 (q, J = 6.2, 3.9 Hz, 1H).

25

Example 143

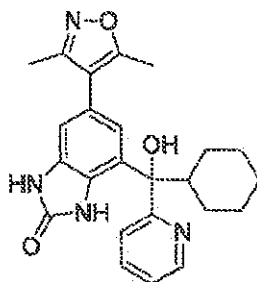
6-(3,5-dimethylisoxazol-4-yl)-4-(1-hydroxy-3,3-dimethyl-1-(pyridin-2-yl)butyl)-1H-benzo[d]imidazol-2(3H)-one



- 5 [00415] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanone (50 mg, 0.14 mmol) was dissolved in dry THF (1.4 mL) and cooled to 0 °C. Neopentylmagnesium chloride (1.0 M, 0.55 mL, 0.55 mmol) was added dropwise and the reaction was allowed to stir for 10 mins and then quenched with water. Reaction was extracted three times with EtOAc and combined organic layers were washed once with water,
- 10 concentrated, and purified by reverse-phase HPLC to give 1-(6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)-3,3-dimethyl-1-(pyridin-2-yl)butan-1-ol intermediate. The intermediate was taken up in EtOH (1.5 mL) and 4.0 M HCl/dioxane and heated to 65 °C for 2 hours, concentrated and purified by reverse-phase HPLC to afford the desired product as a white powder.
- 15 [00416] C₂₃H₂₆N₄O₃ 407.3 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 10.70 (d, J = 4.6 Hz, 1H), 9.94 (d, J = 2.5 Hz, 1H), 8.58 (s, 1H), 7.98 (s, 2H), 7.38 (s, 1H), 7.09 (d, J = 2.5 Hz, 1H), 6.73 (d, J = 2.9 Hz, 1H), 2.51 (s, 2H), 2.35 (s, 3H), 2.17 (d, J = 1.0 Hz, 3H), 0.79 (s, 9H).

Example 144

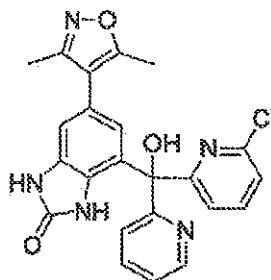
4-(cyclohexyl(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



- 5 [00417] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanone (50 mg, 0.14 mmol) was dissolved in dry THF (1.4 mL) and cooled to 0 °C. Cyclohexylmagnesium chloride (2.0 M, 0.21 mL, 0.41 mmol) was added dropwise and the reaction was allowed to stir for 10 mins and then quenched with water. Reaction was extracted three times with EtOAc and combined organic layers were washed once with water, concentrated, and purified by reverse-phase HPLC to give cyclohexyl(6-(3,5-
- 10 dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanol intermediate. The intermediate was taken up in EtOH (1.5 mL) and 0.2mL concentrated HCl and heated to 65 °C for 2 hours and concentrated afford the desired product as a white powder.
- 15 [00418] C₂₄H₂₆N₄O₃ 419.8 (M+1). ¹H NMR (400 MHz, Methanol-d₄) δ 8.77 (d, J = 5.7 Hz, 1H), 8.54 (t, J = 7.5 Hz, 1H), 8.15 (d, J = 7.9 Hz, 1H), 7.97 (dd, J = 7.3, 5.7 Hz, 1H), 7.24 (d, J = 1.4 Hz, 1H), 6.99 (d, J = 1.2 Hz, 1H), 2.84 (d, J = 10.6 Hz, 1H), 2.42 (s, 3H), 2.27 (s, 3H), 2.00 – 1.72 (m, 5H), 1.55 – 1.33 (m, 5H).

Example 145

4-((6-chloropyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-
1H-benzo[d]imidazol-2(3H)-one

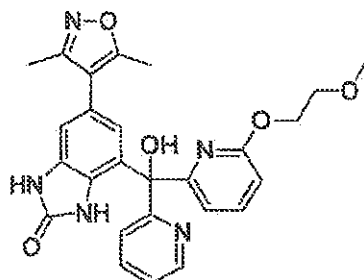


5 [00419] To a solution of 2-bromo-6-chloropyridine (83 mg, 0.43 mmol) in 2-MeTHF (1.5 mL) cooled to -78 °C was added n-BuLi (1.6 M, 0.27 mL, 0.43 mmol) dropwise and the reaction was allowed to stir for 40 mins. A solution of (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanone (100 mg, 0.22 mmol) in 2-MeTHF (0.5 mL) was added to the reaction and the reaction was allowed to stir for an
10 additional 10 mins at -78 °C and then quenched with water. The reaction mixture was extracted three times with EtOAc and combined organic layers were washed once with water, concentrated, and purified by silica gel chromatography to yield (6-chloropyridin-2-yl)(6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)methanol (51 mg, 41%) as a white solid. The solid (26.5 mg, 0.055 mmol) was taken up in EtOH (1 mL)
15 and 4M HCl/dioxane (0.5 mL) and heated for two hours at 65 °C and then concentrated to afford the desired product as a pale yellow powder.

[00420] C₂₃H₁₈ClN₅O₃ 448.9 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 10.80 – 10.72 (m, 1H), 9.87 (s, 1H), 8.54 (d, J = 4.8 Hz, 1H), 7.89 (t, J = 7.9 Hz, 2H), 7.63 (d, J = 8.1 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.45 (d, J = 7.9 Hz, 1H), 7.39 (s, 1H), 6.86 (s, 1H), 6.51 (s,
20 1H), 2.30 (s, 3H), 2.10 (s, 3H).

Example 146

6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(6-(2-methoxyethoxy)pyridin-2-yl)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one

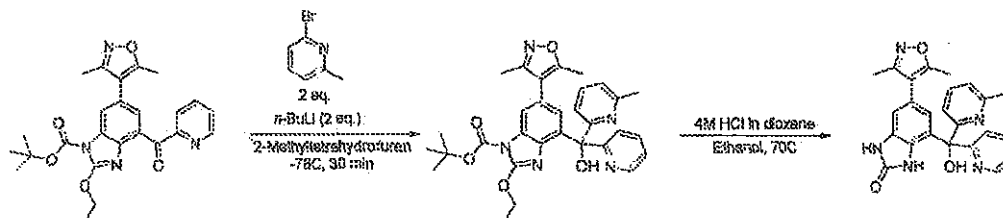


- 5 [00421] 2-methoxyethanol (25 mg, 0.33 mmol) was dissolved in THF (0.5 mL) and cooled to 0 °C. Sodium hydride (8 mg, 0.33 mmol) was added in one portion and the reaction was allowed to come to rt and stir for 10 minutes. The reaction was then cooled back to 0 °C and tert-butyl 4-((6-chloropyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate (24 mg, 0.04 mmol)
- 10 was added and the reaction was sealed and heated to 80 °C overnight. Reaction was concentrated and the residue was taken up in EtOH (1.5 mL) and 4M HCl/dioxane (0.5 mL) and heated for 2 hours at 60 °C. The reaction was cooled to rt and filtered to remove the sodium salt. Filtrate was concentrated to afford the desired product as a brown film.

- [00422] C₂₆H₂₅N₅O₅ 488.5 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 10.81 (s, 1H), 9.97 (s, 1H), 8.63 (s, 1H), 7.77 (d, J = 7.9 Hz, 1H), 7.69 (s, 1H), 7.28 (s, 1H), 6.89 (s, 1H), 6.81 – 6.72 (m, 1H), 6.41 (s, 1H), 4.10 (d, J = 4.5 Hz, 2H), 3.75 – 3.61 (m, 2H), 3.15 (s, 3H), 2.26 (s, 3H), 2.06 (s, 3H).
- 15

Example 147

6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(6-methylpyridin-2-yl)(pyridin-2-yl)methyl)-
1H-benzo[d]imidazol-2(3H)-one



- 5 [00423] In a 2-neck, 50-mL round-bottom flask, a solution of 6-bromo-2-picoline (28.6 mg, 0.177 mmol) in 2 mL of 2-methyltetrahydrofuran was cooled to -78°C in a dry ice/acetone bath while stirring under nitrogen. To this stirring solution, a 1.42 M *n*-butyllithium solution in hexanes (0.12 mL, 0.17 mmol) was added dropwise and the reaction mixture was stirred at -78°C for 30 minutes. *Tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-picolinoyl-1H-benzo[d]imidazole-1-carboxylate (34.8 mg, 0.0752 mmol) was added dropwise in a solution of 1 mL of 2-methyltetrahydrofuran. The reaction mixture was warmed to room temperature for 30 minutes before the reaction was quenched with brine and diluted with ethyl acetate. The organic layer was separated and saved and the aqueous layer was extracted three times with ethyl acetate. The organic layers were dried over sodium sulfate, decanted and concentrated. C₃₁H₃₃N₅O₅. 556.1 (M+1).
- 10
- 15

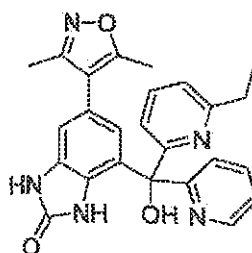
- [00424] The crude intermediate was taken up in 2 mL of ethanol and transferred to a microwave vial. 4M hydrochloric acid in dioxane (0.10 mL, 0.40 mmol) was added to the reaction mixture and the vial was sealed and heated at 70°C for 1 hour or until reaction completion. The reaction mixture was concentrated and the product was isolated by preparatory HPLC as a yellow oil.
- 20

- [00425] C₂₄H₂₁N₅O₃. 428.0 (M+1). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.68 (ddd, *J* = 5.3, 1.8, 0.9 Hz, 1H), 8.25 – 8.16 (m, 2H), 7.92 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.73 – 7.61 (m, 3H), 7.09 (d, *J* = 1.5 Hz, 1H), 6.42 (d, *J* = 1.5 Hz, 1H), 2.75 (s, 3H), 2.31 (s, 3H), 2.14 (s, 3H).
- 25

Example 148

6-(3,5-dimethylisoxazol-4-yl)-4-((6-ethylpyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one

[00426] A procedure similar to that used for Example 162 was used to produce the
 5 intermediate ($C_{22}H_{23}N_5O_3$, 570.1(M+1)), which was taken directly to the deprotection step to yield a yellow oil.

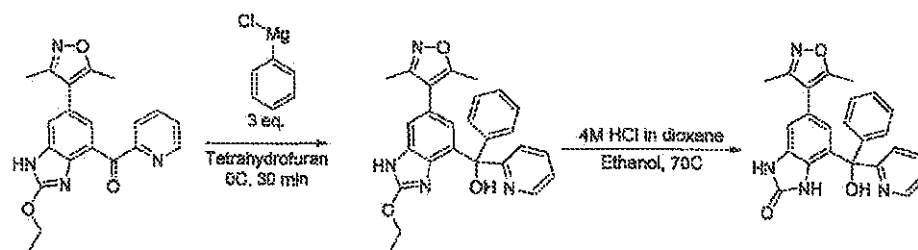


[00427] $C_{25}H_{23}N_5O_3$, 442.0 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 8.75 – 8.68 (m, 1H), 8.29 (td, J = 7.9, 1.7 Hz, 1H), 8.18 (t, J = 7.9 Hz, 1H), 7.94 (dt, J = 8.1, 1.0 Hz, 1H),
 10 7.76 (ddd, J = 7.7, 5.4, 1.1 Hz, 1H), 7.70 – 7.62 (m, 2H), 7.09 (d, J = 1.5 Hz, 1H), 6.43 (d, J = 1.5 Hz, 1H), 3.00 (q, J = 7.6 Hz, 2H), 2.31 (s, 3H), 2.13 (s, 3H), 1.32 (t, J = 7.6 Hz, 3H).

Example 149

6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(phenyl)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one

15



[00428] In a 2-neck, 50-mL round bottom flask, a solution of 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-4-carboxylic acid (31.5 mg, 0.0870 mmol) in 2 mL of tetrahydrofuran was cooled to 0°C while stirring under
 20 nitrogen. A 2M solution of phenylmagnesium chloride in tetrahydrofuran (0.13 mL, 0.26

mmol) was added dropwise to the reaction mixture and allowed to warm to room temperature for 30 minutes. The reaction mixture was quenched with 2 M aqueous hydrochloric acid and neutralized with aqueous sodium bicarbonate. The aqueous layer was extracted with ethyl acetate three times, and the combined organic layers were concentrated and taken directly to the deprotection step. C₂₆H₂₄N₄O₃, 441.1 (M+1).

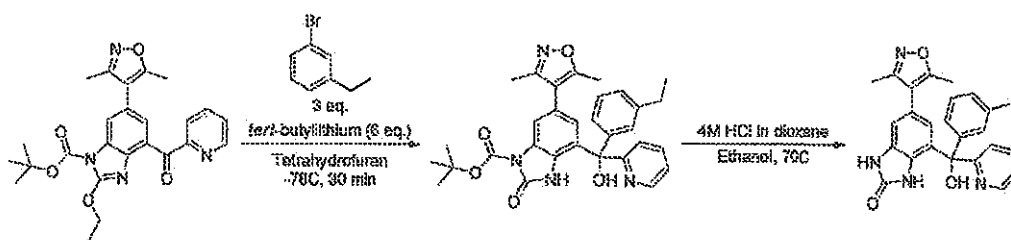
[00429] The crude intermediate was dissolved in 3 mL of ethanol and transferred to a microwave vial. Hydrochloric acid in dioxane (0.10 mL, 0.40 mmol) was added and the reaction vial was sealed and heated at 70°C for 1 hour. The reaction mixture was concentrated down and the product was isolated by preparatory HPLC as a white solid.

10 [00430] C₂₆H₂₄N₄O₃. 413.1 (M+1). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.80 (ddd, *J* = 5.6, 1.7, 0.8 Hz, 1H), 8.38 (td, *J* = 7.9, 1.7 Hz, 1H), 7.89 (ddd, *J* = 7.8, 5.6, 1.2 Hz, 1H), 7.77 (dt, *J* = 8.1, 1.0 Hz, 1H), 7.51 – 7.41 (m, 3H), 7.37 (dd, *J* = 7.9, 1.8 Hz, 2H), 7.08 (d, *J* = 1.5 Hz, 1H), 6.48 (d, *J* = 1.5 Hz, 1H), 2.30 (s, 3H), 2.13 (s, 3H).

15

Example 150

6-(3,5-dimethylisoxazol-4-yl)-4-((3-ethylphenyl)(hydroxy)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one



[00431] In a 2-neck, 50-mL round bottom flask, 1-bromo-3-ethylbenzene (43.2 mg, 0.233 mmol) was cooled to -78°C in 2 mL of tetrahydrofuran while stirring under nitrogen. A 1.47 M solution of *tert*-butyllithium in pentane (310 µL, 0.456 mmol) was added dropwise and the reaction was allowed to stir for 15 minutes. In a solution of 1 mL of tetrahydrofuran, *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-picolinoyl-1H-benzo[d]imidazole-1-carboxylate (35.0 mg, 0.0757 mmol) was added dropwise. The reaction mixture was warmed to room temperature while stirring under nitrogen for 15 minutes or until reaction completion.

The reaction mixture was slowly quenched with brine and diluted with ethyl acetate. The organic layer was separated and saved and the aqueous layer was extracted with ethyl acetate three times. The organic layers were combined, dried over sodium sulfate, decanted and concentrated.

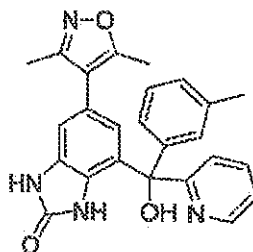
- 5 [00432] The crude intermediate was dissolved in 1 mL of ethanol and transferred to a microwave vial before 4M hydrochloric acid in dioxane (0.100 mL, 0.400 mmol) was added. The vial was sealed and heated at 70°C for one hour or until reaction completion. The reaction mixture was concentrated and isolated by preparatory HPLC to yield the title compound.
- 10 [00433] C₂₆H₂₄N₄O₃. 441.1 (M+1). ¹H NMR (400 MHz, Methanol-d₄) δ 8.89 – 8.81 (m, 1H), 8.58 (td, *J* = 8.0, 1.6 Hz, 1H), 8.08 (ddd, *J* = 7.4, 5.8, 1.2 Hz, 1H), 7.92 – 7.83 (m, 1H), 7.40 (t, *J* = 7.7 Hz, 1H), 7.36 – 7.29 (m, 2H), 7.14 (d, *J* = 1.7 Hz, 1H), 7.11 (d, *J* = 1.5 Hz, 1H), 6.47 (d, *J* = 1.5 Hz, 1H), 2.69 (q, *J* = 7.6 Hz, 2H), 2.31 (s, 3H), 2.13 (s, 3H), 1.23 (t, *J* = 7.6 Hz, 3H).

15

Example 151

6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(pyridin-2-yl)(*m*-tolyl)methyl)-1H-benzo[d]imidazol-2(3H)-one

- [00434] A procedure similar to that used for Example 165 was used to produce the intermediate (C₂₇H₂₆N₄O₃, 455.1 (M+1)) which was immediately taken forward to the deprotection step to yield a yellow solid (7.7 mg, 23%).
- 20



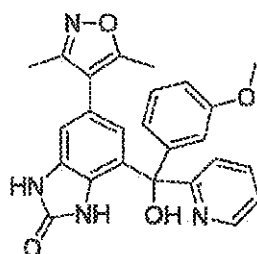
- [00435] C₂₅H₂₂N₄O₃. 427.1 (M+1). ¹H NMR (400 MHz, Methanol-d₄) δ 8.87 (dd, *J* = 6.0, 1.4 Hz, 1H), 8.61 (td, *J* = 7.9, 1.5 Hz, 1H), 8.16 – 8.06 (m, 1H), 7.90 (d, *J* = 8.1 Hz, 1H),

7.39 (t, $J = 7.7$ Hz, 1H), 7.34 – 7.25 (m, 2H), 7.14 (d, $J = 7.8$ Hz, 1H), 7.12 (d, $J = 1.5$ Hz, 1H), 6.48 (d, $J = 1.5$ Hz, 1H), 2.38 (s, 3H), 2.32 (s, 3H), 2.14 (s, 3H).

Example 152

5 6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(3-methoxyphenyl)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one

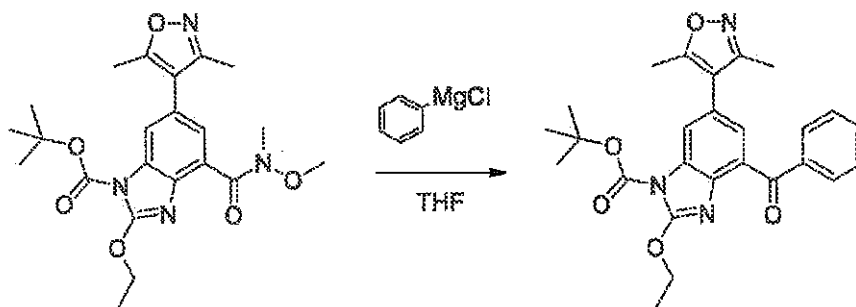
[00436] A procedure similar to that used to synthesize the compound of Example 166 was used to produce the product as a white solid.



10 [00437] $C_{25}H_{22}N_4O_4$. 443.0 (M+1). ^1H NMR (400 MHz, Chloroform- d) δ 8.67 (m, 1H), 8.56 (bs, 1H), 8.43 (bs, 1H), 7.72 (t, 2H), 7.34 (m, 1H), 7.10 (d, $J = 7.8$ Hz, 1H), 6.86 (m, 3H), 6.78 (d, $J = 7.8$ Hz, 1H), 6.25 (s, 1H), 3.75 (s, 3H), 2.25 (s, 3H), 2.10 (s, 3H).

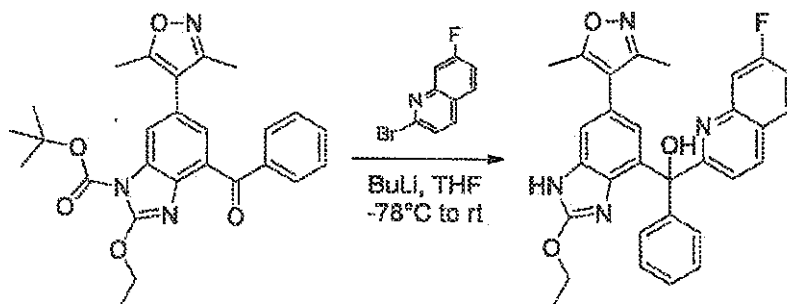
Example 153

15 Preparation of 6-(3,5-dimethylisoxazol-4-yl)-4-((7-fluoroquinolin-2-yl)(hydroxy)(phenyl)methyl)-1H-benzo[d]imidazol-2(3H)-one

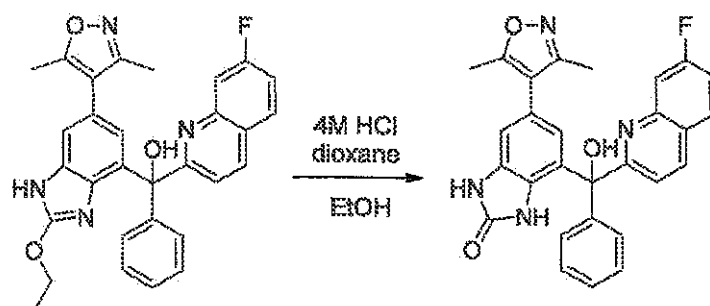


[00438] *Tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-(methoxy(methyl)carbamoyl)-1H-benzo[d]imidazole-1-carboxylate was dissolved in THF (3 mL). To the solution was added a solution of phenyl magnesium chloride (2M in THF, 0.508 mmol, 0.254 mmol) at -78°C. after the addition, the reaction was allowed to warm up to room temperature. The reaction was stirred for 17 hat the same temperature. The reaction mixture was quenched with water (30 mL). The whole was extracted with AcOEt (30 mL x 3). Organic layer was washed with brine (30 mL) and dried over Na₂SO₄. The solvent was removed under a reduced pressure to give the crude product. The crude product was purified by a silica gel column chromatography (hexane: EtOAc, 7:1 to 3:1) to give *tert*-butyl 4-benzoyl-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate.

[00439] C₂₆H₂₇N₃O₅. MS. m/z 462.2 (M+1).



[00440] To a solution of 7-fluoro-2-bromoquinoline (54.1 mg) in THF (2 mL) was added BuLi (1.6 M, 0.25 mL) at -78°C. After 5 min, a solution of phenyl ketone (60.0 mg) in THF (1 mL) was added at -78°C. The reaction was immediately allowed to warm up to room temperature and stirred for 30 min. The reaction mixture was quenched with water (30 mL). The whole was extracted with AcOEt (30 mL x 3). Organic layer was washed with brine (30 mL) and dried over Na₂SO₄. The solvent was removed under a reduced pressure to give the crude product. The crude product was treated with TFA to cleave the Boc group. The crude product was purified by a silica gel column chromatography (hexane: EtOAc, 7:1 to 3:1) to give *tert*-butyl 4-benzoyl-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate (18.0 mg). *tert*-butyl 4-benzoyl-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate. C₂₆H₂₇N₃O₅. MS. m/z 509.2 (M+1).

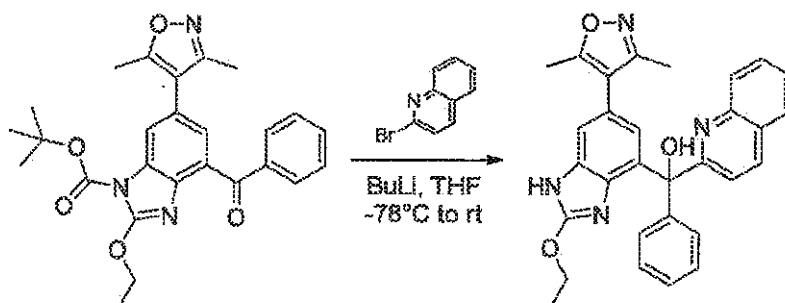


[00441] *Tert*-butyl 4-benzoyl-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate (18.0 mg) was dissolved into EtOH (2 mL) and 4M HCl/dioxane (2 mL). The solution was heated at 70°C for 30 min. The reaction mixture was quenched with water (30 mL). The whole was extracted with EtOAc (30 mL x3). Combined organic layers were washed with brine (50 mL). The solvent was removed under a reduced pressure to give a crude product. The crude product was purified by a silica gel column chromatography (hexane: EtOAc, 7:1 to 3:1) to give *tert*-butyl 4-benzoyl-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate.

10 [00442] C₂₈H₂₁FN₄O₃. MS. *m/z* 481.1 (M+1). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.31 (t, *J* = 8.7 Hz, 1H), 8.13 (dd, *J* = 9.2, 5.3 Hz, 1H), 7.67 – 7.56 (m, 3H), 7.40 – 7.25 (m, 5H), 6.98 (d, *J* = 1.6 Hz, 1H), 6.61 (d, *J* = 1.6 Hz, 1H), 2.28 (s, 3H), 2.11 (s, 3H).

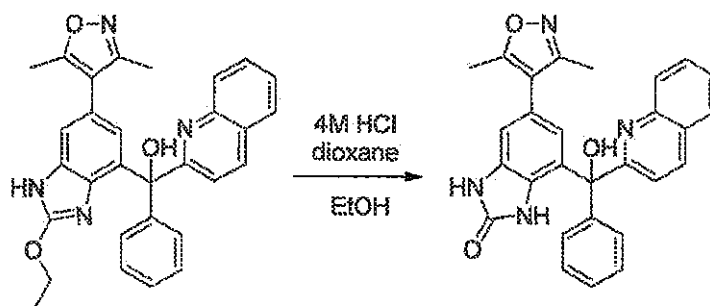
Example 154

15 6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(phenyl)(quinolin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one



[00443] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(phenyl)(quinolin-2-yl)methanol was synthesized in the similar fashion with tert-butyl 4-benzoyl-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate.

[00444] C₃₀H₂₆N₄O₃. MS. m/z 491.2 (M+1).



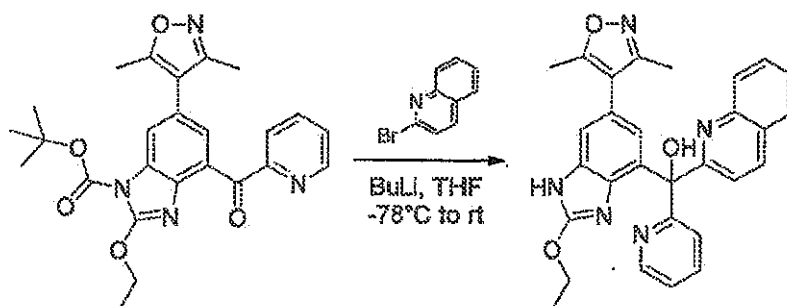
5

[00445] C₂₈H₂₂N₄O₃. MS. m/z 463.1 (M+1). ¹H NMR (400 MHz, Methanol-d₄) δ 8.30 (d, *J* = 8.6 Hz, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.93 (d, *J* = 8.6 Hz, 1H), 7.77 (ddd, *J* = 8.6, 7.0, 1.2 Hz, 1H), 7.61 (ddd, *J* = 8.6, 7.0, 1.2 Hz, 1H), 7.54 (d, *J* = 8.6 Hz, 1H), 7.40-7.26 (m, 5H), 6.98 (d, *J* = 1.5 Hz, 1H), 6.61 (d, *J* = 1.5 Hz, 1H), 2.27 (s, 3H), 2.10 (s, 3H).

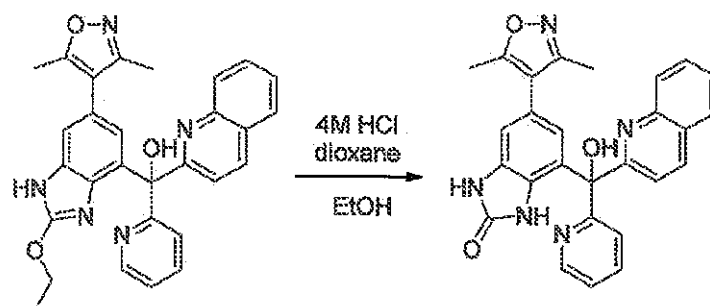
10

Example 155

6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(pyridin-2-yl)(quinolin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one



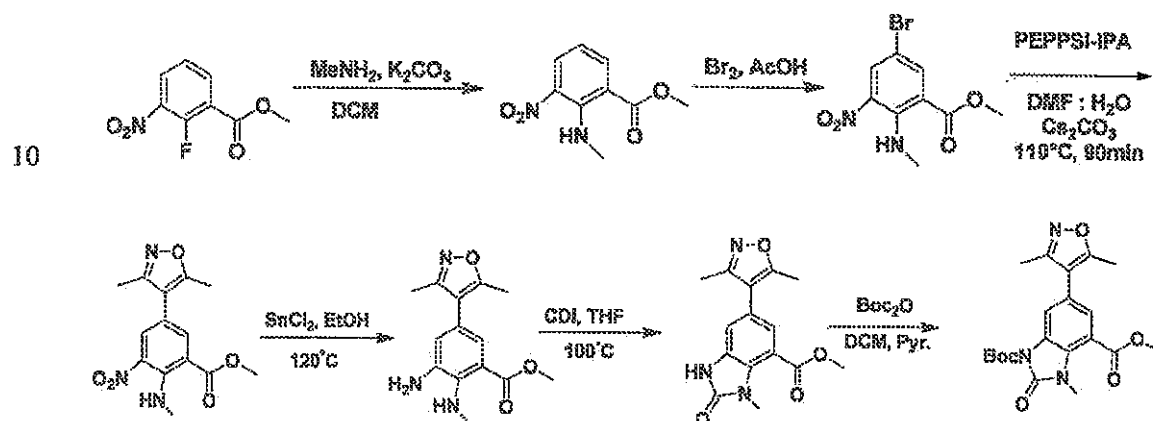
15 [00446] (6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)(pyridin-2-yl)(quinolin-2-yl)methanol was synthesized in the similar fashion with tert-butyl 4-benzoyl-6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazole-1-carboxylate. C₂₉H₂₅N₅O₃. MS. m/z 492.2 (M+1).



[00447] $C_{28}H_{27}N_4O_3$. MS. m/z 463.1 ($M+1$). ^1H NMR (400 MHz, Methanol- d_4) δ 8.78 (dd, $J = 6.6, 1.0$ Hz, 1H), 8.66 (d, $J = 8.8$ Hz, 1H), 8.47 (td, $J = 8.8, 1.0$ Hz, 1H), 8.15 – 8.03 (m, 3H), 8.00 – 7.83 (m, 3H), 7.76 (t, $J = 8.0$ Hz, 1H), 7.07 (d, $J = 1.0$ Hz, 1H), 6.46 (d, $J = 1.0$ Hz, 1H), 2.22 (s, 3H), 2.04 (s, 3H).

Example 156

1-tert-butyl 4-methyl 6-(3,5-dimethylisoxazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-1,4-dicarboxylate



[00448] Methyl 2-fluoro-3-nitrobenzoate (25g, 0.126 mol) was dissolved in DCM (400 ml) and to this was added Potassium carbonate (34.7 g, 0.25 mol) followed by Methylamine (20.63 ml, 0.5 mol). Reaction was stirred at room temperature under argon. Upon completion reaction was diluted with water and extracted with DCM (3x) then dried over magnesium sulfate. Solvents were removed under reduced pressure to afford methyl 2-(methylamino)-3-nitrobenzoate as a yellow solid.

[00449] Methyl 2-(methylamino)-3-nitrobenzoate (25.5 g, 0.121 mol) was dissolved in acetic acid (100 ml) and DCM (40 ml). In a separate flask bromine (7.46 ml, 0.15 mol) was dissolved in acetic acid (15ml). The first solution was then slowly added to the bromine solution via an addition funnel and the reaction was stirred for 90 minutes. At this point the reaction was poured onto ice (200 g). After the ice had melted DCM was added and the reaction was extracted with DCM (3x), dried over magnesium sulfate then solvents removed under reduced pressure to methyl 5-bromo-2-(methylamino)-3-nitrobenzoate as a bright orange solid.

[00450] Methyl 5-bromo-2-(methylamino)-3-nitrobenzoate (20.1 g, 96.5 mmol), 3,5-dimethyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (24.82 g, 111.25 mmol), PEPPSI[®]-IPr catalyst (2.63 g, 3.86 mmol), Cesium carbonate (67.96 g, 208.59 mmol), 1,2-Dimethoxyethane (100 ml) and Water (30 ml) were mixed together and the solution degassed for 5 minutes before heating to 110°C for 1 hour. Reaction mixture was then cooled, diluted with EtAc and water and extracted EtAc (3x). Organics were washed with water then brine, dried over sodium sulfate and evaporated to dryness under reduced pressure. Crude material purified by silica gel chromatography using EtAc/Hex as the eluent to methyl 5-(3,5-dimethylisoxazol-4-yl)-2-(methylamino)-3-nitrobenzoate (20.5 g, 96%).

[00451] To methyl 5-(3,5-dimethylisoxazol-4-yl)-2-(methylamino)-3-nitrobenzoate (2000 mg, 6.55 mmol) was added stannous chloride (3726.66 mg, 19.65 mmol) and Ethanol (100 ml) in a pressure tube. The suspension was then heated in sealed vessel to 120°C for 90 minutes at which point the reaction was cooled then stirred in a mixture of EtAc / 1N NaOH for 1 hour or until precipitates form. Precipitates were filtered and crude mixture was diluted in EtAc and water and extracted 3x with EtAc. Organics were washed with water then brine, dried over sodium sulfate and evaporated to dryness under reduced pressure. Residue was purified by silica gel chromatography using MeOH/DCM as the eluent to afford methyl 3-amino-5-(3,5-dimethylisoxazol-4-yl)-2-(methylamino)benzoate as a dark foam (1.1g, 61%)

Methyl 3-amino-5-(3,5-dimethylisoxazol-4-yl)-2-(methylamino)benzoate (1.1 g, 4 mmol) and 1,1'-carbonyldiimidazole (1.3 g, 7.99 mmol) were stirred in Tetrahydrofuran (100 ml) in a sealed pressure vessel. Reaction was heated to 100°C and allowed to react overnight. Next day solvents were removed under reduced pressure. Material was slurried in minimal DCM, sonicated and filtered. Solids were air dried to afford methyl 6-(3,5-dimethylisoxazol-4-yl)-

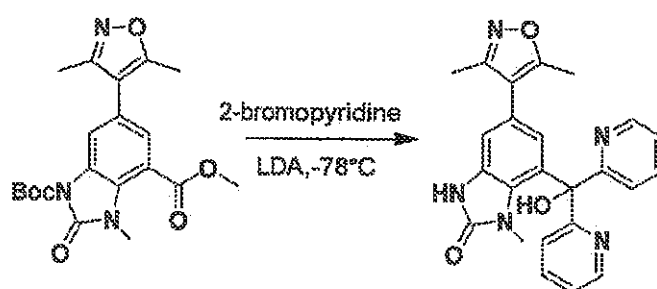
3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carboxylate as an off-white powder (417 mg, 35%).

[00452] Methyl 6-(3,5-dimethylisoxazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carboxylate (410 mg, 1.36 mmol) was dissolved in THF (10 ml) and to this was added Di-tert-butyl dicarbonate 97% (593.97 mg, 2.72 mmol) followed by 4-(Dimethylamino)pyridine (33.25 mg, 0.27 mmol) and finally Triethylamine (0.57 ml, 4.08 mmol). Reaction was allowed to stir at room temperature under argon for 3 hours, or until complete. Reaction was then diluted in EtAc and aqueous ammonium chloride and extracted with EtAc (3x). Organics were washed with ammonium chloride, water and brine and dried over sodium sulfate before evaporating to dryness. Crude material was purified by silica gel chromatography (EtAc / Hexanes as the eluent) to provide 1-tert-butyl 4-methyl 6-(3,5-dimethylisoxazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-1,4-dicarboxylate as an opaque oil.

15

Example 157

5-(3,5-dimethylisoxazol-4-yl)-7-(hydroxydi(pyridin-2-yl)methyl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one



[00453] To a dry, argon purged flask was added 5mL THF and 2-bromopyridine (0.06 ml, 0.62 mmol). Reaction was cooled to -78°C under argon and then slowly was added 1.6M N-butyllithium in hexanes (0.43 ml) over 10 minutes. Lithio species was allowed to form for 30 minutes at which point 1-tert-butyl 4-methyl 6-(3,5-dimethylisoxazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-1,4-dicarboxylate (50 mg, 0.12 mmol) in 0.5 mL THF was added slowly. Reaction stirred at -78°C for 5 minutes then allowed to warm. When reaction vessel neared 0°C was quenched with 1N HCl. Reaction was diluted with

25

EtAc/H₂O and basified with 1N NaOH until neutral. Mixture was extracted with EtAc (3x) then organics were washed with water then brine and dried over sodium sulfate. Solvents were removed under reduced pressure and crude mixture was purified by preparative HPLC to afford GS-650721 (110mg, 21%).

- 5 [00454] C₂₄H₂₁N₃O₃; 428.1 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 11.09 (s, 1H), 8.57–8.50 (m, 2H), 7.89 (t, J = 7.7 Hz, 2H), 7.55 (d, J = 8.0 Hz, 2H), 7.39 (t, J = 6.1 Hz, 2H), 6.97 (d, J = 1.7 Hz, 1H), 5.86 (d, J = 1.7 Hz, 1H), 2.76 (s, 3H), 2.18 (s, 3H), 1.97 (s, 3H).

10

Example 158,

Example 159, and

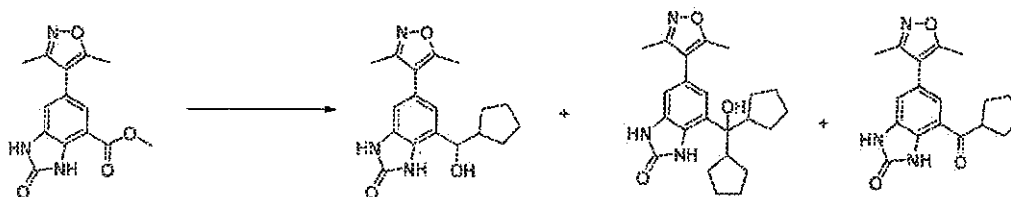
Example 160

f 4-(cyclopentyl(hydroxy)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one;

- 15 4-(dicyclopentyl(hydroxy)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one;

and

4-(cyclopentanecarbonyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



- 20 [00455] To a mixture containing methyl 6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carboxylate (60 mg, 0.21 mmol, 1 equiv.) and THF (3 mL) is added cyclopentyl magnesium chloride (0.88 mL, 1.46 mmol, 7 equiv.) at 0°C for 5 min. After completion, the reaction was quenched and extracted with EtOAc and washed with

water, saturated NH_4Cl . After drying with MgSO_4 , it was filtered and concentrated to dryness. Purification was carried out by reverse phase HPLC.

[00456] ^1H NMR (400 MHz, Methanol- d_4) δ 6.96 (d, $J = 1.5$ Hz, 1H), 6.88 (d, $J = 1.6$ Hz, 1H), 4.66 (d, $J = 8.3$ Hz, 1H), 2.39 (s, 3H), 2.24 (s, 3H), 1.93 – 1.80 (m, 1H), 1.76 – 1.43 (m, 3H), 1.40 (s, 0H), 1.28 (d, $J = 8.3$ Hz, 1H). LCMS ($m/z + 1$) 328.38

[00457] ^1H NMR (400 MHz, Methanol- d_4) δ 6.94 – 6.68 (m, 1H), 2.53 (s, 0H), 2.53 (d, $J = 17.1$ Hz, 1H), 2.38 (s, 2H), 2.23 (s, 2H), 1.84 (dd, $J = 12.4, 6.4$ Hz, 1H), 1.59 – 1.43 (m, 6H), 1.43 – 1.31 (m, 2H). LCMS ($m/z + 1$) 396.49

[00458] ^1H NMR (400 MHz, Methanol- d_4) δ 7.59 (d, $J = 1.5$ Hz, 1H), 7.19 (d, $J = 1.5$ Hz, 1H), 3.86 (t, $J = 7.8$ Hz, 1H), 2.43 (s, 3H), 2.27 (s, 3H), 2.02 – 1.89 (m, 4H), 1.71 (td, $J = 5.4, 3.3$ Hz, 4H). LCMS ($m/z + 1$) 326.36

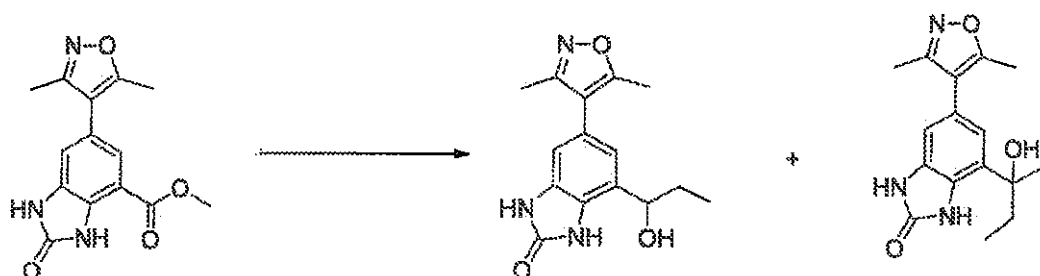
Example 161 and

Example 162

15 (6-(3,5-dimethylisoxazol-4-yl)-4-(3-hydroxypentan-3-yl)-1H-benzo[d]imidazol-2(3H)-one

and

methyl 6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carboxylate



20 [00459] Into a flask containing methyl 6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carboxylate (60 mg, 0.21 mmol, 1 equiv.) is added cyclopentylmagnesium chloride (0.88 mL, 1.46 mmol, 7 equiv., 1M Hexanes) at 0°C for 5

min. After completion, the reaction was quenched and extracted with EtOAc and washed with water, saturated NH_4Cl . After drying with MgSO_4 , it was filtered and concentrated to dryness. Purification was carried out by reverse phase HPLC to GS-646013 and GS-646012. ^1H NMR (400 MHz, Methanol- d_4) δ 7.07 – 6.91 (m, 1H), 6.88 (d, J = 1.6 Hz, 1H), 2.39 (s, 3H), 2.23 (s, 3H), 1.81 (td, J = 7.0, 3.6 Hz, 2H), 0.95 (t, J = 7.4 Hz, 3H). LCMS (m/z +1) 288.15

[00460] ^1H NMR (400 MHz, Methanol- d_4) δ 7.55 (d, J = 1.6 Hz, 1H), 7.18 (d, J = 1.6 Hz, 1H), 3.97 (s, 3H), 2.40 (s, 3H), 2.24 (s, 3H). LCMS (m/z +1) 288.29

[00461] ^1H NMR (400 MHz, Methanol- d_4) δ 6.86 (d, J = 1.5 Hz, 1H), 6.74 (d, J = 1.5 Hz, 1H), 2.39 (s, 3H), 2.23 (s, 3H), 1.94 (dd, J = 14.3, 7.3 Hz, 2H), 1.90 – 1.74 (m, 2H), 0.82 (t, J = 7.4 Hz, 3H). LCMS (m/z +1) 316.38

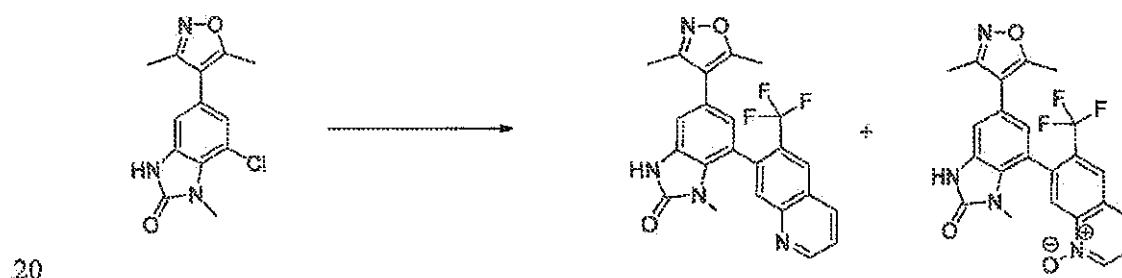
Example 163 and

Example 164

15 5-(3,5-dimethylisoxazol-4-yl)-1-methyl-7-(6-(trifluoromethyl)quinolin-7-yl)-1H-benzo[d]imidazol-2(3H)-one

and

7-(6-(3,5-dimethylisoxazol-4-yl)-3-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-4-yl)-6-(trifluoromethyl)quinoline 1-oxide



[00462] To a microwave vial containing 7-chloro-5-(3,5-dimethylisoxazol-4-yl)-1-methyl-1H-benzo[d]imidazol-2(3H)-one (100 mg, 0.36 mmol, 1 equiv.) was added 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-6-(trifluoromethyl)quinolone (350 mg, 1.08

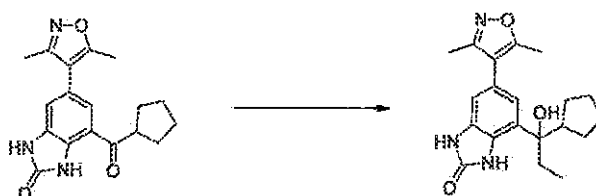
mmol, 3 equiv.), Cs_2CO_3 (704 mg, 2.16 mmol, 6 equiv.) and PEPPSITM-IPr catalyst (98 mg, 0.14 mmol, 0.4 equiv.) and dissolved in DMB- H_2O (4 mL, 0.2 M, 2/1, v/v). The mixture was heated to 120°C for 30 min in microwave. The reaction was concentrated in vacuo and purification was carried out by reverse phase HPLC.

5 [00463] ^1H NMR (400 MHz, Methanol- d_4) δ 9.03 (dd, $J = 4.2, 1.6$ Hz, 1H), 8.32 (d, $J = 9.1$ Hz, 1H), 8.19 (d, $J = 9.0$ Hz, 1H), 7.97 – 7.76 (m, 1H), 7.56 (dd, $J = 8.6, 4.3$ Hz, 1H), 7.16 (d, $J = 1.5$ Hz, 1H), 6.91 (d, $J = 1.4$ Hz, 1H), 2.74 (s, 3H), 2.42 (s, 3H), 2.27 (s, 3H). LCMS ($m/z + 1$) 439.4

[00464] ^1H NMR (400 MHz, Methanol- d_4) δ 9.19 (s, 1H), 8.30 – 8.17 (m, 1H), 8.07 – 7.85 (m, 3H), 7.67 (ddd, $J = 8.3, 7.0, 1.2$ Hz, 1H), 6.79 (d, $J = 1.3$ Hz, 1H), 5.88 (d, $J = 1.3$ Hz, 1H), 3.81 (s, 3H), 2.05 (s, 3H), 1.86 (s, 3H). LCMS ($m/z + 1$) 455.26

Example 165

15 4-(1-cyclopentyl-1-hydroxypropyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



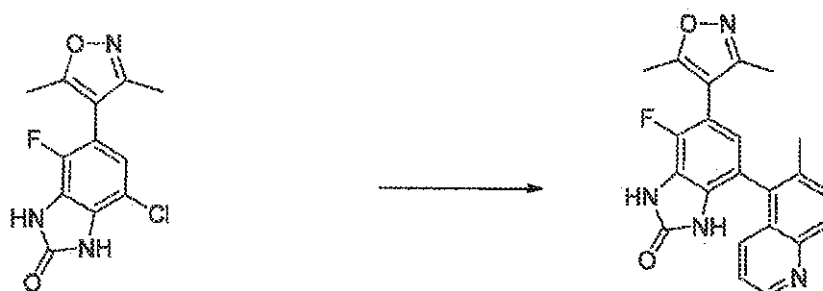
[00465] Into a flask containing the ketone (25 mg, 0.077 mmol, 1 equiv.) is added ethyl magnesium bromide (0.28 mL, 0.28 mmol, 4 equiv., 1M) at 0°C for 5 min. After completion, the reaction was quenched and extracted with EtOAc and washed with water, saturated NH_4Cl . After drying with MgSO_4 , it was filtered and concentrated to dryness. Purification was carried out by reverse phase HPLC.

[00466] ^1H NMR (400 MHz, Methanol- d_4) δ 6.85 (d, $J = 1.5$ Hz, 1H), 6.78 (s, 1H), 2.41 (d, $J = 16.9$ Hz, 4H), 2.25 (d, $J = 17.0$ Hz, 4H), 2.03 – 1.68 (m, 4H), 1.50 (ddd, $J = 29.4$,

15.0, 13.9, 7.8 Hz, 5H), 0.76 (t, $J = 7.4$ Hz, 4H). ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -136.97 (d, $J = 6.5$ Hz). LCMS ($M+1$) 355.96

Example 166

5 5-(3,5-dimethylisoxazol-4-yl)-4-fluoro-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one



[00467] To a microwave vial containing 7-chloro-5-(3,5-dimethylisoxazol-4-yl)-4-fluoro-1H-benzo[d]imidazol-2(3H)-one (16 mg, 0.057 mmol, 1 equiv.) was added 3,5-6-methylquinolin-5-ylboronic acid (53 mg, 0.28 mmol, 5 equiv.), Cs_2CO_3 (111 mg, 0.34 mmol, 6 equiv.) and PEPPSI[™]-IPr catalyst (7 mg, 0.0011 mmol, 0.2 equiv.) and dissolved in DMB- H_2O (20 mL, 0.2 M, 2/1, v/v). The mixture was heated to 140 °C. After 2 h, the reaction was complete. After cooling, the reaction was extracted with EtOAc and washed with water, saturated NH_4Cl . After drying with MgSO_4 , it was filtered and concentrated to dryness. The resulting solid was washed with EtOAc. Purification was carried out by reverse phase HPLC to furnish 5-(3,5-dimethylisoxazol-4-yl)-4-fluoro-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one.

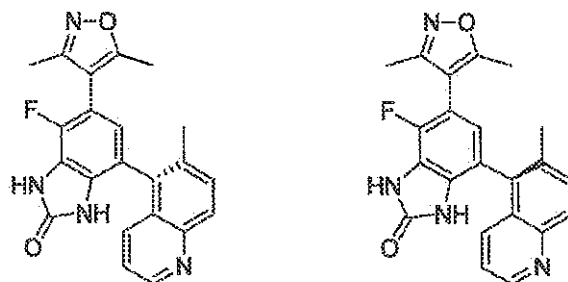
[00468] ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 11.42 (d, $J = 1.8$ Hz, 1H), 10.63 (s, 1H), 8.82 (dd, $J = 4.2, 1.6$ Hz, 1H), 7.99 (d, $J = 8.6$ Hz, 1H), 7.79 – 7.56 (m, 2H), 7.40 (dd, $J = 8.5, 4.2$ Hz, 1H), 6.77 (d, $J = 6.6$ Hz, 1H), 2.34 (d, $J = 0.9$ Hz, 3H), 2.24 (s, 3H), 2.17 (d, $J = 0.9$ Hz, 3H).

[00469] ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ -136.97 (d, $J = 6.5$ Hz). LCMS ($m/z + 1$) 389.28

Example 167 and

Example 168

(7R and 7S)-5-(3,5-dimethylisoxazol-4-yl)-4-fluoro-7-(6-methylquinolin-5-yl)-1H-benzo[d]imidazol-2(3H)-one



5

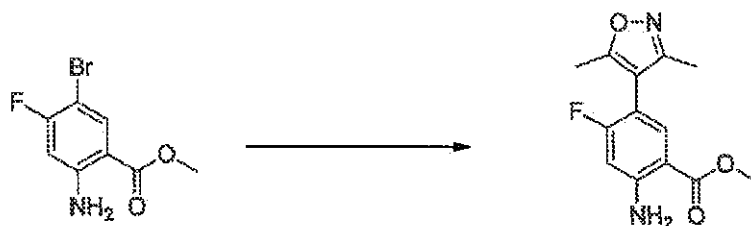
[00470] The racemate of Example 166 was separated with super critical column chromatography (JASCO SFC) using DAICEL AD-H (10 mm x 250 mm, 20% MeOH, 15 mL/min, 40°C, 15 atm). RT 2.733 min, 1.9 mg (GS-649951). RT 3.742 min, 2.6 mg.

10

Example 169

5-(3,5-dimethylisoxazol-4-yl)-4-fluoro-7-(hydroxydl(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one

Step 1: Methyl 2-amino-5-(3,5-dimethylisoxazol-4-yl)-4-fluorobenzoate



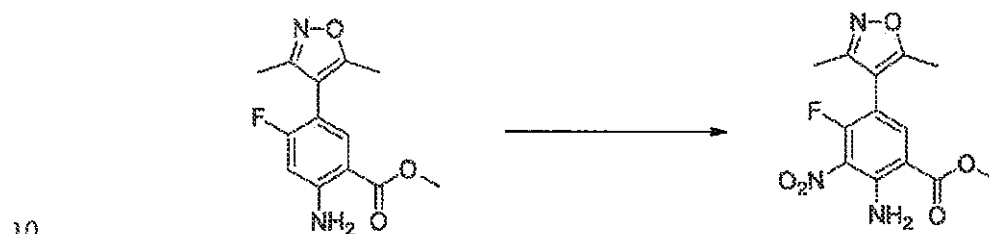
15

[00471] To methyl 2-amino-5-bromo-4-fluorobenzoate (20g, 80.6 mol.) and 3,5-Dimethylisoxazole-4-boronic acid pinacol ester (24.2g, 108.9 mol., 1.35 mmol) was added to a solvent mixture of 1,2-dimethoxymethane (120ml) and water (60 ml). To the above mixture were added PEPPSI-Ipr (3120 mg, 4.2 mmol, 0.05 equiv.) and Cs₂CO₃ (78.8 g, 241 mol., 3 equiv.). The reaction mixture was heated at 120°C for 2 h in a pressure tube. The reaction

mixture was then diluted with EtOAc (100 ml), washed with brine (50mlX2). The organic solvent was evaporated and the residue was dissolved in DCM and purified with combi-flash column chromatography (product came out at 50% EtOAc/Hexane) to afford methyl 2-amino-5-(3,5-dimethylisoxazol-4-yl)-4-fluorobenzoate.

- 5 [00472] ^1H NMR (400 MHz, Chloroform- d) δ 7.79 (dd, J = 8.1, 1.2 Hz, 1H), 6.80 – 6.60 (m, 1H), 3.90 (s, 4H), 2.34 (d, J = 8.3 Hz, 4H), 2.20 (d, J = 5.5 Hz, 4H). ^{19}F NMR (377 MHz, Chloroform- d) δ -96.83 – -101.99 (m), -105.54 (d, J = 13.8 Hz). LCMS (m/z +1) 265.32.

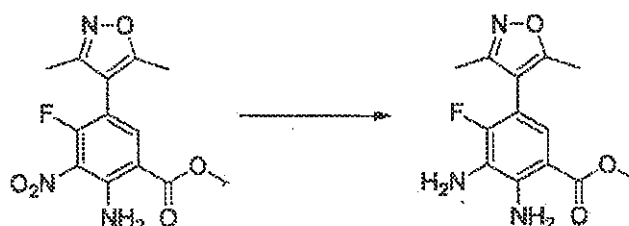
Step 2: Methyl 2-amino-5-(3,5-dimethylisoxazol-4-yl)-4-fluoro-3-nitrobenzoate



- [00473] To a mixture of methyl 2-amino-5-(3,5-dimethylisoxazol-4-yl)-4-fluorobenzoate (14g, 53 mmol, 1 equiv.) and TFA (100 mL) is slowly added nitronium tetrafluoroborate (9.1 g, 68.9 mmol, 1.3 equiv.). After completion, the mixture was concentrated under reduced pressure. The residue was dissolved and then the residue was dissolved in EtOAc (200 ml) and washed with brine (30mlX2). The organic solvent was evaporated. Methyl 2-amino-5-(3,5-dimethylisoxazol-4-yl)-4-fluoro-3-nitrobenzoate was used without further purification. ^1H NMR (400 MHz, Chloroform- d) δ 6.92 (d, J = 5.8 Hz, 1H), 4.24 (s, 4H), 4.07 – 3.85 (m, 5H), 2.46 – 2.34 (m, 4H), 2.31 – 2.22 (m, 5H).

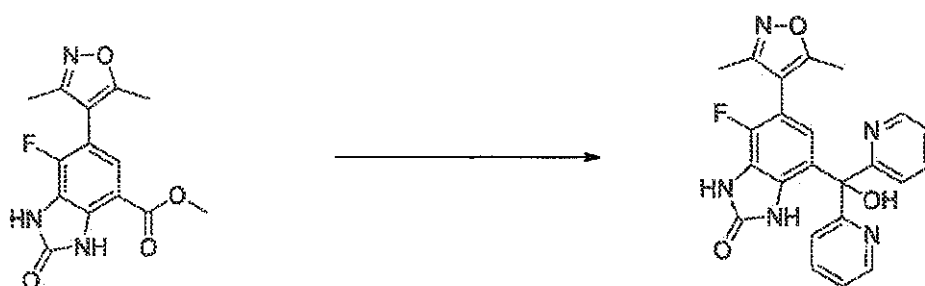
- [00474] ^{19}F NMR (377 MHz, Chloroform- d) δ -76.44, -121.12 (d, J = 5.7 Hz). LCMS (m/z +1) 310.2

Step 3: Methyl 2,3-diamino-5-(3,5-dimethylisoxazol-4-yl)-4-fluorobenzoate



[00475] Into a pressure tube containing N-methyl 2-amino-5-(3,5-dimethylisoxazol-4-yl)-4-fluoro-3-nitrobenzoate (16.5 g, 53.2 mol., 1 equiv.) is added EtOH (200 mL) and tin (II) chloride (20.2 g, 107 mol., 2 equiv.). The reaction was heated for 3 h at 130 °C. The reaction was then stirred in 2N NaOH solution for 20 minutes before being partitioned between water and ethyl acetate. The organic layer was washed with brine and dried over sodium sulfate. Purification was carried out by flash column chromatography to furnish methyl 2,3-diamino-5-(3,5-dimethylisoxazol-4-yl)-4-fluorobenzoate (5700 mg, 39 %). LCMS (m/z +1) 270.2.

Step 4:



[00476] A flask containing 2-bromopyridine (135 μ L, 1.37 mmol, 7 equiv.) and THF (3 mL) is cooled to -78 °C before BuLi (0.86 mL, 1.37 mmol, 7 equiv.) is added. After 30 min, methyl 6-(3,5-dimethylisoxazol-4-yl)-7-fluoro-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carboxylate (60 mg, 0.197 mmol, 1 equiv.) dissolved in THF (2 mL) is added to the reaction mixture. After completion, the reaction was quenched and extracted with EtOAc and washed with water, saturated NH_4Cl . After drying with MgSO_4 , it was filtered and concentrated to dryness. Purification was carried out by reverse phase HPLC.

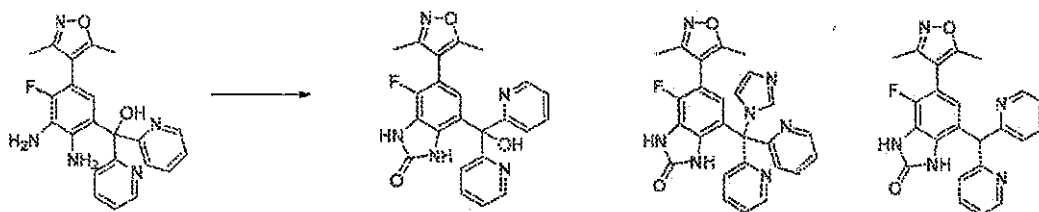
[00477] ^1H NMR (400 MHz, Methanol- d_4) δ 8.62 (dd, J = 5.3, 1.6 Hz, 2H), 8.13 (t, J = 8.0 Hz, 2H), 7.84 (d, J = 8.1 Hz, 2H), 7.60 (dd, J = 7.6, 5.3 Hz, 2H), 6.43 (d, J = 6.4 Hz, 1H), 2.24 (s, 3H), 2.07 (s, 3H). ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.88, -137.06. LCMS (m/z+1) 431.92

Example 170,

Example 171, and

Example 172

5 5-(3,5-dimethylisoxazol-4-yl)-4-fluoro-7-(hydroxydi(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one;
7-((1H-imidazol-1-yl)di(pyridin-2-yl)methyl)-5-(3,5-dimethylisoxazol-4-yl)-4-fluoro-1H-benzo[d]imidazol-2(3H)-one;
and
7-(di(pyridin-2-yl)methyl)-5-(3,5-dimethylisoxazol-4-yl)-4-fluoro-1H-benzo[d]imidazol-
10 2(3H)-one



[00478] Alternatively, the title compound was made from (2,3-diamino-5-(3,5-dimethylisoxazol-4-yl)-4-fluorophenyl)di(pyridin-2-yl)methanol. Into a microwave vial containing (2,3-diamino-5-(3,5-dimethylisoxazol-4-yl)-4-fluorophenyl)di(pyridin-2-yl)methanol (50 mg, 0.12 mmol, 1 equiv.) is added THF (5 m) and CDI (30 mg, 0.185 mmol, 1.5 equiv.). The mixture was heated to 120°C for 30 minutes in a microwave reactor. The reaction was concentrated in vacuo and purified by HPLC.

[00479] ¹H NMR (400 MHz, Methanol-d₄) δ 8.65 (ddt, J = 5.4, 1.6, 0.7 Hz, 2H), 8.33 – 8.14 (m, 2H), 7.92 (dt, J = 8.1, 0.9 Hz, 2H), 7.68 (ddt, J = 7.3, 5.4, 0.9 Hz, 2H), 6.39 (d, J = 6.4 Hz, 1H), 2.24 (s, 4H), 2.06 (s, 4H). ¹⁹F NMR (377 MHz, Methanol-d₄) δ -77.95, -136.55 (d, J = 6.2 Hz).

[00480] LCMS (m/z+1) 431.92

[00481] ¹H NMR (400 MHz, Methanol-d₄) δ 9.50 (t, J = 1.5 Hz, OH), 8.67 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 7.96 – 7.79 (m, 1H), 7.54 (t, J = 1.8 Hz, OH), 7.47 (ddd, J = 7.7, 4.7, 0.9

Hz, 1H), 7.03 (dd, $J = 8.1, 1.0$ Hz, 1H), 5.92 (d, $J = 6.3$ Hz, 0H), 2.23 (d, $J = 0.9$ Hz, 1H), 2.05 (d, $J = 0.9$ Hz, 1H).

[00482] ^{19}F NMR (377 MHz, Methanol- d_4) δ -77.74, -134.19 (d, $J = 6.2$ Hz). LCMS ($m/z+1$) 482.17

5 [00483] ^1H NMR (400 MHz, DMSO- d_6) δ 7.70 (dt, $J = 4.8, 1.3$ Hz, 1H), 6.98 (td, $J = 7.8, 1.9$ Hz, 1H), 6.50 (ddd, $J = 7.6, 4.9, 1.1$ Hz, 1H), 6.45 (d, $J = 7.9$ Hz, 1H), 5.83 (d, $J = 6.5$ Hz, 1H), 5.16 (s, 1H), 1.44 (d, $J = 0.9$ Hz, 2H), 1.27 (d, $J = 0.8$ Hz, 2H). ^{19}F NMR (377 MHz, DMSO- d_6) δ -78.29, -128.15, -140.19 (d, $J = 6.3$ Hz). LCMS ($m/z+1$) 416.19.

10

Example 173 and

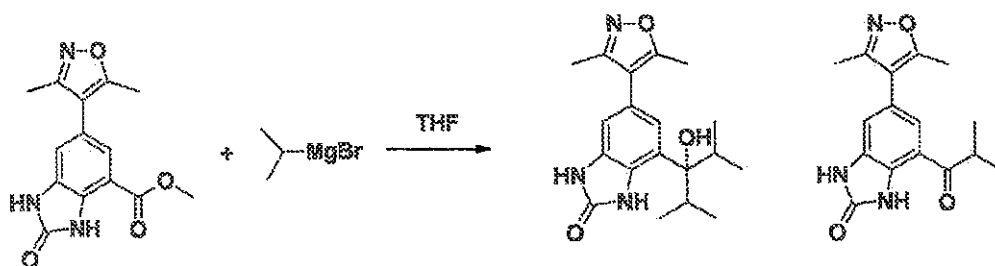
Example 174

6-(3,5-dimethylisoxazol-4-yl)-4-(3-hydroxy-2,4-dimethylpentan-3-yl)-1H-benzo[d]imidazol-2(3H)-one

and

15

6-(3,5-dimethylisoxazol-4-yl)-4-isobutyryl-1H-benzo[d]imidazol-2(3H)-one



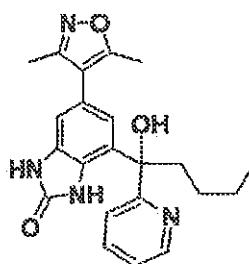
[00484] Methyl 6-(3,5-dimethylisoxazol-4-yl)-2-oxo-2,3-dihydro-1H-benzo[d]imidazole-4-carboxylate (100 mg, 0.35 mmol) was dissolved in 5 mL of THF and stirred at room temperature followed by the addition of isopropylmagnesium bromide (0.87 mL, 2.0 mmol). Addition Grignard was added in 1 hour intervals until the starting material was consumed. Once complete, the crude reaction mixture was quenched with DI water and extracted 3x with ethyl acetate. Combined organic layers were washed with brine, dried over sodium sulphate, filtered, concentrated in vacuo, and purified via HPLC.

[00485] C₁₉H₂₅N₃O₃; 344.2 (m/z +1). ¹H NMR (400 MHz, cd₃od) δ 6.88 (d, J = 1.4 Hz, 1H), 6.70 (s, 1H), 2.39 (s, 3H), 2.34 (dd, J = 13.4, 6.7 Hz, 2H), 2.23 (s, 3H), 0.91 (d, J = 6.7 Hz, 6H), 0.85 (d, J = 6.8 Hz, 6H).

[00486] C₁₆H₁₇N₃O₃; 300.1 (m/z +1). ¹H NMR (400 MHz, cd₃od) δ 7.59 (s, 1H),
 5 7.20 (d, J = 1.3 Hz, 1H), 3.68 (dt, J = 13.6, 6.8 Hz, 1H), 2.43 (s, 3H), 2.27 (s, 3H), 1.23 (d, J = 6.8 Hz, 6H).

Example 17S

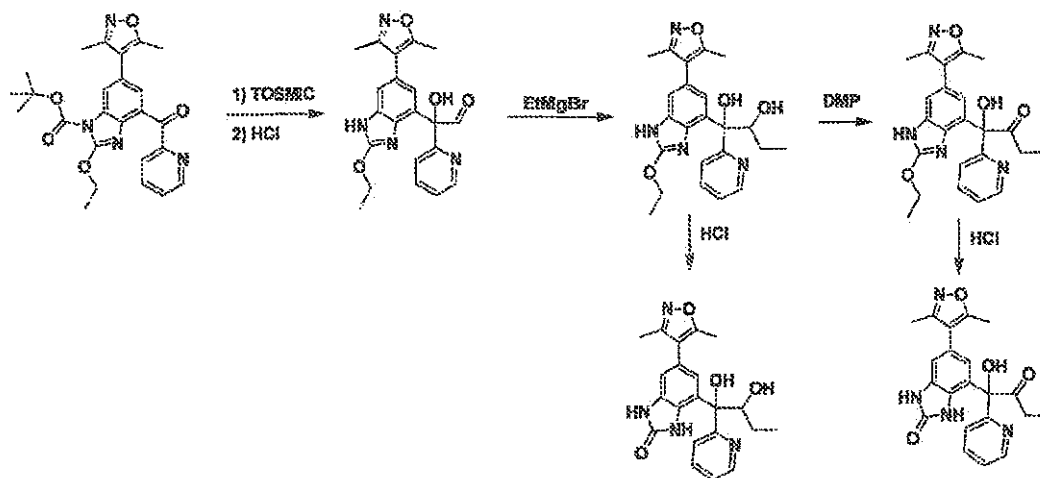
6-(3,5-dimethylisoxazol-4-yl)-4-(1-hydroxy-1-(pyridin-2-yl)pentyl)-1H-
 10 benzo[d]imidazol-2(3H)-one



[00487] A solution of tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-picolinoyl-
 1H-benzo[d]imidazole-1-carboxylate was treated with n-BuLi (1.5 equiv) at -78°C. The
 reaction was stirred for 15 minutes and quenched with 1M HCl, concentrated, dissolved in
 15 ethanol (1 mL) and 4M HCl in dioxane (0.5 mL) and heated to 80°C for 1h. The reaction
 mixture was concentrated and purified by reverse-phase HPLC to give the desired product.

[00488] C₂₂H₂₄N₄O₃. 393.1 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 10.68 (s,
 1H), 9.89 (d, J = 1.9 Hz, 1H), 8.56 (d, J = 4.9 Hz, 1H), 7.88 (d, J = 7.7 Hz, 2H), 7.37 (s, 1H),
 6.96 (d, J = 1.6 Hz, 1H), 6.74 (d, J = 1.5 Hz, 1H), 2.34 (m, 4H), 2.15 (s, 3H), 1.37 – 1.22 (m,
 20 4H), 1.22 – 1.01 (m, 1H), 0.80 (t, J = 7.0 Hz, 4H).

Example 176



[00489] A solution of tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-picolinoyl-1H-benzo[d]imidazole-1-carboxylate (360 mg, 0.79 mmol) and p-Toluenesulfonylmethyl isocyanide (183.95 mg, 0.94 mmol) in methanol (5 mL) was stirred at room temperature overnight. The reaction mixture was concentrated and 1M aqueous HCl (3 mL) and concentrated HCl (3 mL) was added. The reaction mixture was stirred for 30 minutes, concentrated and purified by reverse-phase HPLC to give 2-(6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)-2-hydroxy-2-(pyridin-2-yl)acetaldehyde.

[00490] Ethyl magnesiumbromide (3M, 0.61 mL, 1.84 mmol) was added to a solution of 2-(6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-1H-benzo[d]imidazol-4-yl)-2-hydroxy-2-(pyridin-2-yl)acetaldehyde (120 mg, 0.31 mmol) in methyl-THF at 0°C. After 15 min, the reaction mixture was quenched with 1M HCl, concentrated and a portion of this material was purified by reverse-phase HPLC to give the major diastereomer 4-(1,2-dihydroxy-1-(pyridin-2-yl)butyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one.

[00491] 4-(1,2-dihydroxy-1-(pyridin-2-yl)butyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one.

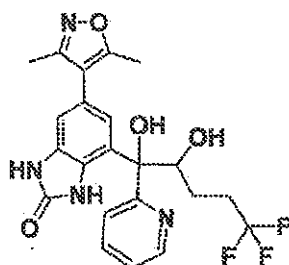
[00492] C₂₁H₂₂N₄O₄. 395.1 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.73 – 10.59 (m, 1H), 9.81 (s, 1H), 8.63 (d, *J* = 4.7 Hz, 1H), 8.04 (s, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.50 (s, 1H), 7.11 (d, *J* = 1.7 Hz, 1H), 6.77 (s, 1H), 4.39 (d, *J* = 9.6 Hz, 1H), 2.34 (s, 3H), 2.15 (s, 3H), 1.40 – 1.14 (m, 2H), 0.86 (t, *J* = 7.3 Hz, 3H).

[00493] Dess-Martin Periodinane (90 mg, 0.24 mmol) was added to a solution of 4-(1,2-dihydroxy-1-(pyridin-2-yl)butyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one (50 mg, 0.12 mmol) in a mixture of dichloromethane and THF. The reaction was stirred for 72 h at room temperature, concentrated and purified by reverse-phase HPLC. A
 5 portion of this product was dissolved in concentrated HCl (0.1 mL) and ethanol (1 mL), heated at 80°C for 3 h and concentrated to give 6-(3,5-dimethylisoxazol-4-yl)-4-(1-hydroxy-2-oxo-1-(pyridin-2-yl)butyl)-1H-benzo[d]imidazol-2(3H)-one.

[00494] C₂₁H₂₀N₄O₄. 393.1 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.73 (s, 1H), 9.87 (s, 1H), 8.62 – 8.39 (m, 1H), 7.89 (t, *J* = 7.9 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.50 – 7.27 (m, 1H), 6.83 (s, 1H), 6.40 (s, 1H), 2.83 (dd, *J* = 18.2, 8.0 Hz, 2H), 2.27 (s, 3H), 2.07 (s, 3H), 0.91 (t, *J* = 7.2 Hz, 3H).

Example 177

6-(3,5-dimethylisoxazol-4-yl)-4-(5,5,5-trifluoro-1,2-dihydroxy-1-(pyridin-2-yl)pentyl)-
 15 1H-benzo[d]imidazol-2(3H)-one



[00495] The following two diastereomers were likewise prepared using trifluoromethylethylmagnesium bromide in place of ethylmagnesium bromide.

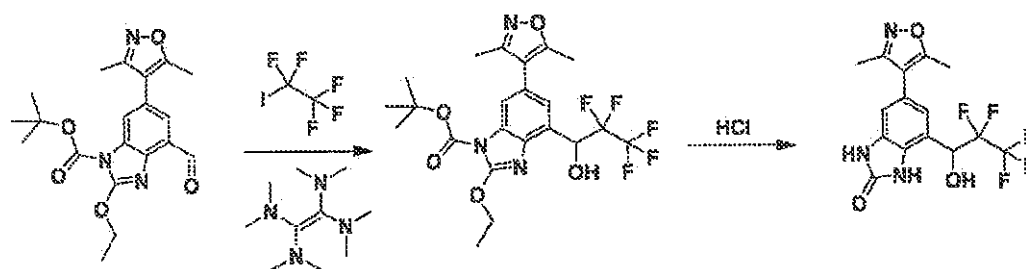
[00496] Major diastereomer: C₂₂H₂₁F₃N₄O₄. 463.1 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.67 (s, 1H), 9.80 (d, *J* = 6.8 Hz, 1H), 8.59 (s, 1H), 7.91 (s, 1H), 7.76 (s, 1H), 7.39 (s, 1H), 7.06 (s, 1H), 6.76 (s, 1H), 4.58 (d, *J* = 9.9 Hz, 1H), 2.40-2.50 (m, 2H), 2.42 – 2.30 (m, 3H), 2.13 (s, 3H), 1.48 (m, 2H).

[00497] Minor diastereomer: C₂₂H₂₁F₃N₄O₄. 463.1 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.59 (s, 1H), 10.03 (s, 1H), 8.56 (dd, *J* = 5.4, 1.7 Hz, 1H), 7.52 (s, 1H), 6.64 (d,

$J = 1.6$ Hz, 1H), 6.41 (s, 1H), 5.07 (s, 1H), 2.40 (m, 2H) 2.17 (s, 3H), 1.99 (s, 3H), 1.65 (d, $J = 15.9$ Hz, 2H).

Example 178

5 6-(3,5-dimethylisoxazol-4-yl)-4-(2,2,3,3,3-pentafluoro-1-hydroxypropyl)-1H-benzo[d]imidazol-2(3H)-one



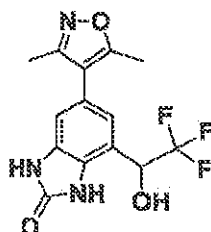
[00498] A solution of tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-formyl-1H-benzo[d]imidazole-1-carboxylate (100 mg, 0.26 mmol), pentafluoroiodoethane (350 mg, 1.42 mmol) and DMF was cooled to -15°C under nitrogen. Tetra(dimethylamino)ethylene was added (0.33 mL, 1.42 mmol) and the reaction mixture was irradiated with a sun lamp. A thick precipitate formed, and after 30 minutes, the reaction mixture was diluted with ethyl acetate filtered. The filtrate was washed with water and the organic layer was concentrated and dissolved in ethanol (3 mL) and 4M HCl in dioxane (1 mL) and heated to 70°C for 1h.

15 The reaction mixture was concentrated and purified by reverse-phase HPLC to give the desired product as a white powder.

[00499] $\text{C}_{15}\text{H}_{12}\text{F}_5\text{N}_3\text{O}_3$. 378.1 (M+1). ^1H NMR (400 MHz, DMSO- d_6) δ 11.02 (d, $J = 2.0$ Hz, 1H), 10.82 (s, 1H), 7.14 – 6.64 (m, 3H), 5.64 – 5.45 (m, 1H), 2.36 (s, 3H), 2.18 (s, 3H).

Example 179

6-(3,5-dimethylisoxazol-4-yl)-4-(2,2,2-trifluoro-1-hydroxyethyl)-1H-benzo[d]imidazol-2(3H)-one



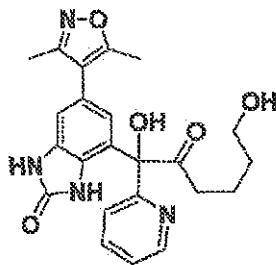
5 [00500] The following compound was likewise prepared from trifluoriodomethane to give 6-(3,5-dimethylisoxazol-4-yl)-4-(2,2,2-trifluoro-1-hydroxyethyl)-1H-benzo[d]imidazol-2(3H)-one as a white powder.

[00501] C₁₄H₁₂F₃N₃O₃. 328.1 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.95 – 10.85 (m, 1H), 10.82 (d, *J* = 1.9 Hz, 1H), 7.11 – 7.00 (m, 1H), 6.90 (dd, *J* = 13.1, 3.6 Hz, 2H), 5.43 (d, *J* = 8.0 Hz, 1H), 2.35 (s, 3H), 2.17 (s, 3H).

Example 180

4-(1,6-dihydroxy-2-oxo-1-(pyridin-2-yl)hexyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

15 [00502] The following compound was isolated as a side product from the previous series of reactions:



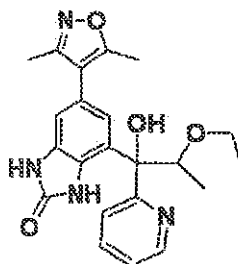
[00503] C₂₃H₂₄N₄O₅. 437.1 (M+1). ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.74 (d, *J* = 1.9 Hz, 1H), 9.89 (d, *J* = 1.9 Hz, 1H), 8.53 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.87 (td, *J* = 7.7, 1.7 Hz,

1H), 7.60 (d, $J = 8.0$ Hz, 1H), 7.37 (dd, $J = 7.5, 4.8$ Hz, 1H), 6.96 (s, 1H), 6.85 – 6.77 (m, 1H), 6.41 (d, $J = 1.5$ Hz, 1H), 3.27 (t, $J = 6.5$ Hz, 2H), 2.82 (ddd, $J = 17.9, 8.6, 6.2$ Hz, 1H), 2.45 – 2.36 (m, 1H), 2.26 (s, 3H), 2.07 (s, 3H), 1.55 – 1.34 (m, 2H), 1.29 (td, $J = 8.8, 4.6$ Hz, 2H).

5

Example 181

6-(3,5-dimethylisoxazol-4-yl)-4-(2-ethoxy-1-hydroxy-1-(pyridin-2-yl)propyl)-1H-benzo[d]imidazol-2(3H)-one

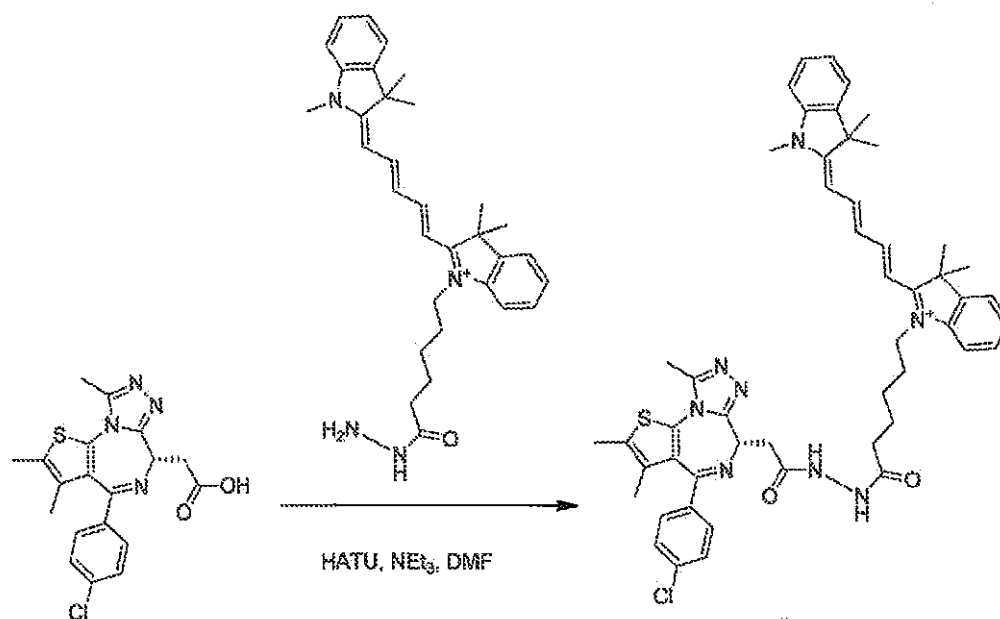


10 [00504] Prepared analogously to give 6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(pyridin-2-yl)(tetrahydro-2H-pyran-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one using ethyl vinyl ether in place of 2,3-dihydro-2H-pyran.

[00505] C₂₂H₂₄N₄O₄. 409.1 (M+1). ¹H NMR (400 MHz, DMSO-d₆) δ 10.67 (d, $J = 2.1$ Hz, 1H), 9.72 (s, 1H), 8.69 – 8.55 (m, 1H), 7.87 (t, $J = 7.6$ Hz, 1H), 7.73 (d, $J = 8.1$ Hz, 1H), 7.36 (d, $J = 7.2$ Hz, 1H), 7.15 (d, $J = 1.5$ Hz, 1H), 6.77 (d, $J = 1.5$ Hz, 1H), 4.50 (q, $J = 6.1$ Hz, 1H), 3.62 – 3.44 (m, 1H), 3.26 – 3.09 (m, 1H), 2.36 (s, 3H), 2.18 (s, 3H), 1.02 – 0.85 (m, 6H).

Example 182

1-(6-(2-(2-((6S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)hydrazinyl)-6-oxohexyl)-3,3-dimethyl-2-((1E,3E,5E)-5-(1,3,3-trimethylindolin-2-ylidene)penta-1,3-dien-1-yl)-3H-indol-1-ium



5

[00506] 2-((6S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetic acid (7 mg, 0.018 mmol) was dissolved in 1ml DMF, to the solution was added HATU (10mg, 0.027 mmol) and the reaction mixture was stirred at RT for 30mins, then to the reaction mixture was added 1-(6-hydrazinyl-6-oxohexyl)-3,3-dimethyl-2-((1E,3E,5E)-5-(1,3,3-trimethylindolin-2-ylidene)penta-1,3-dien-1-yl)-3H-indol-1-ium (5mg, 0.009 mmol) at RT. The reaction was stirred at RT overnight. The solvent was then evaporated, the residue was purified with Prep HPLC to afford 3.6 mg product 1-(6-(2-(2-((6S)-4-(4-chlorophenyl)-2,3,9-trimethyl-6H-thieno[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepin-6-yl)acetyl)hydrazinyl)-6-oxohexyl)-3,3-dimethyl-2-((1E,3E,5E)-5-(1,3,3-trimethylindolin-2-ylidene)penta-1,3-dien-1-yl)-3H-indol-1-ium.

15

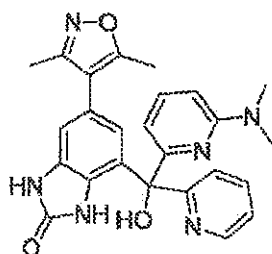
[00507] $C_{51}H_{56}ClN_8O_2S$. 879.4 (M-1). ^1H NMR (400MHz, CD_3OD) δ 7.18-7.10 (m, 2H), 6.44-6.38 (m, 4H), 6.35-6.28 (m, 4H), 6.22-6.17 (m, 5H), 5.58-5.45 (m, 1H), 5.23-5.17 (m, 2H), 3.62-3.58 (m, 1H), 3.08-2.97 (m, 2H), 2.58-2.52 (m, 1H), 2.48 (s, 3H), 2.22 (s, 3H), 1.60 (s, 3H), 1.38 (s, 3H), 1.23-1.20 (m, 2H), 0.82-0.65 (m, 4H), 0.62-0.60 (m, 12H), 0.54-0.48 (m, 2H).

20

Example 183

4-((6-(dimethylamino)pyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

[00508] A procedure similar to that used for 6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(6-methylpyridin-2-yl)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one, using 6-bromo-2-N,N-dimethylaminopyridine as the starting material was used to produce the intermediate ($C_{32}H_{36}N_6O_5$, 585.2 (M+1)), which was taken directly to the deprotection step to yield the title compound as a yellow oil.



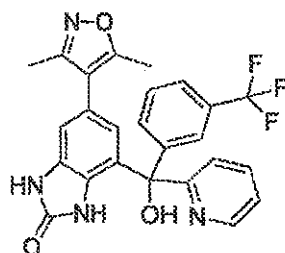
10 [00509] $C_{25}H_{24}N_6O_3$. 457.1 (M+1). ^1H NMR (400 MHz, Chloroform-*d*) δ 8.78 (ddd, J = 5.4, 1.7, 0.9 Hz, 1H), 8.30 (td, J = 7.9, 1.7 Hz, 1H), 8.03 (dt, J = 8.2, 1.0 Hz, 1H), 7.87 (dd, J = 8.9, 7.4 Hz, 1H), 7.78 (ddd, J = 7.7, 5.3, 1.2 Hz, 1H), 7.24 (t, J = 7.5 Hz, 1H), 7.03 (d, J = 1.5 Hz, 1H), 6.96 (dd, J = 9.0, 0.8 Hz, 1H), 6.58 (d, J = 1.5 Hz, 1H), 3.20 (s, 6H), 2.30 (s, 3H), 2.13 (s, 3H).

15

Example 184

6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(pyridin-2-yl)(3-(trifluoromethyl)phenyl)methyl)-1H-benzo[d]imidazol-2(3H)-one

20 [00510] A procedure analogous to 6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(6-methylpyridin-2-yl)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one was used to synthesize the intermediate ($C_{32}H_{31}F_3N_4O_5$, 609.2 (M+1)) which was immediately taken on to the deprotection step to yield a yellow solid.



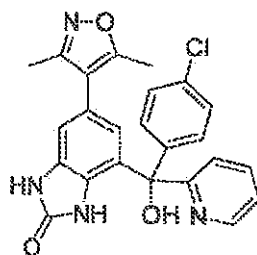
[00511] C₂₅H₁₉F₃N₄O₃. 481.1 (M+1). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.77 – 8.69 (m, 1H), 8.22 (td, *J* = 7.9, 1.7 Hz, 1H), 7.76 (s, 1H), 7.72 (ddt, *J* = 9.2, 6.6, 3.1 Hz, 3H), 7.59 (t, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.05 (d, *J* = 1.5 Hz, 1H), 6.43 (d, *J* = 1.5 Hz, 1H), 2.27 (s, 3H), 2.10 (s, 3H).

Example 185

4-((4-chlorophenyl)(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

10

[00512] A procedure similar to 6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(6-methylpyridin-2-yl)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one was used to synthesize the intermediate (C₃₁H₃₁ClN₄O₃, 575.2 (M+1)) which was taken directly to the deprotection step to yield a yellow solid (9.8 mg).



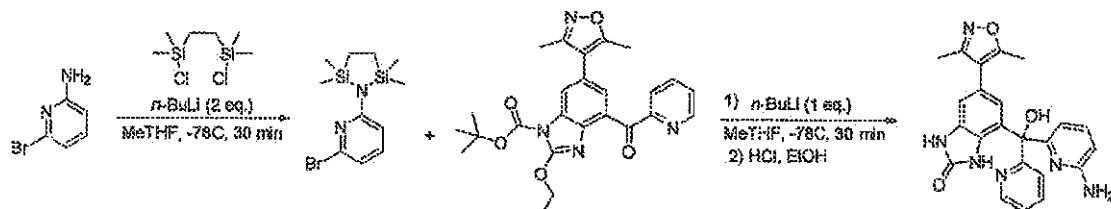
15

[00513] C₂₄H₁₉ClN₄O₃. 447.1 (M+1). ¹H NMR (400 MHz, Methanol-*d*₄) δ 8.71 (ddd, *J* = 5.3, 1.7, 0.9 Hz, 1H), 8.19 (td, *J* = 7.9, 1.7 Hz, 1H), 7.74 – 7.66 (m, 2H), 7.44 – 7.38 (m, 2H), 7.33 – 7.28 (m, 2H), 7.03 (d, *J* = 1.5 Hz, 1H), 6.48 (d, *J* = 1.5 Hz, 1H), 2.29 (s, 3H), 2.12 (s, 3H).

20

Example 186

4-((6-aminopyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



- 5 In a 2-neck, 50-mL round-bottom flask, a solution of 2-amino-6-bromopyridine (265.5 mg, 1.535 mmol) and 1,2-bis(chlorodimethylsilyl)ethane (329.9 mg, 1.532 mmol) in 2-methyltetrahydrofuran (12 mL) were cooled to -78°C while stirring under a nitrogen atmosphere. A solution of *n*-butyllithium (1.42 M in hexanes, 3.26 mL, 2.30 mmol) was added dropwise in 4 equal fractions (waiting five minutes in between) and the reaction
- 10 mixture was stirred for 30 minutes after the final addition. A solution of tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-picolinoyl-1H-benzo[d]imidazole-1-carboxylate (300.8 mg, 0.6504 mmol) in 2-methyltetrahydrofuran (1.5 mL) was added dropwise. The reaction mixture was stirred for 45 minutes while warming to room temperature or until reaction completion. The reaction mixture was quenched with brine and diluted with ethyl acetate.
- 15 The organic layer was separated and saved and the aqueous layer was extracted with ethyl acetate (three times, 40 mL each). The organic fractions were combined, dried over MgSO_4 , filtered and concentrated. The crude product was taken directly to the deprotection step. $\text{C}_{25}\text{H}_{24}\text{N}_6\text{O}_3$. 457.2 (M+1).

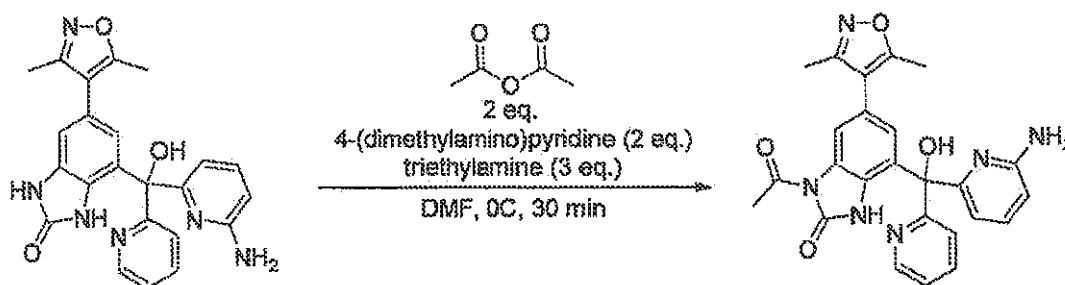
- [00514] The crude material was dissolved in ethanol (15 mL) and transferred to a
- 20 microwave vial. Hydrochloric acid was added (4M in dioxane, 1.6 mL, 6.4 mmol) and the reaction vial was sealed and heated at 70°C for 2 hours. The reaction mixture was cooled to room temperature and concentrated to yield a brown oil, which was triturated with dichloromethane. The remaining oil was taken up in acetonitrile and concentrated to yield a yellow-white solid, which was further purified by preparatory HPLC to yield a yellow oil.

- 25 [00515] $\text{C}_{23}\text{H}_{20}\text{N}_6\text{O}_3$. 429.1 (M+1). $R_f = 0.2$ in 20% MeOH:DCM. ^1H NMR (400 MHz, Methanol- d_4) δ 8.67 (ddd, $J = 5.0, 1.8, 0.9$ Hz, 1H), 7.96 (td, $J = 7.8, 1.8$ Hz, 1H), 7.85 (dd, $J = 9.0, 7.4$ Hz, 1H), 7.70 (dt, $J = 8.0, 1.0$ Hz, 1H), 7.47 (ddd, $J = 7.6, 4.8, 1.1$ Hz, 1H),

7.04 (d, $J = 1.5$ Hz, 1H), 6.97 (dd, $J = 9.0, 1.0$ Hz, 1H), 6.66 (dd, $J = 7.4, 1.0$ Hz, 1H), 6.42 (d, $J = 1.5$ Hz, 1H), 2.28 (s, 3H), 2.11 (s, 3H).

Example 187

5 1-acetyl-4-((6-aminopyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one



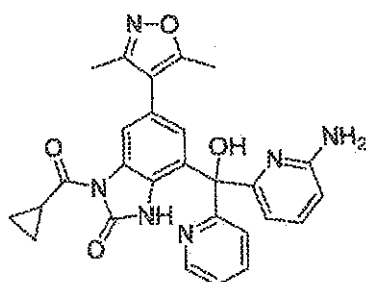
[00516] To a microwave vial capped with a septum, 4-(dimethylamino)pyridine (5.8 mg, 0.047 mmol) and triethylamine (9 μ L, 0.07 mmol) in N,N-dimethylformamide (0.5 mL) were cooled to 0°C in a nitrogen atmosphere. Acetic anhydride (4.4 μ L, 0.047 mmol) was added and the reaction mixture was stirred for 15 minutes at 0°C before a solution of 4-((6-aminopyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one (10 mg, 0.023 mmol) in N,N-dimethylformamide (0.25 mL) was added dropwise to the reaction mixture. The reaction was allowed to warm to room temperature and stirred for thirty minutes (or until completion). The reaction was quenched with water and diluted with ethyl acetate. The organic layer was separated and saved and the organic layer was extracted with ethyl acetate (three times, 20 mL each). The organic fractions were collected, dried over MgSO_4 , filtered and concentrated. The product was isolated by preparatory HPLC to yield a clear oil.

20 [00517] $\text{C}_{25}\text{H}_{22}\text{N}_6\text{O}_4$. 471.1 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 8.68 (d, $J = 4.8$ Hz, 1H), 8.18 (d, $J = 1.6$ Hz, 1H), 8.02 – 7.93 (m, 1H), 7.85 (dd, $J = 9.0, 7.4$ Hz, 1H), 7.72 – 7.65 (m, 1H), 7.52 – 7.43 (m, 1H), 6.98 (dd, $J = 9.2, 1.0$ Hz, 1H), 6.68 – 6.61 (m, 1H), 6.57 (d, $J = 1.6$ Hz, 1H), 2.70 (s, 3H), 2.30 (s, 3H), 2.11 (s, 3H).

Example 188

4-((6-aminopyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-1-(cyclopropanecarbonyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

- 5 [00518] A procedure similar to 1-acetyl-4-((6-aminopyridin-2-yl)(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one was used.

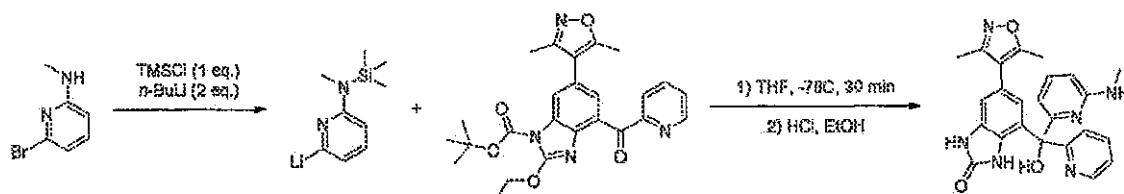


- [00519] $C_{27}H_{24}N_6O_4$. 497.2 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 8.68 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 8.13 (d, J = 1.6 Hz, 1H), 7.97 (td, J = 7.8, 1.8 Hz, 1H), 7.85 (dd, J = 9.0, 7.4 Hz, 1H), 7.69 (dt, J = 8.0, 1.0 Hz, 1H), 7.48 (ddd, J = 7.6, 4.8, 1.1 Hz, 1H), 7.25 – 7.08 (m, 2H), 6.98 (dd, J = 8.9, 1.0 Hz, 1H), 6.65 (dd, J = 7.4, 1.0 Hz, 1H), 6.56 (d, J = 1.6 Hz, 1H), 3.48 (ddd, J = 8.0, 4.6, 3.2 Hz, 1H), 2.29 (s, 3H), 2.10 (s, 3H), 1.21 (dt, J = 5.2, 3.4 Hz, 2H), 1.15 – 1.06 (m, 2H).
- 10

15

Example 189

6-(3,5-dimethylisoxazol-4-yl)-4-(hydroxy(6-(methylamino)pyridin-2-yl)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one



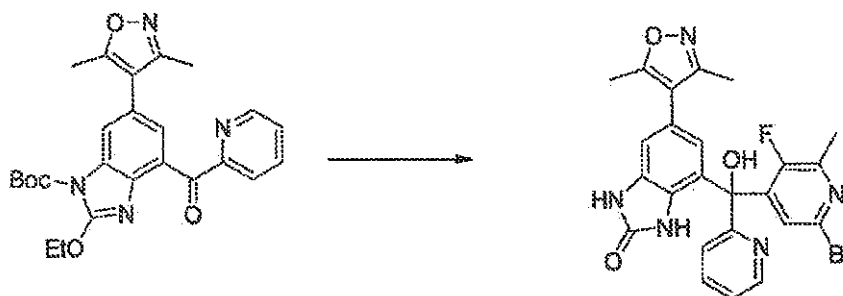
[00520] To a 50-mL, 2-neck round-bottom flask, 6-bromo-N-methylpyridin-2-amine (41.5 mg, 0.222 mmol) and chlorotrimethylsilane (29 μ L, 0.23 mmol) were dissolved in tetrahydrofuran (2 mL). The cloudy white suspension was stirred under nitrogen for thirty minutes at room temperature. The reaction mixture was then cooled to -78°C before a 1.6 M *n*-butyllithium solution in hexanes (0.23 mL, 0.37 mmol) was added dropwise and the solution was stirred for thirty minutes. A solution of *tert*-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-picolinoyl-1*H*-benzo[d]imidazole-1-carboxylate in tetrahydrofuran (1 mL) was added dropwise and the reaction was warmed to ambient temperature and stirred for twenty minutes or until reaction completion. The reaction mixture was quenched with brine and diluted with ethyl acetate. The organic layer was separated and saved and the aqueous layer was neutralized and subsequently extracted with ethyl acetate twice. The combined organic fractions were dried over sodium sulfate, decanted and concentrated. The crude intermediate was taken directly to the deprotection step. $\text{C}_{21}\text{H}_{34}\text{N}_6\text{O}_5$. 611.3 (M+1).

[00521] In a microwave vial, the crude intermediate was dissolved in ethanol (3 mL) and 4M hydrochloric acid in dioxane (1 mL) was added. The vial was sealed and heated at 65°C for 1 hour. The reaction mixture was concentrated, filtered and the title compounds was purified via preparatory HPLC to yield a yellow solid.

[00522] $\text{C}_{24}\text{H}_{22}\text{N}_6\text{O}_3$. 443.1 (M+1). ^1H NMR (400 MHz, Methanol- d_4) δ 8.70 (ddd, J = 5.0, 1.8, 0.9 Hz, 1H), 8.03 (td, J = 7.8, 1.7 Hz, 1H), 7.90 (dd, J = 9.0, 7.4 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.53 (ddd, J = 7.6, 4.9, 1.1 Hz, 1H), 7.02 (d, J = 1.5 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 6.87 (d, J = 7.4 Hz, 1H), 6.48 (d, J = 1.5 Hz, 1H), 3.06 (s, 3H), 2.28 (s, 3H), 2.10 (s, 3H).

Example 190

4-((6-bromo-3-fluoro-2-methylpyridin-4-yl)(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

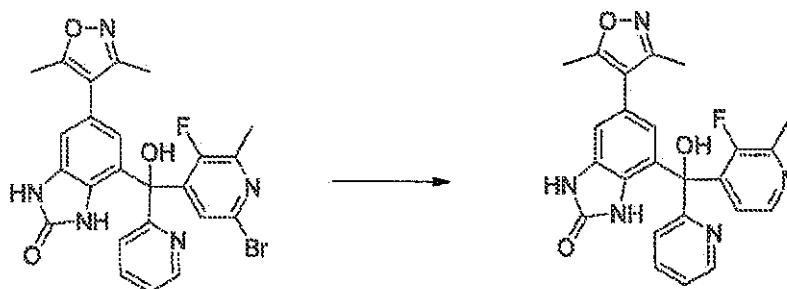


- 5 [00523] To a solution of 2-bromo-5-fluoro-6-methyl-2-pyridine (411 mg, 2.16 mmol) in THF (10 mL) was added BuLi (0.86 mL, 2.16 mmol, 2.5 M in THF) and the solution was stirred at -78 °C for 1h. To the solution of tert-butyl 6-(3,5-dimethylisoxazol-4-yl)-2-ethoxy-4-picolinoyl-1H-benzo[d]imidazole-1-carboxylate (200 mg, 0.43 mmol) in THF (5 mL) was added the solution of the lithiate and the solution was stirred at -78 °C for 1h. Aq NH₄Cl was
- 10 added and the solution was extracted with EtOAc (200 mL). The organic solution was washed with brine and dried over Na₂SO₄. Solvent was removed and the residue was dissolved in EtOH (6 mL) with 0.8 mL of 4N HCl in dioxane. The solution was heated at microwave at 70 °C for 1h. Solvent was removed and the residue was purified by HPLC to give 4-((6-bromo-3-fluoro-2-methylpyridin-4-yl)(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-
- 15 dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one

[00524] C₂₄H₁₉BrFN₅O₃. MS m/z 523.9 (M+1).

Example 191

6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoro-2-methylpyridin-4-yl)(hydroxy)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one



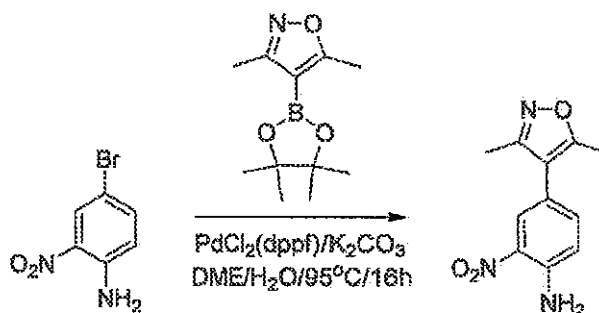
- 5 [00525] A mixture of 4-((6-bromo-3-fluoro-2-methylpyridin-4-yl)(hydroxy)(pyridin-2-yl)methyl)-6-(3,5-dimethylisoxazol-4-yl)-1H-benzo[d]imidazol-2(3H)-one obtained above and Pd/C (5 % 100 mg) in MeOH (10 mL) was stirred under H₂ balloon for 1h. Reaction mixture was filtered and the filtrate was concentrated to dryness. The residue was purified by HPLC to give 6-(3,5-dimethylisoxazol-4-yl)-4-((3-fluoro-2-methylpyridin-4-yl)(hydroxy)(pyridin-2-yl)methyl)-1H-benzo[d]imidazol-2(3H)-one.

[00526] C₂₄H₂₀FN₅O₃. MS m/z 446.02 (M+1). ¹H NMR (400 MHz, Methanol-d₄) δ 8.56 (ddd, J = 5.1, 1.8, 0.9 Hz, 1H), 8.42 (d, J = 5.6 Hz, 1H), 8.00 (td, J = 7.8, 1.7 Hz, 1H), 7.76 – 7.64 (m, 2H), 7.49 (ddd, J = 7.6, 5.0, 1.1 Hz, 1H), 7.02 (d, J = 1.5 Hz, 1H), 6.59 (t, J = 1.8 Hz, 1H), 2.53 (d, J = 3.0 Hz, 3H), 2.30 (s, 3H), 2.13 (s, 3H).

15

Example 192

4-(3,5-dimethylisoxazol-4-yl)-2-nitroaniline



[00527] To a mixture of 4-bromo-2-nitro-phenylamine (150 g, 0.691 mol, 1.0 eq) and 3,5-dimethylisoxazole-4-boronic acid pinacol ester (169 g, 0.725 mol, 1.05 eq) in 1,2-dimethoxyethane (1.5 L) and water (700 mL) were added PdCl₂(dppf) (56 g, 69 mmol, 0.1 eq) and K₂CO₃ (190 g, 1.38 mol, 2.0 eq). The reaction mixture was heated at 95 °C overnight.

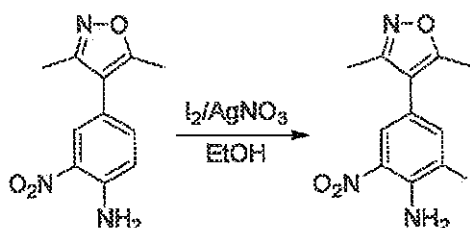
- 5 The reaction mixture was diluted with EtOAc (3 L), washed with brine (2 x 500 mL). The organic solvent was evaporated and the residue was purified with flash chromatography on silica (PE/EA = 10:1 - 1:1) to give 150 g 4-(3,5-dimethylisoxazol-4-yl)-2-nitroaniline as a red solid.

[00528] C₁₁H₁₁N₃O₃. 234.2 (M+1)

10

Example 193

4-(3,5-dimethylisoxazol-4-yl)-2-iodo-6-nitroaniline

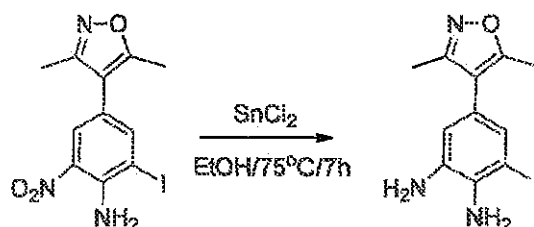


- [00529] To a solution of compound 4-(3,5-dimethylisoxazol-4-yl)-2-nitroaniline (334 g, 1.43 mol, 1.0 eq) in ethanol (3.3 L) were added iodine (726 g, 2.8 mol, 2.0 eq) and silver nitrate (485 g, 2.8 mol, 2.0 eq). The reaction mixture was stirred at rt overnight, filtered, and the filtrate was evaporated to dryness. The residue was dissolved in EtOAc (5 L) and washed with water and brine, and dried over sodium sulfate. The organic solvent was evaporated to give a residue, which was purified by flash column chromatography on silica gel (PE/EA = 4:1-3:1) to give compound 393g of 4-(3,5-dimethylisoxazol-4-yl)-2-iodo-6-nitroaniline as an orange solid.
- 15
- 20

[00530] C₁₁H₁₀IN₃O₃. 360.1 (M+1)

Example 194

5-(3,5-dimethylisoxazol-4-yl)-3-iodobenzene-1,2-diamine

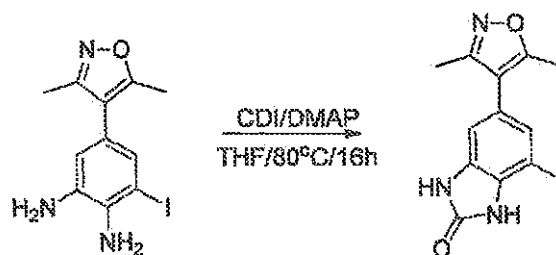


[00531] To a solution of 4-(3,5-dimethylisoxazol-4-yl)-2-iodo-6-nitroaniline (393 g,
 5 1.09 mol, 1.0 eq) in ethanol (4 L) was added tin (II) chloride (1.03 kg, 5.46 mol, 5.0 eq). The reaction mixture was stirred at 75 °C for 10 h. The solvent was evaporated and the residue was dissolved in EtOAc (5 L), washed with 1 N sodium hydroxide (3 x 1 L) (the solid precipitated out should be filtered). The organic phase was dried over Na₂SO₄ and the solvent was removed to give a residue. The residue was purified by flash chromatography on silica
 10 (PE/EA = 2:1-3:2) to give 253g of 5-(3,5-dimethylisoxazol-4-yl)-3-iodobenzene-1,2-diamine as a slightly brown solid.

[00532] C₁₁H₁₂IN₃O. 330.1 (M+1)

Example 195

6-(3,5-dimethylisoxazol-4-yl)-4-iodo-1H-benzo[d]imidazol-2(3H)-one



[00533] 5-(3,5-dimethylisoxazol-4-yl)-3-iodobenzene-1,2-diamine (253 g, 0.77 mol, 1.0 eq) was treated with carbonyl diimidazole (187 g, 1.15 mol, 1.5 eq) and DMAP (47 g, 384 mmol, 0.5 eq) in THF (2.5 L) at 80 °C for 16 h. The precipitate was obtained by

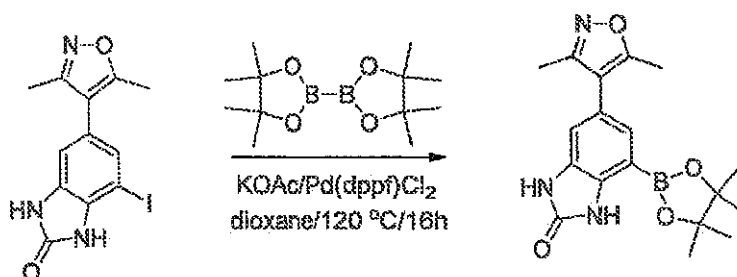
filtration. The solid was triturated with EA/PE (1/1) to give 197g of 6-(3,5-dimethylisoxazol-4-yl)-4-iodo-1H-benzo[d]imidazol-2(3H)-one as a white solid.

[00534] $C_{12}H_{10}IN_3O_2$ 356.1 (M+1) ^1H NMR (400 MHz, DMSO- d_6) δ 10.97 (s, 1H), 10.91 (s, 1H), 7.23 (s, 1H), 5.86 (s, 1H), 2.35 (s, 3H), 2.17 (s, 3H).

5

Example 196

6-(3,5-dimethylisoxazol-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one



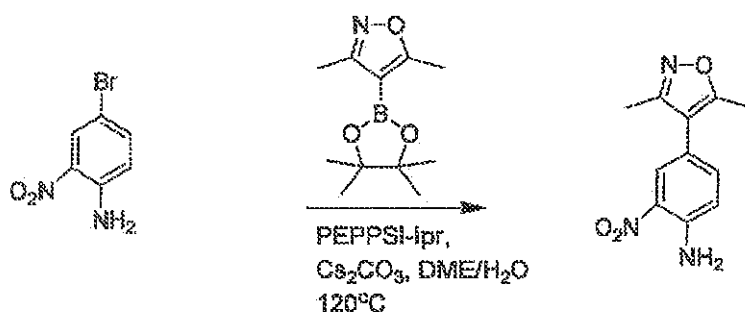
10 [00535] A mixture of 6-(3,5-dimethylisoxazol-4-yl)-4-iodo-1H-benzo[d]imidazol-2(3H)-one (166 g, 468 mmol 1.0 eq), Pd(dppf)Cl₂ (19 g, 5% mol), KOAc (92 g, 935 mmol, 2 eq) and bispinacolato diboron (237 g, 935 mmol, 2.0 eq) in degassed dioxane (3.5 L) was flushed with nitrogen. The reaction mixture was heated at 120 °C under N₂ overnight. Then the reaction mixture was concentrated and dry-loaded onto silica gel and purified by flash
15 chromatography (PE/EA = 10:1-3:1) to give 72g of 6-(3,5-dimethylisoxazol-4-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-benzo[d]imidazol-2(3H)-one.

[00536] $C_{19}H_{22}BN_3O_4$ 356.0 (M+1) ^1H NMR (400 MHz, DMSO- d_6) δ 10.78 (s, 1H), 9.84 (s, 1H), 7.04 (s, 1H), 6.97 (s, 1H), 2.34 (s, 3H), 2.16 (s, 3H).

20

Example 197

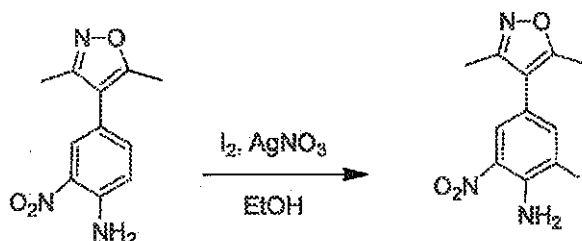
4-(3,5-dimethylisoxazol-4-yl)-2-nitroaniline



- 5 [00537] 4-bromo-2-nitroaniline (1g, 4.6 mmol) and 3,5-Dimethylisoxazole-4-boronic acid pinacol ester (2g, 9.2mmol) was added to a solvent mixture of 1,2-dimethoxymethane (12 ml) and water (6 ml). To the above mixture were added PEPPSI-Ipr (312mg, 0.46 mmol) and Cs_2CO_3 (4.5g, 13.8 mmol). The reaction mixture was heated at 120°C for 30 min. The reaction mixture was then diluted with EtOAc (100 ml), washed with brine (50 ml x 2). The
- 10 organic solvent was evaporated and the residue was dissolved in DCM and purified with flash column chromatography (50% EtOAc/Hexane) to afford 4-(3,5-dimethylisoxazol-4-yl)-2-nitroaniline.

Example 198

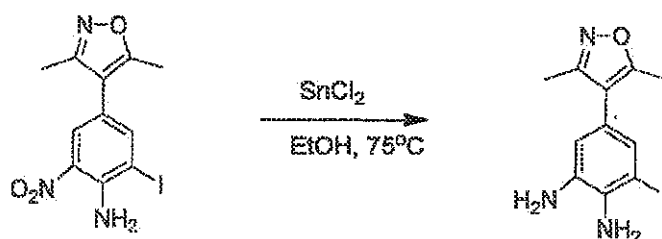
- 15 4-(3,5-dimethylisoxazol-4-yl)-2-iodo-6-nitroaniline



[00538] 4-(3,5-dimethylisoxazol-4-yl)-2-nitroaniline (1g, 4.6 mmol) was added to EtOH (50 ml), to the mixture was added I_2 (1.4g, 5.5 mmol) and $AgNO_3$ (0.94g, 5.5 mmol). The reaction mixture was stirred at room temperature overnight. The solvent was evaporated and then the residue was dissolved in EtOAc (50 ml) and washed with brine (30 ml x 2). The organic solvent was evaporated and the residue was dissolved in DCM and purified with flash column chromatography (product came out at 35% EtOAc/Hexane) to afford 4-(3,5-dimethylisoxazol-4-yl)-2-iodo-6-nitroaniline.

Example 199

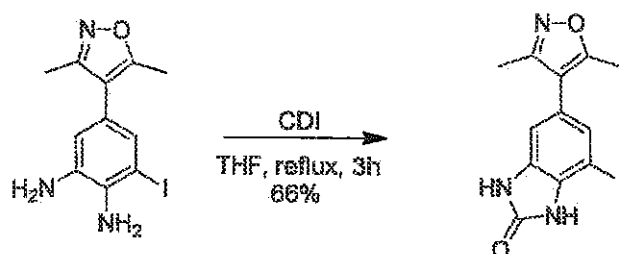
5-(3,5-dimethylisoxazol-4-yl)-3-iodobenzene-1,2-diamine



[00539] 4-(3,5-dimethylisoxazol-4-yl)-2-iodo-6-nitroaniline (0.9g, 2.5 mmol) was added to EtOH (50 ml), to the mixture were added $SnCl_2$ (2.4g, 12.5 mmol). The reaction mixture was stirred at 75°C for 7h. The solvent was evaporated and then the residue was dissolved in EtOAc (100 ml) and washed with 1N NaOH (100mLx3). The organic solvent was evaporated and the residue was dissolved in DCM and purified with combi-flash column chromatography (product came out at 60% EtOAc/Hexane) to afford 5-(3,5-dimethylisoxazol-4-yl)-3-iodobenzene-1,2-diamine. LCMS m/z $[M+H]^+$ $C_{11}H_{12}IN_2O$ requires: 330.00. Found 330.03 ^1H NMR (400 MHz, CD_3OD) δ 2.21 (s, 3H), 2.39 (s, 3H), 7.16 (d, 1H), 7.62 (d, 1H).

Example 200

6-(3,5-dimethylisoxazol-4-yl)-4-iodo-1H-benzo[d]imidazol-2(3H)-one



- 5 [00540] A mixture of 5-(3,5-dimethylisoxazol-4-yl)-3-iodobenzene-1,2-diamine (15 g, 45.6 mmol, 1.0 eq), DMAP (2.9 g, 22.7 mmol, 0.5 eq) and carbonyl diimidazole (11.0 g, 68.4 mmol, 1.5 eq) in THF (200 mL) was refluxed for 3 h. The reaction was cooled to room temperature, purified by flash column chromatography to give a solid, which contained some imidazole and DMAP. The solid was triturated with THF (2x) and filtered to afford 6-(3,5-
- 10 dimethylisoxazol-4-yl)-4-iodo-1H-benzo[d]imidazol-2(3H)-one. LC-MS: 354.0 [M-H]⁻ ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.9 (br s, 2H), 7.24 (d, J = 1.6 Hz, 1H), 6.97 (d, J = 1.6 Hz, 1H), 2.37 (s, 3H), 1.78 (s, 3H).

Example 201

15 Biochemical Alpha Assay

- [00541] Binding of the bromodomain BRD4₁ to an acetylated histone H4 peptide was measured using a bead based Amplified Luminescent Proximity Homogeneous Assay (ALPHA). The synthetic peptide containing amino acids 1-18 of histone H4 was acetylated at lysine 5, 8, 12, 16 and conjugated to biotin (SGRGACKGGACKGLGACKGGAACKRH-
- 20 GSGSK-biotin) was purchased from Millipore. BRD4₁ was expressed and purified from *Escherichia coli* as an N-terminal His₆-tagged protein. Nickel-Chelate ALPHA acceptor beads (Perkin Elmer) were used to specifically bind BRD4₁ and ALPHA streptavidin donor beads (Perkin Elmer) were used because they specifically recognized the biotinylated H4 peptide. Binding of BRD4₁ to the peptide resulted in proximity of the donor and acceptor
- 25 beads which leads to an increase in ALPHA signal whereas disruption of this protein-peptide interaction with a small molecule inhibitor resulted in a decrease in ALPHA signal. Assays

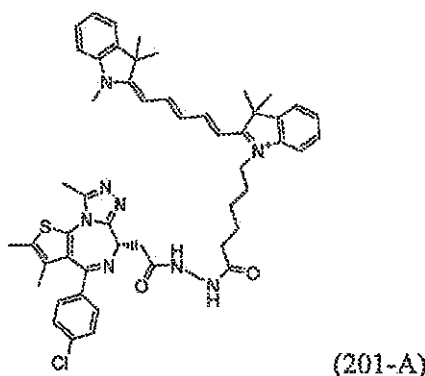
were performed in 50 mM Hepes (pH 7.5), 150 mM NaCl, 0.1mg/ml BSA, 0.01% (v/v) Brij, 0.5% (v/v) DMSO, 200nM H4 peptide and 15nM of BRD4_1 protein. After an assay reaction time of 60 minutes at 25°C, binding was measured with 20µg/ml streptavidin donor beads and 20µg/ml nickle-chelate acceptor beads. ALPHA signal was detected on an Envision plate reader (Ex: 320 nm; Em: 570 nm; Ex time: 180ms). Data were normalized based on a positive (2 µM I-BET) and negative (DMSO) controls and IC₅₀ values were calculated from the fit of the dose-response curves to a four-parameter equation. All IC₅₀ values represent geometric mean values of a minimum of four determinations. These assays generally produced results within 3-fold of the reported mean.

10 Biochemical HTRF Assay

[00542] Binding of the two tandem bromodomains, BRD4_1 and BRD4_2, to an acetylated histone H4 peptide were measured using a homogeneous time resolved fluorescence resonance energy transfer (TR-FRET) assay. The synthetic peptide containing amino acids 1-18 of histone H4 was acetylated at lysine 5, 8, 12, 16 and conjugated to biotin (SGRGACKGGACKGLGACKGGAACKRH-GSGSK-biotin) was purchased from Millipore. BRD4_1 and BRD4_2 were expressed and purified from *Escherichia coli* as N-terminal His₆-tagged proteins. An XL665 labeled anti-His antibody (Cisbio) was used to specifically bind BRD4 and a cryptate labeled streptavidin protein was used because it specifically recognized the biotinylated H4 peptide. Binding of BRD4 to the peptide resulted in an increase in FRET signal whereas disruption of this protein-peptide interaction with a small molecule inhibitor resulted in a decrease in FRET signal. Assays were performed in 50 mM Hepes (pH 7.5), 150 mM NaCl, 0.1mg/ml BSA, 0.01% (v/v) Brij, 0.5% (v/v) DMSO and 200nM H4 peptide at the following concentrations for each BRD4 isoform: 60 nM BRD4_1 and 120 nM BRD4_2. After an assay reaction time of 60 minutes at 25 °C, binding was measured with 2 nM cryptate labeled streptavidin and 10 nM anti-His-XL665 antibody. TR-FRET signal was detected on an Envision plate reader (Ex: 320 nm; Em: 615/665 nm; 100µs delay and 200µs read window). Data were normalized based on a positive (2 µM I-BET) and negative (DMSO) controls and IC₅₀ values were calculated from the fit of the dose-response curves to a four-parameter equation. All IC₅₀ values represent geometric mean values of a minimum of four determinations. These assays generally produced results within 3-fold of the reported mean.

BRD4-1 Ligand KI and BRD4-2 Ligand KI Assays:

[00543] Binding of the two tandem bromodomains, BRD4-1 and BRD4-2, to a Cy5 labeled probe/ligand (Compound 201-A) were measured using a homogeneous time resolved fluorescence resonance energy transfer (TR-FRET) assay.



5

[00544] The labeled ligand specifically binds BRD4-1 and BRD4-2 and can be displaced by a small molecule inhibitor that shares a similar or overlapping binding site. BRD4-1 and BRD4-2 were expressed and purified from *Escherichia coli* as N-terminal His₆-tagged proteins. A Eu-cryptate labeled anti-His antibody (Perkin Elmer) was used to specifically bind BRD4. Binding of BRD4 to the labeled probe/ligand resulted in an increase in FRET signal whereas displacement of this labeled ligand from BRD4 with a small molecule inhibitor resulted in a decrease in FRET signal. Assays were performed in 50 mM Hepes (pH 7.5), 150 mM NaCl, 0.1mg/ml BSA, 0.01% (v/v) Brij, 0.5% (v/v) DMSO and 10nM labeled ligand at the following concentrations for each BRD4 isoform: 2 nM BRD4-1 and 0.5 nM BRD4-2. After an assay reaction time of 60 minutes at 25 °C, binding was measured with 2 nM Eu-cryptate labeled anti-His antibody. TR-FRET signal was detected on an Envision plate reader (Ex: 320 nm; Em: 615/665 nm; 100µs delay and 200µs read window). Data were normalized based on a positive (2 µM I-BET) and negative (DMSO) controls and IC₅₀ values were calculated from the fit of the dose-response curves to a four-parameter equation. All IC₅₀ values represent geometric mean values of a minimum of four determinations. The IC₅₀ values were converted to K_i values (dissociation constant for BRD4-inhibitor complex) using the Cheng and Prusoff equation for a competitive inhibitor mode of action. These assays generally produced results within 3-fold of the reported mean.

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MT-4 Proliferation Assay in 384-well Format

[00545] Compounds were tested in a standardized high-throughput 384-well assay format. Each compound was serially diluted 3-fold in 100% DMSO in polypropylene 384-well plates using a Biomek FX Workstation, and 0.4 μ L compound added to an assay plate containing 40 μ L RPMI media. Compounds were arranged in a horizontal pattern, with 10 concentrations per compound, and 8 compounds added per plate. Due to low DMSO tolerability, the final DMSO concentration never exceeded 0.5% (v/v). Each assay plate contained 10 μ M Puromycin and 0.5% DMSO in RPMI-1640 as positive and negative controls respectively. MT-4 cells (HTLV-1 transformed, human T lymphoblastoid cells, NIH Aids Reagent program) were added in volumes of 35 μ L per well and 2,000 cells per well using a Biotek uFlow Workstation (Biotek, Winooski, VT), and the plates subsequently incubated for 5 days at 37°C in an incubator set at 5% CO₂ and 90% humidity.

[00546] After 5 days, 22 μ L Cell Titer Glo (Promega) was added to the assay plates with a Biotek uFlow Workstation. Plates were subsequently placed on a Perkin Elmer Envision Plate Reader for 5 minutes before the luminescence signal was read. CC₅₀ values were calculated from the compound concentration that caused a 50% decrease in luminescence signal, a measure of toxicity, and calculated by non-linear regression using Pipeline Pilot software (Accelrys, San Diego, CA).

c-Myc Down Regulation and Viability Assays

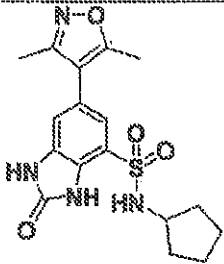
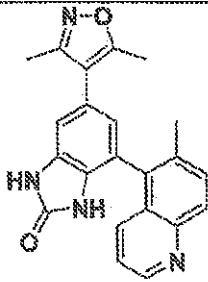
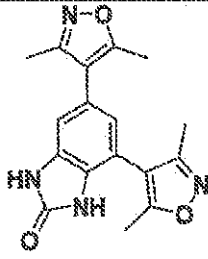
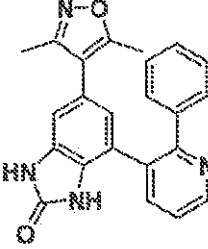
[00547] An enzyme linked immunosorbent assay using the Meso Scale Diagnostic (MSD) technology was used to detect levels of c-Myc produced in MM1S cells (ATCC). MM1S cells were cultured in RPMI-1640 media (Corning), supplemented with 10% FBS (Hyclone), 1% penicillin-streptomycin (Cellgro), 2-mercaptoethanol (Gibco) and seeded onto 384-tissue culture treated filter binding plates (Millipore) at a density of 40K cells/well containing titrations of small molecule inhibitors or DMSO (0.4 %) in a volume of 100 μ L of media. After an incubation time of 24 hrs, cells were lysed (1 X lysis buffer (Thermo) supplemented with protease and phosphatase inhibitor cocktail (Thermo)) and the plates centrifuged (1000 rpm, 1min) to capture c-Myc on MSD plates coated with a monoclonal c-Myc antibody (Origene). Assay wells were washed (3X Invitrogen wash buffer) and probed with a polyclonal c-Myc antibody (Abcam) and MSD detection antibody solution in order to detect levels of c-Myc on the MSD platform. c-Myc capture was reported in pg/ml based on

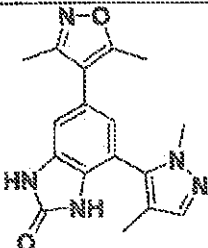
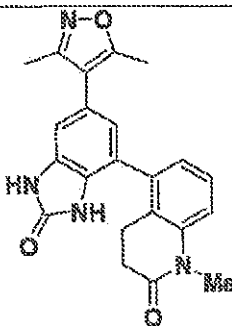
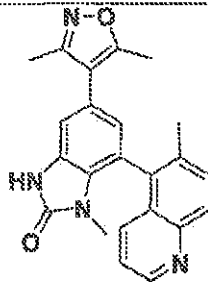
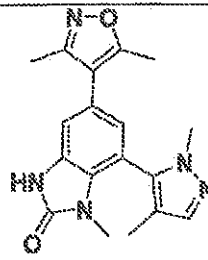
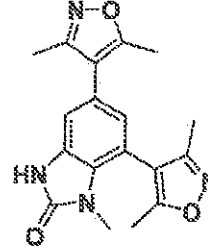
a standard curve using recombinant c-Myc protein (Prosci). EC50 values were calculated from the fit of the dose-response curves to a four-parameter equation. All EC50 values represent geometric mean values of a minimum of four determinations. These assays generally produced results within 3-fold of the reported mean.

- 5 [00548] For cell viability in the MM1S cell line, cells were seeded onto 384-tissue culture treated plates (Greiner) at a density of 60K cells/well containing titrations of small molecule inhibitors or DMSO (0.2 %). After 72 hr incubation cells were analyzed for cell viability by addition of CellTiter Glo (Promega) to the assay plates. After 15 min incubation at room temperature the signal from the viable cells was analyzed on an Envision plate reader
- 10 (Perkin Elmer). EC50 values were calculated from the fit of the dose-response curves to a four-parameter equation. All EC50 values represent geometric mean values of a minimum of four determinations. These assays generally produced results within 3-fold of the reported mean.

- [00549] Results are shown in Tables 1 and 2. An 'n/a' indicates that assay was not
- 15 performed for that compound.

Table 1

Compound of Example No.	Structure	BRD4_1- ALPHA A [nM]	IC ₅₀ HTBS BRD4-1 HTRF [nM]	IC ₅₀ HTBS BRD4-2 HTRF [nM]	CC ₅₀ MT4 384 [nM]
1		n/a	1412	1068	1123.8
2		30.8	135	119	18.951
3		119.4	295	n/a	196.26
4		37.2	119	141	102.76

5		233.5	350	144	232.94
6		46.8	132	108	53.911
7		37.3	121	101	17.543
8		240.6	511	168	116.58
9		270.3	497	227	203.9

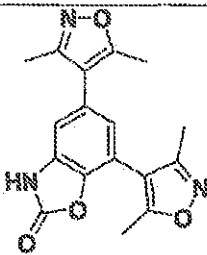
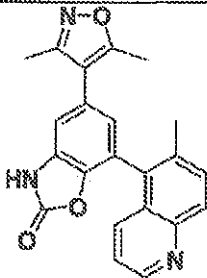
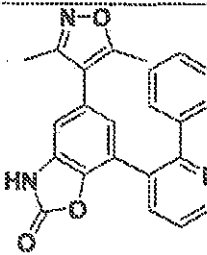
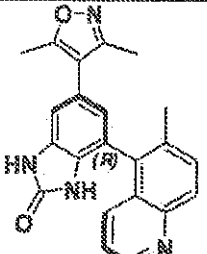
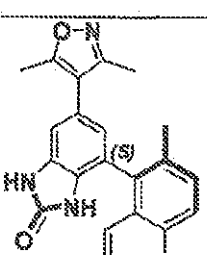
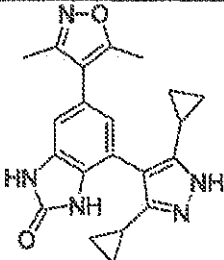
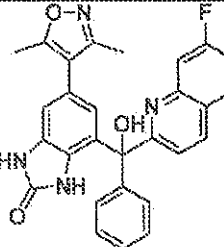
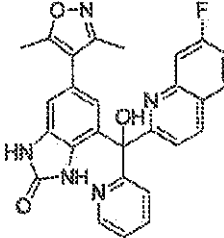
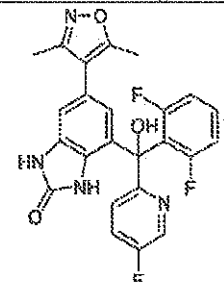
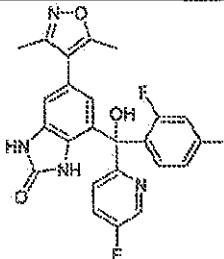
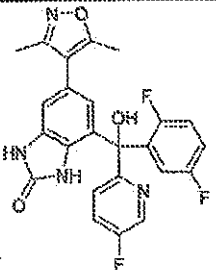
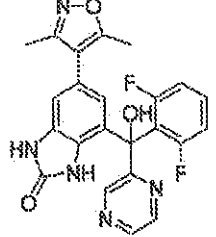
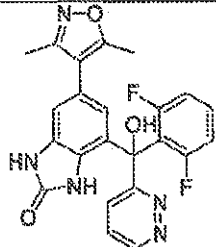
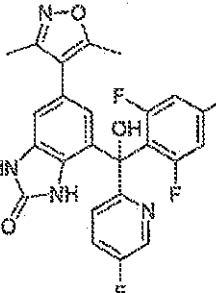
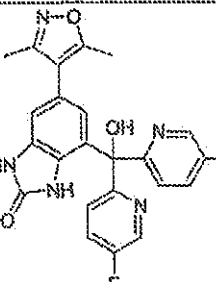
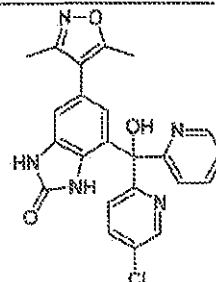
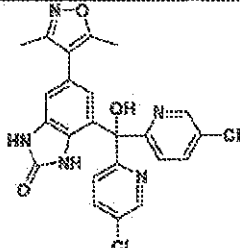
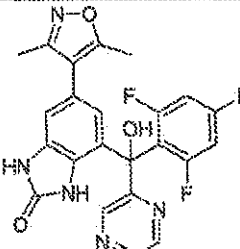
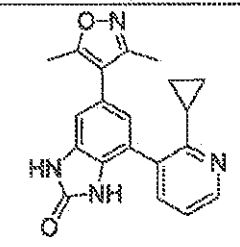
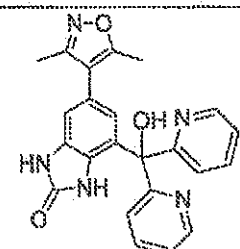
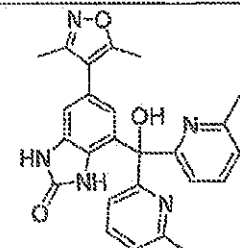
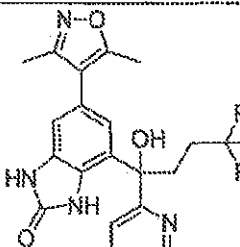
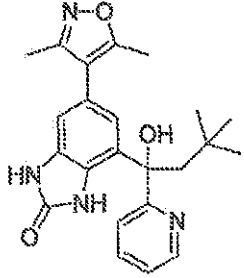
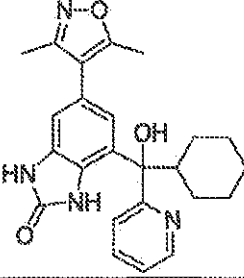
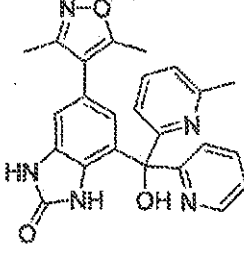
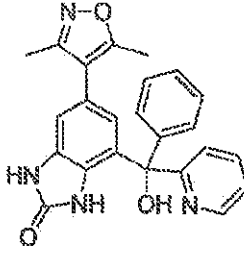
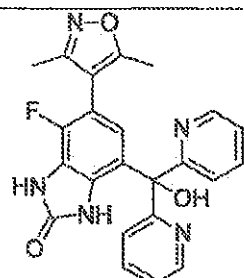
10		196.5	313	396	1027.6
11		222	438	174	420.62
12		232.7	316	314	761.13
13		45.2	n/a	n/a	51.551
14		14	n/a	n/a	9.543

Table 2

Compound of Example No.	Structure	BRD4-1 Ligand K1 [nM]	BRD4-1 Ligand K2 [nM]	CC ₅₀ MT4 384 [nM]	cMYC EC ₅₀ [nM]
23		12.9	3.0	9.1	13.2
33		14.1	5.3	29.1	176.5
36		14.1	5.3	29.1	176.5
38		7.8	4.4	29.7	84.7
39		11.8	5.9	42.1	127.7

41		12.8	5.0	47.3	104.0
49		8.1	2.7	9.7	n/a
50		8.7	5.9	16.0	n/a
52		8.9	6.4	36.1	134.9
53		26.6	24.1	28.6	171.7
54		22.7	14.1	27.1	111.2

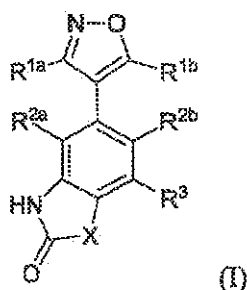
55		14.5	18.2	41.0	141.2
56		6.0	3.6	24.8	40.9
73		34.2	24.0	61.0	153.6
133		40.3	15.8	25.5	44.3
134		69.9	5.3	19.1	74.4
140		35.2	43.8	78.3	216.7

143		29.3	8.0	20.4	118.2
144		7.7	2.7	n/a	n/a
147		81.6	16.0	56.5	107.3
149		17.3	4.6	17.5	73.8
169		62.0	33.5	41.4	128.2

[00550] While the foregoing description describes specific embodiments and aspects, those with ordinary skill in the art will appreciate that various modifications and alternatives can be developed. Accordingly, the particular embodiments and aspects described above are meant to be illustrative only, and not to limit the scope of the invention, which is to be given the full breadth of the appended claims, and any and all equivalents thereof.

We claim:

1. A compound of Formula (I)



wherein

R^{1a} and R^{1b} are each independently C₁-C₆ alkyl, C₁-C₆ alkoxy, C₁-C₆ haloalkyl, C₁-C₆ haloalkoxy, C₁-C₆ hydroxyalkyl, C₃-C₆ cycloalkyl, or CH₂-C₃-C₆ cycloalkyl;

R^{2a} and R^{2b} are each independently H or halogen;

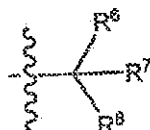
R³ is

C₅-C₁₀ aryl, C₅-C₁₀ heteroaryl, or C₅-C₁₀ heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups; or

-S(O)₂NHR⁴,

wherein R⁴ is C₁-C₆ alkyl or C₃-C₇ cycloalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups; or

a moiety of the formula



wherein

R⁶ is H, OH, or halogen; and R⁷ and R⁸ are each independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, or C₅-C₁₂ heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups; or R⁶ is H, C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, phenyl, naphthyl, or C₃-C₁₂ heteroaryl; and R⁷ and R⁸ together form a C₁-C₆ alkylidene group having a double bond with the carbon to which each of R⁶, R⁷, and R⁸ are bound wherein each of the C₁-C₆

alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, -C₃-C₆ cycloalkyl, phenyl, naphthyl, or C₃-C₁₂ heteroaryl groups is optionally substituted with from 1 to 5 R²⁰ groups;

X is N-Q, or O;

Q is H, C₁-C₃ alkyl, C₁-C₃ haloalkyl, benzyl or substituted benzyl;

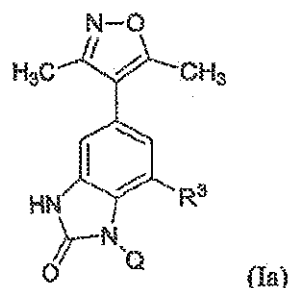
each R²⁰ is independently C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, halogen, oxo, -OR^a, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -OC(O)NR^aR^b, -NR^aR^b, -NR^aC(O)R^b, -NR^aC(O)OR^b, -S(O)₀₋₂R^a, -S(O)₂NR^aR^b, -NR^aS(O)₂R^b, -N₃, -CN, or -NO₂, wherein each C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl is optionally substituted with from one to five halogen, oxo, -OR^a, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -OC(O)NR^aR^b, -NR^aR^b, -NR^aC(O)R^b, -NR^aC(O)OR^b, -S(O)₀₋₂R^a, -S(O)₂NR^aR^b, -NR^aS(O)₂R^b, -N₃, -CN, or -NO₂;

each R^a and R^b is independently H; or C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, each of which is optionally substituted with from one to five R²¹, or R^a and R^b together with the atoms to which they are attached form a heterocycle, and;

each R²¹ is independently C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, or halogen;

or a pharmaceutically acceptable salt thereof.

2. A compound of claim 1, of Formula (Ia)



wherein

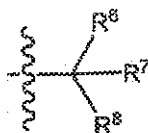
R³ is

C₅-C₁₀ aryl, C₅-C₁₀ heteroaryl, or C₅-C₁₀ heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups; or



wherein R^4 is C_1 - C_6 alkyl or C_3 - C_7 cycloalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; or

a moiety of the formula



wherein

R^6 is H, OH, or halogen; and R^7 and R^8 are each independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl, or C_5 - C_{12} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; or R^6 is H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, phenyl, naphthyl, or C_3 - C_{12} heteroaryl; and R^7 and R^8 together form a C_1 - C_6 alkylidene group having a double bond with the carbon to which each of R^6 , R^7 , and R^8 are bound wherein each of the C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, phenyl, naphthyl, or C_3 - C_{12} heteroaryl groups is optionally substituted with from 1 to 5 R^{20} groups;

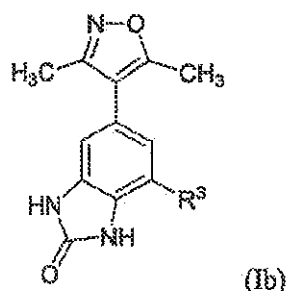
Q is H, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, benzyl or substituted benzyl;

each R^{20} is independently C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_3 - C_6 heterocyclic, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl, halogen, oxo, $-\text{OR}^a$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{OC}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^b$, $-\text{S}(\text{O})_{0-2}\text{R}^a$, $-\text{S}(\text{O})_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{S}(\text{O})_2\text{R}^b$, $-\text{N}_3$, $-\text{CN}$, or $-\text{NO}_2$, wherein each C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_3 - C_6 heterocyclic, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl is optionally substituted with from one to five halogen, oxo, $-\text{OR}^a$, $-\text{C}(\text{O})\text{R}^a$, $-\text{C}(\text{O})\text{OR}^a$, $-\text{C}(\text{O})\text{NR}^a\text{R}^b$, $-\text{OC}(\text{O})\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{R}^b$, $-\text{NR}^a\text{C}(\text{O})\text{OR}^b$, $-\text{S}(\text{O})_{0-2}\text{R}^a$, $-\text{S}(\text{O})_2\text{NR}^a\text{R}^b$, $-\text{NR}^a\text{S}(\text{O})_2\text{R}^b$, $-\text{N}_3$, $-\text{CN}$, or $-\text{NO}_2$;

each R^a and R^b is independently H; or C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_3 - C_6 heterocyclic, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl, each of which is optionally substituted with from one to five R^{21} ; or R^a and R^b together with the atoms to which they are attached form a heterocycle, and;

each R^{21} is independently C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_3 - C_6 heterocyclic, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl, or halogen; or a pharmaceutically acceptable salt thereof.

3. A compound of claim 1, of Formula (Ib)



wherein

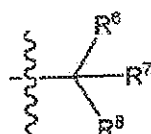
R^3 is

C_5 - C_{10} aryl, C_5 - C_{10} heteroaryl, or C_5 - C_{10} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; or

$-S(O)_2NHR^4$,

wherein R^4 is C_1 - C_6 alkyl or C_3 - C_7 cycloalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; or

a moiety of the formula

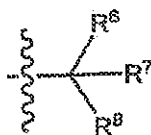


wherein

R^6 is H, OH, or halogen; and R^7 and R^8 are each independently C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl, or C_5 - C_{12} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups; or R^6 is H, C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, phenyl, naphthyl, or C_3 - C_{12} heteroaryl; and R^7 and R^8 together form a C_1 - C_6 alkylidene group having a double bond with the carbon to which each of R^6 , R^7 , and R^8 are bound wherein each of the C_1 - C_6 alkyl, C_2 - C_6 alkenyl, C_2 - C_6 alkynyl, C_3 - C_6 cycloalkyl, phenyl,

- naphthyl, or C₃-C₁₂ heteroaryl groups is optionally substituted with from 1 to 5 R²⁰ groups;
- each R²⁰ is independently C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, halogen, oxo, -OR^a, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -OC(O)NR^aR^b, -NR^aR^b, -NR^aC(O)R^b, -NR^aC(O)OR^b, -S(O)₀₋₂R^a, -S(O)₂NR^aR^b, -NR^aS(O)₂R^b, -N₃, -CN, or -NO₂, wherein each C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl is optionally substituted with from one to five halogen, oxo, -OR^a, -C(O)R^a, -C(O)OR^a, -C(O)NR^aR^b, -OC(O)NR^aR^b, -NR^aR^b, -NR^aC(O)R^b, -NR^aC(O)OR^b, -S(O)₀₋₂R^a, -S(O)₂NR^aR^b, -NR^aS(O)₂R^b, -N₃, -CN, or -NO₂;
- each R^a and R^b is independently H; or C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, each of which is optionally substituted with from one to five R²¹; or R^a and R^b together with the atoms to which they are attached form a heterocycle, and;
- each R²¹ is independently C₁-C₆ alkyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₃-C₆ heterocyclic, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, or halogen;
- or a pharmaceutically acceptable salt thereof.

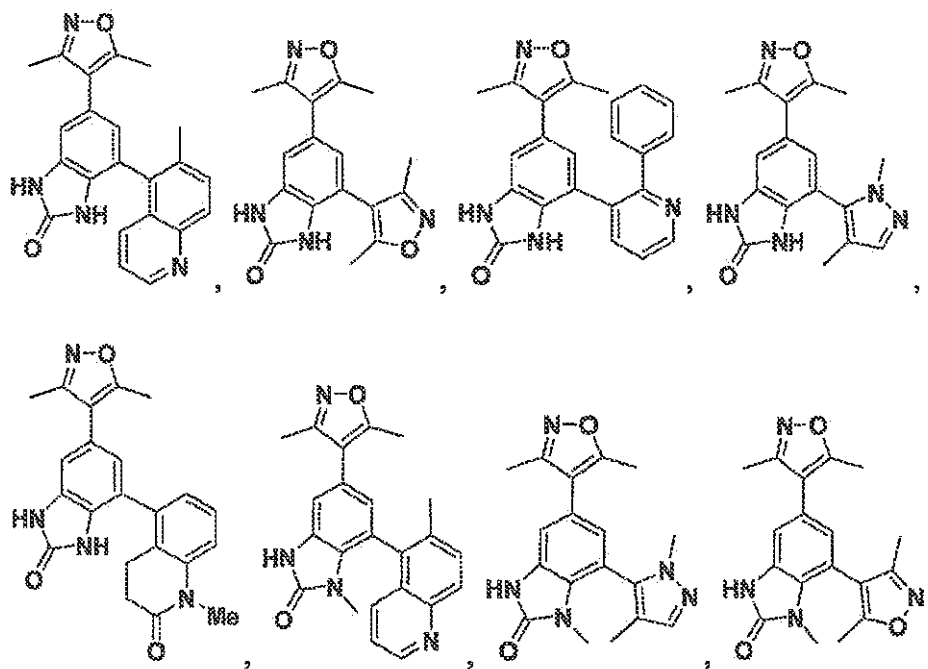
4. A compound of any of claims 1-3, wherein R³ is C₅-C₁₀ aryl, C₅-C₁₀ heteroaryl, or C₅-C₁₀ heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups.
5. A compound of any of claims 1-3, wherein R³ is a moiety of the formula

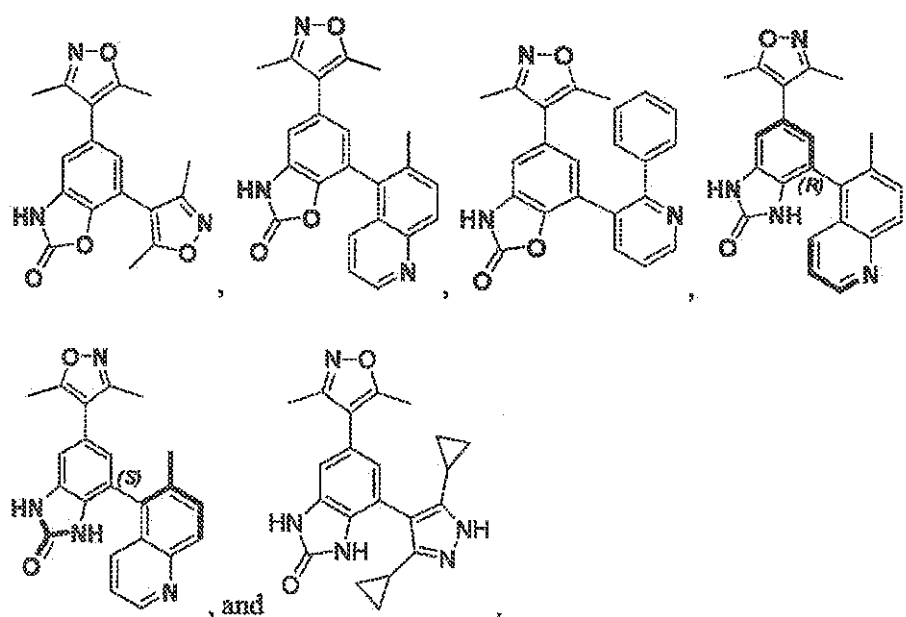


wherein R⁶ is H, OH, or halogen; and

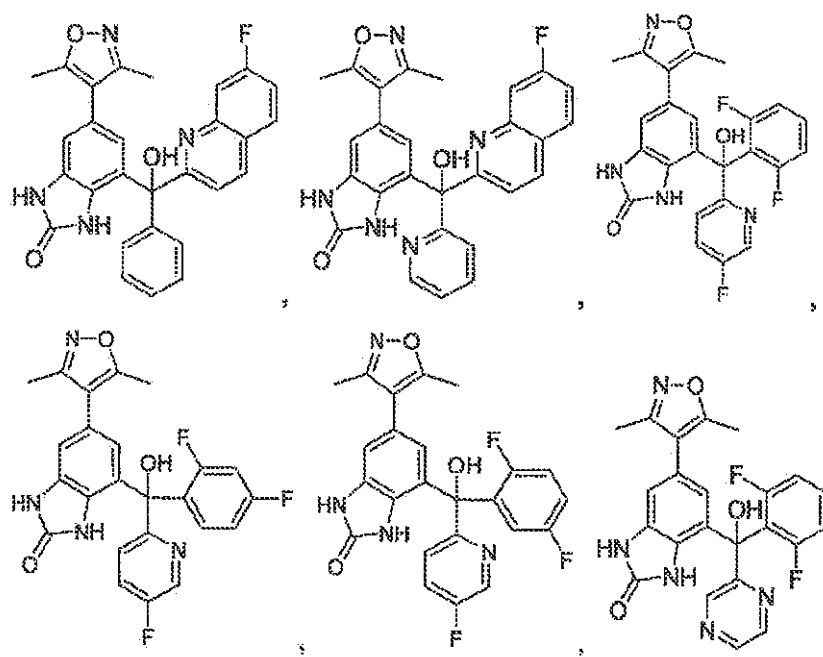
R⁷ and R⁸ are each independently C₁-C₆ alkyl, C₂-C₆ alkenyl, C₂-C₆ alkynyl, C₃-C₆ cycloalkyl, C₁-C₆ heteroalkyl, C₅-C₁₂ aryl, C₅-C₁₂ heteroaryl, or C₅-C₁₂ heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R²⁰ groups.

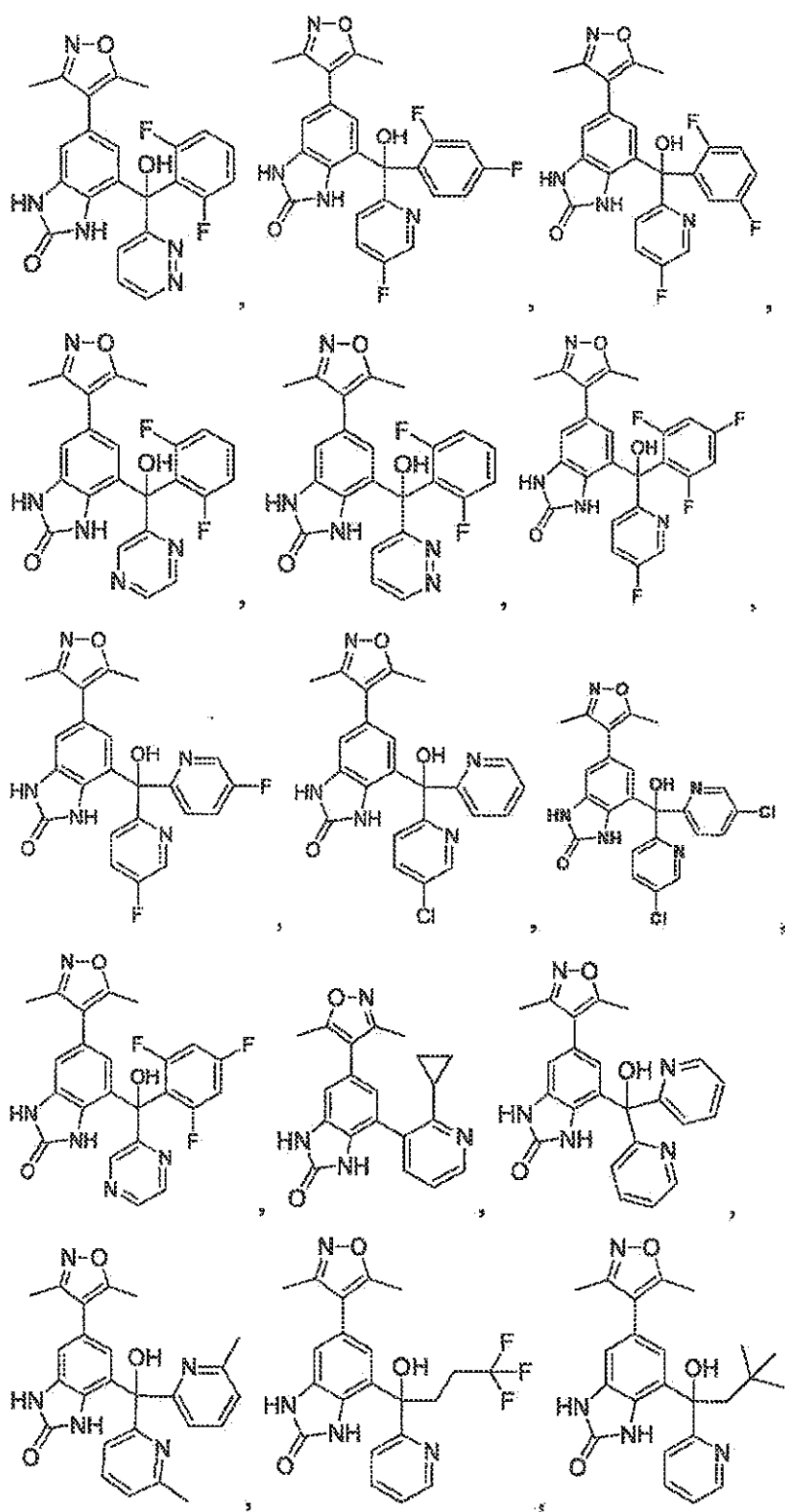
6. A compound of claim 5, wherein R^6 is OH.
7. A compound of claim 5, wherein R^7 and R^8 are each independently C_1 - C_6 alkyl, C_3 - C_6 cycloalkyl, C_1 - C_6 heteroalkyl, C_5 - C_{12} aryl, C_5 - C_{12} heteroaryl, or C_5 - C_{12} heteroarylalkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups.
8. A compound of claim 5, wherein R^7 and R^8 are each independently C_1 - C_6 alkyl, C_6 aryl or C_6 heteroaryl, each of which is optionally substituted with from 1 to 5 R^{20} groups.
9. A compound of claim 5, wherein R^7 and R^8 are each independently C_6 aryl or C_6 heteroaryl, each of which is optionally substituted with from 1 to 5 R^{20} groups.
10. A compound of claim 5, wherein R^7 and R^8 are each independently C_1 - C_6 alkyl, each of which is optionally substituted with from 1 to 5 R^{20} groups.
11. A compound chosen from the following list:

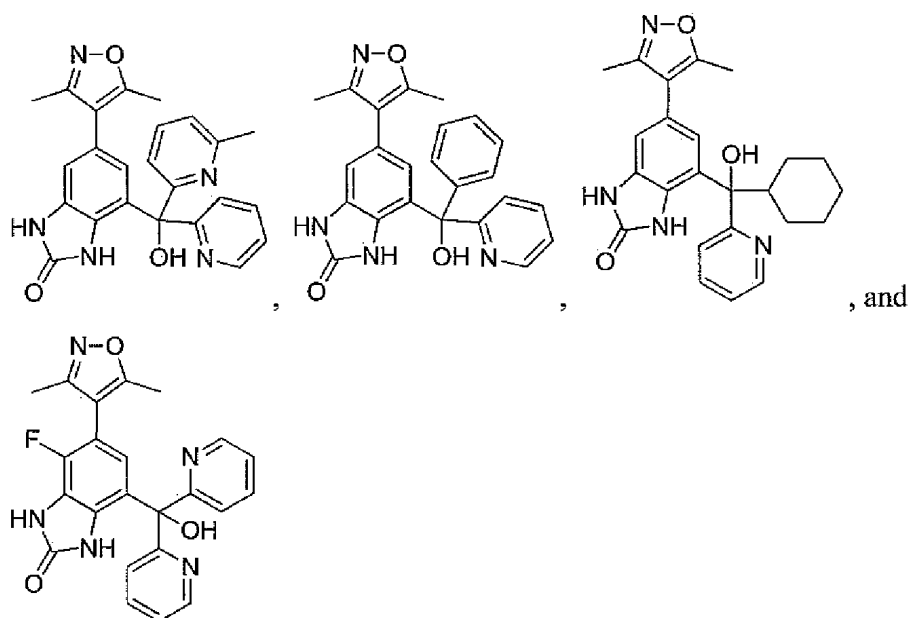




12. A compound chosen from the following list:







13. A pharmaceutical composition comprising a compound of any of claims 1-12, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.
14. A use of a compound of any of claims 1-12 for the manufacture of a medicament for the treatment of a human having a disease or condition responsive to the inhibition of a bromodomain-containing protein.
15. The use of claim 14, wherein the bromodomain-containing protein is BRD4.
16. The use of claim 14, wherein the disease or condition is a solid tumor of the colon, rectum, prostate, lung, pancreas, liver, kidney, cervix, stomach, ovaries, breast, skin, brain, meninges, or central nervous system.
17. The use of claim 14, wherein the disease or condition is multiple myeloma.
18. The use of claim 14, wherein the disease or condition is a B-cell lymphoma.

19. The use of claim 14, wherein the disease or condition is diffuse large B-cell lymphoma or Burkitt's lymphoma.