COMPOUNDS AND COMPOSITIONS AS c-Kit KINASE INHIBITORS

FIELD OF THE INVENTION

The invention relates to inhibitors of PDGFR and/or c-kit kinases, and methods of using such compounds.

BACKGROUND OF THE INVENTION

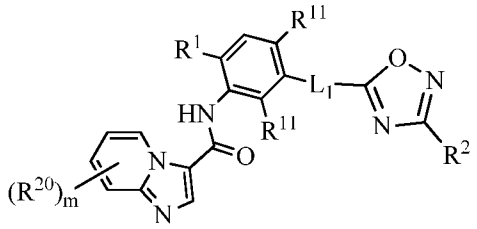
Protein kinases (PK) are a large set of structurally related phosphoryl transferases having highly conserved structures and catalytic functions. Protein kinases are enzymatic components of the signal transduction pathways which catalyze the transfer of the terminal phosphate from ATP to the hydroxy group of tyrosine, serine and/or threonine residues of proteins, and are therefore categorized into families by the substrates they phosphorylate: Protein Tyrosine Kinases (PTK), and Protein Serine/Threonine Kinases.

Protein kinases play a critical role in the control of cell growth and differentiation and are responsible for the control of a wide variety of cellular signal transduction processes, wherein protein kinases are key mediators of cellular signals leading to the production of growth factors and cytokines. The overexpression or inappropriate expression of normal or mutant protein kinases plays a significant role in the development of many diseases and disorders including, central nervous system disorders such as Alzheimer's, inflammatory disorders such as arthritis, bone diseases such as osteoporosis, metabolic disorders such as diabetes, blood vessel proliferative disorders such as angiogenesis, autoimmune diseases such as rheumatoid arthritis, ocular diseases, cardiovascular disease, atherosclerosis, cancer, thrombosis, psoriasis, restenosis, schizophrenia, pain sensation, transplant rejection and infectious diseases such as viral, and fungal infections.

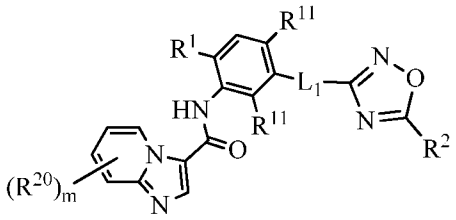
SUMMARY OF THE INVENTION

Provided herein are compounds, and pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, which are inhibitors of c-kit kinase, or inhibitors of c-kit and PDGFR (PDGFRα and PDGFRβ) kinases.

In one aspect provided herein such compounds, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, have a structure according to Formula (I) or Formula (II):



Formula (I)



Formula (II)

wherein:

m is 1 and R^{20} is selected from H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, deuterium, deuterated C_1-C_6alkyl, -CN, $-(CR^9_2)_nOR^4$, $-C(O)R^4$, $-(CR^9_2)_nC(=O)OR^4$, R^{10}, $-(CR^9_2)_nR^{10}$, $-((CR^9_2)_nO)_tR^4$, $-(CR^9_2)_nO(CR^9_2)_nR^7$, $-(CR^9_2)_nC(=O)R^4$, $-C(=O)N(R^4)_2$, $-OR^4$ and $-(CR^9_2)_nCN$;

or m is 4 and R^{20} is deuterium;

R^1 is selected from C_1-C_6alkyl and halo;

each R^{11} is independently selected from H, halo, and C_1-C_6alkyl;

L_1 is a bond, –NH- or -C(=O)NH-;

L_2 is $-(CR^9_2)_n-$, $-CHR^6-$, $-(CR^9_2)_nO-$, -NH-, $-(CR^9_2)_nC(=O)-$, $-C(=O)O(CR^9_2)_n-$, $-(CR^9_2)_nOC(=O)NR^4-$, $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_n-$, $-(CR^9_2)_nNR^4C(=O)-$ or $-(CR^9_2)_nNR^4C(=O)O-$;

R^2 is R^3 or L_2R^3;

R^3 is selected from an unsubstituted C_3-C_8cycloalkyl, a cyclobutanone, a cyclopentanone and a substituted C_3-C_8cycloalkyl, wherein the substituted C_3-C_8cycloalkyl of R^2 is substituted with 1-4 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, $-OR^4$, -CN, $-C(=O)OR^4$, $-C(=O)R^4$, $-C(=O)R^7$, $-C(=O)OR^5$, $-(CR^9_2)_nOR^4$, $-O(CR^9_2)_nOR^4$, $-C(=O)O(CR^9_2)_nOR^4$, $-N(R^4)_2$, $=N-OR^4$, $=N-O-(CR^9_2)_nR^5$, $-C(=O)NR^4_2$, $-NR^4C(=O)OR^4$, $-NR^4C(=O)(CR^9_2)_nOR^4$, $-NR^4(CR^9_2)_nOR^4$, $-NR^4S(=O)_2R^4$, $-N(C(=O)OR^4)_2$, $=CH_2$, $=CH(CR^9_2)_nOR^4$, R^8, $-(CR^9_2)_nR^8$, deuterated C_1-C_6alkoxy, $-S(=O)_2R^4$, $-S(=O)_2R^7$, $-S(=O)_2R^8$, $-S(=O)_2N(R^4)_2$, $-S(=O)_2NHC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nOR^4$, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with C_1-C_6alkyl, a spiro attached dioxane, a spiro attached tetrahyrofuranly, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a C_1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S, a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S substituted with 1-3 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, $-OR^4$ and R^8;

each R^4 is independently selected from H and C_1-C_6alkyl;

R^5 is an unsubstituted C_3-C_8cycloalkyl , an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N or O or a C_3-C_8cycloalkyl substituted with 1-3 substituents independently selected from C_1-C_6alkyl;

each R^6 is independently selected from -NHC(O)OR^4, -OR^4 and -$(CR^9_2)_nOR^4$;

each R^7 is independently selected from C_1-C_6haloalkyl;

R^8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, -$(C(R^9)_2)_nOR^4$, -$(C(R^9)_2)_nR^5$, -$(C(R^9)_2)_nC(O)OR^4$, -$C(O)OR^4$ and -$S(O)_2R^4$;

each R^9 is independently selected from H and C_1-C_6alkyl;

R^{10} is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are

substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$ and $-S(O)_2R^4$;

t is 1, 2 or 3, and

each n is independently selected from 1, 2, 3 and 4.

In certain embodiments of compounds of Formula (I) or Formula (II),

m is 1 and R^{20} is selected from H, F, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, deuterium, deuterated C_1-C_6alkyl, -CN, $-(CR^9_2)_nOR^4$, $-C(O)R^4$, $-(CR^9_2)_nC(=O)OR^4$, R^{10}, $-(CR^9_2)_nR^{10}$, $-((CR^9_2)_nO)_tR^4$, $-(CR^9_2)_nO(CR^9_2)_nR^7$, $-(CR^9_2)_nC(=O)R^4$, $-C(=O)N(R^4)_2$, $-OR^4$ and $-(CR^9_2)_nCN$;

or m is 4 and R^{20} is deuterium;

R^1 is selected from C_1-C_6alkyl and halo;

each R^{11} is independently selected from H, halo, and C_1-C_6alkyl;

L_1 is a bond, –NH- or -C(=O)NH-;

L_2 is $-(CR^9_2)_n$-, $-CHR^6$-, $-(CR^9_2)_nO$-, -NH-, $-(CR^9_2)_nC(=O)$-, $-C(=O)O(CR^9_2)_n$-, $-(CR^9_2)_nOC(=O)NR^4$-, $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_n$ -, $-(CR^9_2)_nNR^4C(=O)$- or $-(CR^9_2)_nNR^4C(=O)O$- ;

R^2 is R^3 or L_2R^3;

R^3 is selected from an unsubstituted C_3-C_8cycloalkyl, a cyclobutanone, a cyclopentanone and a substituted C_3-C_8cycloalkyl,

wherein the substituted C_3-C_8cycloalkyl of R^2 is substituted with 1-4 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, $-OR^4$, -CN, $-C(=O)OR^4$, $-C(=O)R^4$, $-C(=O)R^7$, $-C(=O)OR^5$, $-(CR^9_2)_nOR^4$, $-O(CR^9_2)_nOR^4$, $-C(=O)O(CR^9_2)_nOR^4$, $-N(R^4)_2$, $=N-OR^4$, $=N-O-(CR^9_2)_nR^5$, $-C(=O)NR^4_2$, $-NR^4C(=O)OR^4$, $-NR^4C(=O)(CR^9_2)_nOR^4$, $-NR^4(CR^9_2)_nOR^4$, $-NR^4S(=O)_2R^4$, $-N(C(=O)OR^4)_2$, $=CH_2$, $=CH(CR^9_2)_nOR^4$, R^8, $-(CR^9_2)_nR^8$, deuterated C_1-C_6alkoxy, $-S(=O)_2R^4$, $-S(=O)_2R^7$, $-S(=O)_2R^8$, $-S(=O)_2N(R^4)_2$, $-S(=O)_2NHC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nOR^4$, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with C_1-C_6alkyl, a spiro attached dioxane, a spiro attached tetrahyrofuranly, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a C_1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S, a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S substituted with 1-3 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, $-OR^4$ and R^8;

each R^4 is independently selected from H and C_1-C_6alkyl;

R^5 is an unsubstituted C_3-C_8cycloalkyl , an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N or O or a C_3-C_8cycloalkyl substituted with 1-3 substituents independently selected from C_1-C_6alkyl;

each R^6 is independently selected from -NHC(O)OR^4, -OR^4 and -$(CR^9_2)_nOR^4$;

each R^7 is independently selected from C_1-C_6haloalkyl;

R^8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, -$(C(R^9)_2)_nOR^4$, -$(C(R^9)_2)_nR^5$, -$(C(R^9)_2)_nC(O)OR^4$, -$C(O)OR^4$ and -$S(O)_2R^4$;

each R^9 is independently selected from H and C_1-C_6alkyl;

R^{10} is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

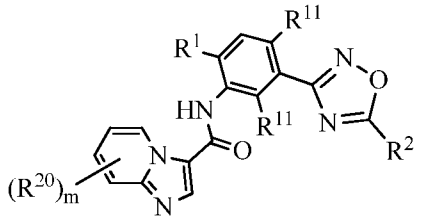
wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are

substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$ and $-S(O)_2R^4$;

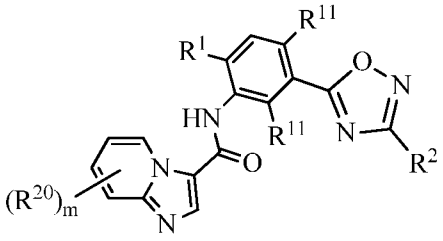
t is 1, 2 or 3, and

each n is independently selected from 1, 2, 3 and 4.

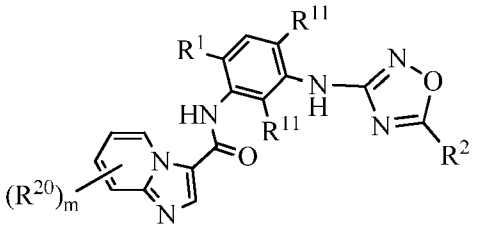
In certain embodiments of compounds of Formula (I) or Formula (II), and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, the compound of Formula (I) or Formula (II) is a compound having a structure of Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf):



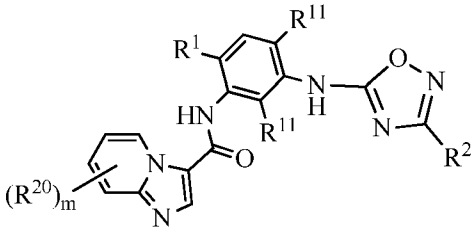
Formula (Ia)



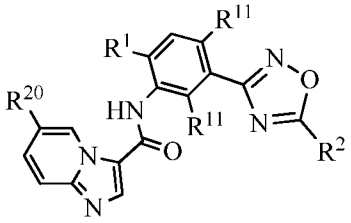
Formula (IIa)



Formula (Ib)



Formula (IIb)



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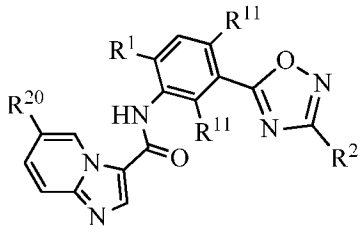
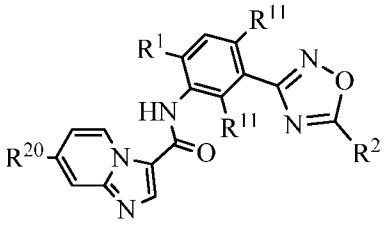
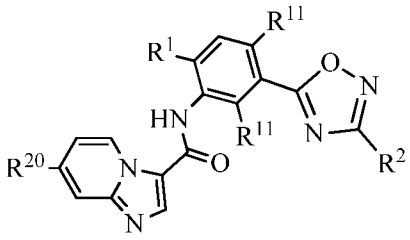


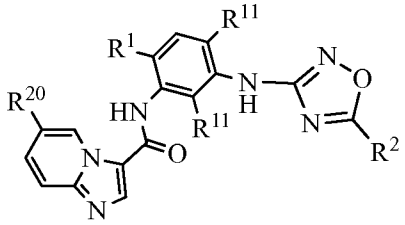
Formula (IIc)



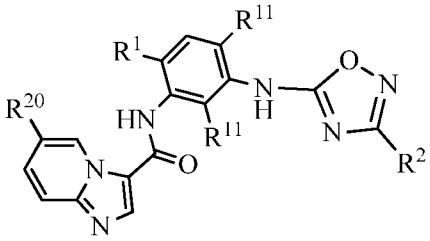
Formula (Id)



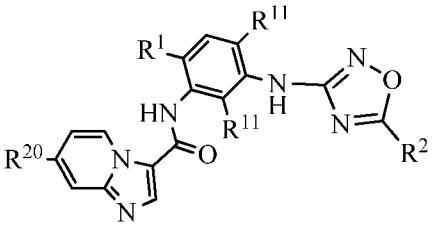
Formula (IId)



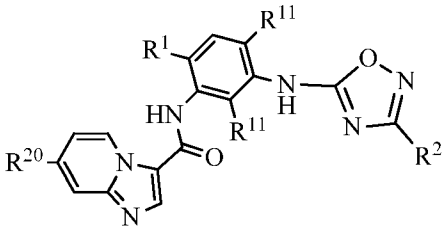
Formula (Ie)



Formula (IIe)



Formula (If)



Formula (IIf)

wherein:

m is 1 and R^{20} is selected from H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, deuterium, deuterated C_1-C_6alkyl, -CN, $-(CR^9_2)_nOR^4$, $-C(O)R^4$, $-(CR^9_2)_nC(=O)OR^4$, R^{10}, $-(CR^9_2)_nR^{10}$, $-((CR^9_2)_nO)_tR^4$, $-(CR^9_2)_nO(CR^9_2)_nR^7$, $-(CR^9_2)_nC(=O)R^4$, $-C(=O)N(R^4)_2$, $-OR^4$ and $-(CR^9_2)_nCN$;

or m is 4 and R^{20} is deuterium;

R^1 is selected from C_1-C_6alkyl and halo;

each R^{11} is independently selected from H, halo, and C_1-C_6alkyl;

L_2 is $-(CR^9_2)_n-$, $-CHR^6-$, $-(CR^9_2)_nO-$, -NH-, $-(CR^9_2)_nC(=O)-$, $-C(=O)O(CR^9_2)_n-$, $-(CR^9_2)_nOC(=O)NR^4-$, $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_n-$, $-(CR^9_2)_nNR^4C(=O)-$ or $-(CR^9_2)_nNR^4C(=O)O-$;

R^2 is R^3 or L_2R^3;

R^3 is selected from an unsubstituted C_3-C_8cycloalkyl, a cyclobutanone, a cyclopentanone and a substituted C_3-C_8cycloalkyl,

wherein the substituted C_3-C_8cycloalkyl of R^2 is substituted with 1-4 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl,

$-OR^4$, -CN, $-C(=O)OR^4$, $-C(=O)R^4$, $-C(=O)R^7$, $-C(=O)OR^5$, $-(CR^9_2)_nOR^4$, $-O(CR^9_2)_nOR^4$, $-C(=O)O(CR^9_2)_nOR^4$, $-N(R^4)_2$, $=N-OR^4$, $=N-O-(CR^9_2)_nR^5$, $-C(=O)NR^4_2$, $-NR^4C(=O)OR^4$, $-NR^4C(=O)(CR^9_2)_nOR^4$, $-NR^4(CR^9_2)_nOR^4$, $-NR^4S(=O)_2R^4$, $-N(C(=O)OR^4)_2$, $=CH_2$, $=CH(CR^9_2)_nOR^4$, R^8, $-(CR^9_2)_nR^8$, deuterated C_1-C_6alkoxy, $-S(=O)_2R^4$, $-S(=O)_2R^7$, $-S(=O)_2R^8$, $-S(=O)_2N(R^4)_2$, $-S(=O)_2NHC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nOR^4$, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with C_1-C_6alkyl, a spiro attached dioxane, a spiro attached tetrahyrofuranly, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a C_1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S, a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S substituted with 1-3 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, $-OR^4$ and R^8;

each R^4 is independently selected from H and C_1-C_6alkyl;

R^5 is an unsubstituted C_3-C_8cycloalkyl , an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N or O or a C_3-C_8cycloalkyl substituted with 1-3 substituents independently selected from C_1-C_6alkyl;

each R^6 is independently selected from $-NHC(O)OR^4$, $-OR^4$ and $-(CR^9_2)_nOR^4$;

each R^7 is independently selected from C_1-C_6haloalkyl;

R^8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are

substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$, $-C(O)OR^4$ and $-S(O)_2R^4$;

each R^9 is independently selected from H and C_1-C_6alkyl;

R^{10} is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$ and $-S(O)_2R^4$;

t is 1, 2 or 3, and

each n is independently selected from 1, 2, 3 and 4.

In certain embodiments of compounds of Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf),

m is 1 and R^{20} is selected from H, -F, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, deuterium, deuterated C_1-C_6alkyl, -CN, $-(CR^9_2)_nOR^4$, $-C(O)R^4$, $-(CR^9_2)_nC(=O)OR^4$, R^{10}, $-(CR^9_2)_nR^{10}$, $-((CR^9_2)_nO)_tR^4$, $-(CR^9_2)_nO(CR^9_2)_nR^7$, $-(CR^9_2)_nC(=O)R^4$, $-C(=O)N(R^4)_2$, $-OR^4$ and $-(CR^9_2)_nCN$;

or m is 4 and R^{20} is deuterium;

R^1 is selected from C_1-C_6alkyl and halo;

each R^{11} is independently selected from H, halo, and C_1-C_6alkyl;

L_2 is $-(CR^9_2)_n-$, $-CHR^6-$, $-(CR^9_2)_nO-$, -NH-, $-(CR^9_2)_nC(=O)-$, $-C(=O)O(CR^9_2)_n-$, $-(CR^9_2)_nOC(=O)NR^4-$, $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_n-$, $-(CR^9_2)_nNR^4C(=O)-$ or $-(CR^9_2)_nNR^4C(=O)O-$;

R^2 is R^3 or L_2R^3;

R^3 is selected from an unsubstituted C_3-C_8cycloalkyl, a cyclobutanone, a cyclopentanone and a substituted C_3-C_8cycloalkyl,

wherein the substituted C_3-C_8cycloalkyl of R^2 is substituted with 1-4 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, $-OR^4$, -CN, $-C(=O)OR^4$, $-C(=O)R^4$, $-C(=O)R^7$, $-C(=O)OR^5$, $-(CR^9_2)_nOR^4$, $-O(CR^9_2)_nOR^4$, $-C(=O)O(CR^9_2)_nOR^4$, $-N(R^4)_2$, $=N-OR^4$, $=N-O-(CR^9_2)_nR^5$, $-C(=O)NR^4_2$, $-NR^4C(=O)OR^4$, $-NR^4C(=O)(CR^9_2)_nOR^4$, $-NR^4(CR^9_2)_nOR^4$, $-NR^4S(=O)_2R^4$, $-N(C(=O)OR^4)_2$, $=CH_2$, $=CH(CR^9_2)_nOR^4$, R^8, $-(CR^9_2)_nR^8$, deuterated C_1-C_6alkoxy, $-S(=O)_2R^4$, $-S(=O)_2R^7$, $-S(=O)_2R^8$, $-S(=O)_2N(R^4)_2$, $-S(=O)_2NHC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nOR^4$, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with C_1-C_6alkyl, a spiro attached dioxane, a spiro attached tetrahyrofuranly, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a C_1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S, a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S substituted with 1-3 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, $-OR^4$ and R^8;

each R^4 is independently selected from H and C_1-C_6alkyl;

R^5 is an unsubstituted C_3-C_8cycloalkyl , an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N or O or a C_3-C_8cycloalkyl substituted with 1-3 substituents independently selected from C_1-C_6alkyl;

each R^6 is independently selected from $-NHC(O)OR^4$, $-OR^4$ and $-(CR^9_2)_nOR^4$;

each R^7 is independently selected from C_1-C_6haloalkyl;

R^8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted

C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$, $-C(O)OR^4$ and $-S(O)_2R^4$;

each R^9 is independently selected from H and C_1-C_6alkyl;

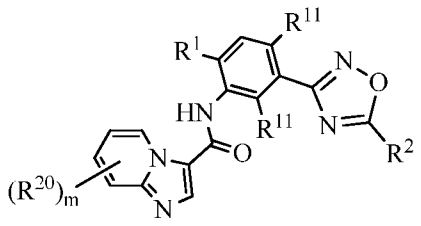
R^{10} is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$ and $-S(O)_2R^4$;

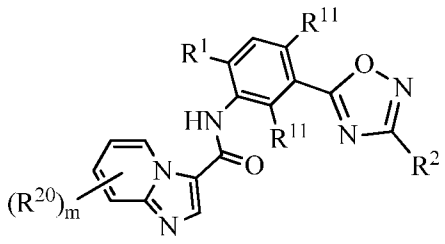
t is 1, 2 or 3, and

each n is independently selected from 1, 2, 3 and 4.

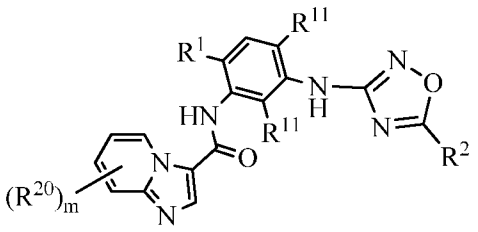
In certain embodiments of compounds of Formula (I) or Formula (II), and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, the compound of Formula (I) or Formula (II) is a compound having a structure of Formula (Ia), Formula (IIa), Formula (Ib) or Formula (IIb):



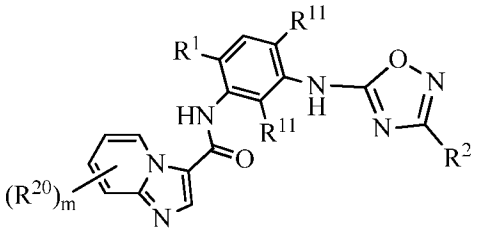
Formula (Ia)



Formula (IIa)



Formula (Ib)



Formula (IIb)

wherein:

m is 1 and R^{20} is selected from H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, deuterium, deuterated C_1-C_6alkyl, -CN, $-(CR^9_2)_nOR^4$, $-C(O)R^4$, $-(CR^9_2)_nC(=O)OR^4$, R^{10}, $-(CR^9_2)_nR^{10}$, $-((CR^9_2)_nO)_tR^4$, $-(CR^9_2)_nO(CR^9_2)_nR^7$, $-(CR^9_2)_nC(=O)R^4$, $-C(=O)N(R^4)_2$, $-OR^4$ and $-(CR^9_2)_nCN$;

or m is 4 and R^{20} is deuterium;

R^1 is selected from C_1-C_6alkyl and halo;

each R^{11} is independently selected from H, halo, and C_1-C_6alkyl;

L_2 is $-(CR^9_2)_n-$, $-CHR^6-$, $-(CR^9_2)_nO-$, -NH-, $-(CR^9_2)_nC(=O)-$, $-C(=O)O(CR^9_2)_n-$, $-(CR^9_2)_nOC(=O)NR^4-$, $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_n-$, $-(CR^9_2)_nNR^4C(=O)-$ or $-(CR^9_2)_nNR^4C(=O)O-$;

R^2 is R^3 or L_2R^3;

R^3 is selected from an unsubstituted C_3-C_8cycloalkyl, a cyclobutanone, a cyclopentanone and a substituted C_3-C_8cycloalkyl,

wherein the substituted C_3-C_8cycloalkyl of R^2 is substituted with 1-4 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, $-OR^4$, -CN, $-C(=O)OR^4$, $-C(=O)R^4$, $-C(=O)R^7$, $-C(=O)OR^5$, $-(CR^9_2)_nOR^4$, $-O(CR^9_2)_nOR^4$, $-C(=O)O(CR^9_2)_nOR^4$, $-N(R^4)_2$, $=N-OR^4$, $=N-O-(CR^9_2)_nR^5$, $-C(=O)NR^4_2$, $-NR^4C(=O)OR^4$, $-NR^4C(=O)(CR^9_2)_nOR^4$, $-NR^4(CR^9_2)_nOR^4$, $-NR^4S(=O)_2R^4$, $-N(C(=O)OR^4)_2$, $=CH_2$, $=CH(CR^9_2)_nOR^4$, R^8, $-(CR^9_2)_nR^8$, deuterated C_1-C_6alkoxy, $-S(=O)_2R^4$, $-S(=O)_2R^7$, $-S(=O)_2R^8$, $-S(=O)_2N(R^4)_2$, $-S(=O)_2NHC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nOR^4$, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with C_1-C_6alkyl, a spiro attached dioxane, a spiro attached tetrahyrofuranly, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a C_1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S, a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S substituted with 1-3 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, $-OR^4$ and R^8;

each R^4 is independently selected from H and C_1-C_6alkyl;

R^5 is an unsubstituted C_3-C_8cycloalkyl , an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N or O or a C_3-C_8cycloalkyl substituted with 1-3 substituents independently selected from C_1-C_6alkyl;

each R^6 is independently selected from -NHC(O)OR^4, -OR^4 and -$(CR^9{}_2)_nOR^4$;

each R^7 is independently selected from C_1-C_6haloalkyl;

R^8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, -$(C(R^9)_2)_nOR^4$, -$(C(R^9)_2)_nR^5$, -$(C(R^9)_2)_nC(O)OR^4$, -C(O)OR^4 and -$S(O)_2R^4$;

each R^9 is independently selected from H and C_1-C_6alkyl;

R^{10} is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted

C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$ and $-S(O)_2R^4$;

t is 1, 2 or 3, and

each n is independently selected from 1, 2, 3 and 4.

In certain embodiments of compounds of Formula (Ia), Formula (IIa), Formula (Ib) or Formula (IIb),

m is 1 and R^{20} is selected from H, -F, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, deuterium, deuterated C_1-C_6alkyl, -CN, $-(CR^9_2)_nOR^4$, $-C(O)R^4$, $-(CR^9_2)_nC(=O)OR^4$, R^{10}, $-(CR^9_2)_nR^{10}$, $-((CR^9_2)_nO)_tR^4$, $-(CR^9_2)_nO(CR^9_2)_nR^7$, $-(CR^9_2)_nC(=O)R^4$, $-C(=O)N(R^4)_2$, $-OR^4$ and $-(CR^9_2)_nCN$;

or m is 4 and R^{20} is deuterium;

R^1 is selected from C_1-C_6alkyl and halo;

each R^{11} is independently selected from H, halo, and C_1-C_6alkyl;

L_2 is $-(CR^9_2)_n-$, $-CHR^6-$, $-(CR^9_2)_nO-$, -NH-, $-(CR^9_2)_nC(=O)-$, $-C(=O)O(CR^9_2)_n-$, $-(CR^9_2)_nOC(=O)NR^4-$, $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_n-$, $-(CR^9_2)_nNR^4C(=O)-$ or $-(CR^9_2)_nNR^4C(=O)O-$;

R^2 is R^3 or L_2R^3;

R^3 is selected from an unsubstituted C_3-C_8cycloalkyl, a cyclobutanone, a cyclopentanone and a substituted C_3-C_8cycloalkyl,

wherein the substituted C_3-C_8cycloalkyl of R^2 is substituted with 1-4 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, $-OR^4$, -CN, $-C(=O)OR^4$, $-C(=O)R^4$, $-C(=O)R^7$, $-C(=O)OR^5$, $-(CR^9_2)_nOR^4$, $-O(CR^9_2)_nOR^4$, $-C(=O)O(CR^9_2)_nOR^4$, $-N(R^4)_2$, $=N-OR^4$, $=N-O-(CR^9_2)_nR^5$, $-C(=O)NR^4_2$, $-NR^4C(=O)OR^4$, $-NR^4C(=O)(CR^9_2)_nOR^4$, $-NR^4(CR^9_2)_nOR^4$, $-NR^4S(=O)_2R^4$, $-N(C(=O)OR^4)_2$, $=CH_2$, $=CH(CR^9_2)_nOR^4$, R^8, $-(CR^9_2)_nR^8$, deuterated C_1-C_6alkoxy, $-S(=O)_2R^4$, $-S(=O)_2R^7$, $-S(=O)_2R^8$, $-S(=O)_2N(R^4)_2$, $-S(=O)_2NHC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nOR^4$, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with C_1-C_6alkyl, a spiro attached dioxane, a spiro attached tetrahyrofuranly, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a C_1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S, a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S substituted with 1-3 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, $-OR^4$ and R^8;

each R^4 is independently selected from H and C_1-C_6alkyl;

R^5 is an unsubstituted C_3-C_8cycloalkyl , an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N or O or a C_3-C_8cycloalkyl substituted with 1-3 substituents independently selected from C_1-C_6alkyl;

each R^6 is independently selected from -NHC(O)OR^4, -OR^4 and -$(CR^9{}_2)_nOR^4$;

each R^7 is independently selected from C_1-C_6haloalkyl;

R^8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, -$(C(R^9)_2)_nOR^4$, -$(C(R^9)_2)_nR^5$, -$(C(R^9)_2)_nC(O)OR^4$, -C(O)OR^4 and -$S(O)_2R^4$;

each R^9 is independently selected from H and C_1-C_6alkyl;

R^{10} is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted

C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$ and $-S(O)_2R^4$;

t is 1, 2 or 3, and

each n is independently selected from 1, 2, 3 and 4.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), R^1 is selected from $-CH_3$ and F.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), R^1 is $-CH_3$.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), each R^{11} is independently selected from H, F and $-CH_3$.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), each R^{11} is H.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), R^3 is selected from an unsubstituted C_3-C_8cycloalkyl, a cyclobutanone, a cyclopentanone and a substituted C_3-C_8cycloalkyl, wherein the substituted C_3-C_8cycloalkyl of R^3 is substituted with 1-4 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, $-OR^4$, $-(CR^9_2)_nOR^4$, $-O(CR^9_2)_nOR^4$, $-N(R^4)_2$, $=N-OR^4$, $=N-O-(CR^9_2)_nR^5$, $-NR^4C(=O)OR^4$, $-NR^4C(=O)(CR^9_2)_nOR^4$, $-NR^4(CR^9_2)_nOR^4$, $-NR^4S(=O)_2R^4$, $-N(C(=O)OR^4)_2$, $=CH_2$, $=CH(CR^9_2)_nOR^4$, R^8, deuterated C_1-C_6alkoxy, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with C_1-C_6alkyl, a spiro attached dioxane, a spiro attached tetrahyrofuranly, a spiro attached cyclobutanone, a spiro attached cyclobutanol, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N and O and a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N and O substituted with 1-3 substituents independently selected from C_1-C_6alkyl.

In certain embodiments of any of the aforementioned compounds of Formula (I),

Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), each R^6 is independently selected from, $-OR^4$ and $-(CR^9_2)_nOR^4$.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), each R^4 is independently selected from H, methyl, ethyl, propyl, butyl, i-propyl and t-butyl.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), each R^5 is independently selected from cyclopropyl or morpholinyl.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), each R^6 is independently selected from OH and $-CH_2OH$.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), each R^7 is independently selected from CH_2F, $-CHF_2$, $-CH_2CHF_2$, $-CH_2CF_3$ and $-CF_3$.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), each R^9 is independently selected from H, methyl and ethyl.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), R^8 is selected from an an unsubstituted C_3-C_8cycloalkyl and an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), R^2 is R^3.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or

Formula (IIf), R^3 is selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, , each of which is unsubstituted or each of which is substituted with 1-4 substituents independently selected from -F, $-CH_3$, $-CH_2CH_3$, $-CF_3$, -OH, $-OCH_3$, $-CH_2OCH_3$, $-NH_2$, $-N(CH_3)_2$, $-OCH_2CH_2OCH_3$, =N-OCH_3, =N-OCH_2CH_3, =N-$OCH(CH_3)_2$, =N-OH, =N-O-CH_2R^5, =N-O-$CH_2CH_2R^5$, $-NHC(=O)OC(CH_3)_3$, $-NHC(=O)OCH_3$, $-NHC(=O)CH_2OCH_3$, $-NHCH_2CH_2OCH_3$, $-NHCH_2CH_2OH$, $-NHS(=O)_2CH_3$, $-N(C(=O)OCH_3)_2$, $=CH_2$, $=CHCH_2CH_2OH$, $-OCD_3$, cyclopropyl, triazolyl, pyrazolyl, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with a $-CH_3$, a spiro attached dioxane, a spiro attached tetrahyrofuranly, a spiro attached cyclobutanone, a spiro attached cyclobutanol, piperidinyl and piperazinyl substituted with a $-CH_3$, or R^3 is a cyclobutanone or a cyclopentanone.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), R^3 is cyclopropyl substituted with 1 or 2 F, or R^3 is cyclobutyl substituted with 2 ..

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), m is 1 and R^{20} is selected from H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, deuterated C_1-C_6alkyl, -CN, $-(CR^9_2)_nOR^4$, $-(CR^9_2)_nC(=O)OR^4$, R^{10}, $-(CR^9_2)_nR^{10}$, $-((CR^9_2)_nO)_tR^4$, $-(CR^9_2)_nO(CR^9_2)_nR^7$, $-(CR^9_2)_nC(=O)R^4$, and $-C(=O)N(R^4)_2$.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), m is 1 and R^{20} is selected from H, -F, $-CH_3$, $-CF_3$, $-CD_3$, -CN, $-OCHF_2$, $-C(CH_3)OH$, $-CH_2CH_2C(=O)OC(CH_3)_3$, $-CH_2OCH_2CH_2OH$, $-CH_2OCH_2CF_3$, $-C(=O)NH_2$, $-CH_2CH_2C(CH_3)_2OH$, $-CH_2OCH_2CH_2OCH_3$, $-CH_2OCH_2CH_2F$, $-CH_2CH_2C(=O)CH_3$, $-CH_2OH$ and $-CH_2OCH_3$.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), m is 1 and R^{20} is $-CH_3$.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), m is 1 and R^{20} is H.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), R^{10} is selected from morpholinyl, piperidinyl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazinyl, piperazin-1-yl, pyrazolyl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, triazolyl, 1H-1,2,3-triazol-4-yl, 4H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, thiazolyl, thiazol-4-yl, thiazol-5-yl, imidazolyl, imidazol-1-yl, imidazol-2-yl, each of which is unsubstituted or each of which is substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(CR^9{}_2)_nOR^4$, $-(C(R^9)_2)_nC(O)OR^4$, $-(C(R^9)_2)_nR^5$ and $-S(=O)_2R^4$, or R^{10} is selected from a oxazolidin-2-one and a pyrrolidin-2-one.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), R^{10} is selected from morpholinyl, piperidinyl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazinyl, piperazin-1-yl, pyrazolyl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, triazolyl, 1H-1,2,3-triazol-4-yl, 4H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, thiazolyl, thiazol-4-yl, thiazol-5-yl, imidazolyl, imidazol-1-yl, imidazol-2-yl, each of which is unsubstituted or each of which is substituted with 1-3 substituents independently selected from $-CH_3$, $-CH_2CH_2OH$, $-CH_2C(O)OH$, $-CH_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-S(O)_2CH_3$ and $-CH_2CH_2$-R_5.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib) or Formula (IIb), m is 4 and R^{20} is deuterium.

Certain embodiments of the compounds of Formula (I) or Formula (II) are selected from:

N-{5-[3-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-5-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(3-oxocyclopentyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxy-3-methylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[3-(hydroxyimino)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(4,4-difluorocyclohexyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxy-3-methylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[3-(methoxyimino)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-{5,8-dioxaspiro[3.4]octan-2-yl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(2-methyl-5-{5-[(6R)-6-methyl-5,8-dioxaspiro[3.4]octan-2-yl]-1,2,4-oxadiazol-3-

yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-{5,9-dioxaspiro[3.5]nonan-2-yl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(3-oxocyclobutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(2-methyl-5-{5-[(6S)-6-methyl-5,8-dioxaspiro[3.4]octan-2-yl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[3-(ethoxyimino)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-{3-[(cyclopropylmethoxy)imino]cyclobutyl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-{3-[(propan-2-yloxy)imino]cyclobutyl}-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-aminocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[3-(2-methoxyethoxy)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-methoxycyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[1-(methoxymethyl)cyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl N-{1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclopropyl}carbamate; N-{5-[5-(1-methanesulfonamidocyclopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; methyl N-{1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclopropyl}-N-(methoxycarbonyl)carbamate; methyl N-{1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclopropyl}carbamate; N-(5-{5-[3-hydroxy-3-(trifluoromethyl)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; 1-methylcyclopropyl N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate; methyl N-{1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclobutyl}carbamate; N-{5-[5-(1-methanesulfonamidocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[1-(dimethylamino)cyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(3-methylidenecyclobutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-cyclopropyl-3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[3-(3-hydroxypropylidene)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-{5-oxaspiro[3.4]octan-2-yl}-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-{[(3,3-difluorocyclobutyl)amino]methyl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-

a]pyridine-3-carboxamide; N-(2-methyl-5-{5-[(2,2,3,3-tetrafluorocyclobutoxy)methyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-fluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2-hydroxyethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(methoxymethyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[1-(2-hydroxyethyl)-1H-pyrazol-4-yl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(1-methyl-1H-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl]imidazo[1,2-a]pyridine-3-carboxamide; N-(2-methyl-5-{5-[3-(1H-pyrazol-1-yl)cyclobutyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(1,3-thiazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-fluorophenyl}-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-fluorophenyl}-6-[1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(1-methanesulfonylpiperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-4-yl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-fluorophenyl}-6-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-4-yl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2,2,2-trifluoroethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(3-hydroxy-3-methylbutyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[2-(1-hydroxycyclopropyl)ethyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[2-(morpholin-4-yl)ethyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-dimethylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-

methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(morpholin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide; 6-cyano-N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-fluorophenyl}-6-(5-methyl-4H-1,2,4-triazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide; 3-N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3,6-dicarboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[2-(4-methylpiperazin-1-yl)ethyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(2,2-difluorocyclopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-[1-(2-hydroxyethyl)-1H-1,2,3-triazol-4-yl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2,4-dimethylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(2-oxo-1,3-oxazolidin-3-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-methylimidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-methylimidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-fluoroimidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-fluoroimidazo[1,2-a]pyridine-3-carboxamide; 7-cyano-N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-cyclopentyl-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[2-methyl-5-(5-{6-oxospiro[3.3]heptan-2-yl}-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(2-oxopyrrolidin-1-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2,2-difluoroethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-ethylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(5-methyl-4H-1,2,4-triazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-methylimidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(morpholin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(1H-imidazol-1-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2-

fluoroethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[3-(methoxymethyl)-1H-1,2,4-triazol-5-yl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(2,2-difluorocyclopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2,2,2-trifluoroethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-2-methylphenyl]-6-[(2,2,2-trifluoroethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1R)-2,2-difluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1S)-2,2-difluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[3-hydroxy-3-(trifluoromethyl)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide; 6-fluoro-N-(5-{5-[3-hydroxy-3-(trifluoromethyl)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1R,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-5,6,7,8-tetradeuteroimidazo[1,2-a]pyridine-3-carboxamide; N-{5-[(3,3-difluorocyclobutyl)carbamoyl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; 7-fluoro-N-(5-{5-[3-hydroxy-3-(trifluoromethyl)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(4-methyl-1H-imidazol-1-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[3-methoxy-3-(trifluoromethyl)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-fluoro-N-(5-{5-[1-(methoxymethyl)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[1-(2-methoxyethyl)-5-methyl-1H-1,2,4-triazol-3-yl]imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-{6-hydroxyspiro[3.3]heptan-2-yl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; 7-methyl-N-(2-methyl-5-{5-[(2,2,3,3-tetrafluorocyclobutoxy)methyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-methyl-N-(2-methyl-5-{5-[(2,2,3,3-tetrafluorocyclobutoxy)methyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(cyclopropylmethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1R,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1S,2R)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-

methylphenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1R)-2,2-difluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2,4-dimethylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1S)-2,2-difluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2,4-dimethylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1R,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-fluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-methylimidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-fluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-methylimidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1S,2R)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; methyl N-{3,3-difluoro-1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclobutyl}carbamate; methyl N-{3,3-difluoro-1-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]cyclobutyl}carbamate, and N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2-fluoroethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide.

Other preffered embodiments of the compounds of Formula (I) or Formula (II) are selected from:

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1R)-2,2-difluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1S)-2,2-difluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1S,2R)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide, and N-(5-{5-[(1R,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide.

Certain embodiments of the compounds of Formula (I) or Formula (II) are selected from:

N-[5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,3,4-oxadiazol-2-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxy-3-methylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(3Z)-3-(methoxyimino)cyclopentyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(3Z)-3-(hydroxyimino)cyclopentyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-methyl-5-{5-[1-(trifluoromethyl)cyclopropyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-hydroxy-3-methylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(3-oxocyclobutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(2-methyl-5-{5-[3-(piperidin-1-yl)cyclobutyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-methyl-5-{5-[3-(morpholin-4-yl)cyclobutyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-methyl-5-{5-[3-(4-methylpiperazin-1-yl)cyclobutyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{2-methyl-5-[5-(3-{[2-(morpholin-4-yl)ethoxy]imino}cyclobutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; tert-butyl N-{3-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclobutyl}carbamate; N-{5-[5-(3-aminocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3-methanesulfonamidocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; 1-methylcyclopropyl N-{2-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]ethyl}carbamate; N-{5-[5-(1-aminocyclopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[1-(2-methoxyacetamido)cyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-{3-[(2-methoxyethyl)amino]cyclobutyl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-fluorophenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[3-methoxy-3-(trifluoromethyl)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)-N-methylimidazo[1,2-a]pyridine-3-carboxamide; tert-butyl N-{1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclobutyl}carbamate; N-{5-[5-(1-aminocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{2-fluoro-5-[5-(3-methylidenecyclobutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[1-(hydroxymethyl)cyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-{[(2,2-difluorocyclopropyl)formamido]methyl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; 1-methylcyclopropyl N-[(3-{4-methyl-3-[7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-amido]phenyl}-1,2,4-oxadiazol-5-yl)methyl]carbamate; methyl N-{3-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclobutyl}carbamate; tert-butyl 3-[3-({5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}carbamoyl)imidazo[1,2-a]pyridin-6-yl]propanoate; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(4-methylpiperazin-1-yl)methyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2-methoxyethoxy)methyl]imidazo[1,2-a]pyridine-3-

carboxamide; 2-{4-[3-({5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}carbamoyl)imidazo[1,2-a]pyridin-6-yl]-1H-pyrazol-1-yl}acetic acid; N-{5-[5-(1-hydroxycyclopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(difluoromethoxy)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-methyl-5-{5-[3-(1H-1,2,4-triazol-1-yl)cyclobutyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide; 6-fluoro-N-{5-[5-(3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-[5-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-2-fluorophenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(2-hydroxy-2-methylpropyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2-oxo-1,3-oxazolidin-3-yl)methyl]imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(2-hydroxy-2-methylpropyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-dimethylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-fluorophenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-fluorophenyl}-6-(5-methyl-4H-1,2,4-triazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide; 6-fluoro-N-{5-[5-(3-hydroxy-3-methylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(2-hydroxycyclopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{3-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2,6-dimethylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; 7-cyano-N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(1-hydroxyethyl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(5-methyl-1H-imidazol-1-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2-methoxyethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(5-{5-[(1S)-2,2-difluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(1-fluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(1-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide; N-{5-[5-(1-carbamoylcyclopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-fluoroimidazo[1,2-a]pyridine-3-carboxamide and N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(piperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide.

Another aspect provided herein are pharmaceutical compositions that include a therapeutically effective amount of a compound of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id),

Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), and a pharmaceutically acceptable carrier. In certain embodiments of such pharmaceutical compositions, the pharmaceutical composition is formulated for intravenous administration, intravitrial administration, intramuscular administration, oral administration, rectal administration, transdermal administration, pulmonary administration, inhalation administration, nasal administration, topical administration, ophthalmic administration or otic administration. In other embodiments, such pharmaceutical compositions are in the form of a tablet, a pill, a capsule, a liquid, an inhalant, a nasal spray solution, a suppository, a solution, an emulsion, an ointment, eye drop or ear drop. In other embodiments, such pharmaceutical compositions are formulated for oral administration and are in the form of a tablet, a pill, a capsule, a liquid, a solution, or an emulsion. In other embodiments, such pharmaceutical compositions are formulated for oral administration and are in the form of a tablet, a pill, or a capsule. In other embodiments, such pharmaceutical compositions further include one or more additional therapeutic agents. In other embodiments, such aforementioned pharmaceutical compositions further include one or more additional therapeutic agents.

Another aspect provided herein are medicaments for treating a patient with a disease or disorder associated with c-kit or PDGFR kinase activity, or c-kit and PDGFR kinase activity, and such medicaments include a therapeutically effective amount of a compound of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf). In certain embodiments of this aspect the disease is a mast-cell associated disease, a respiratory disease, an inflammatory disorder, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), an autoimmune disorder, a metabolic disease, a fibrosis disease, a dermatological disease, pulmonary arterial hypertension (PAH) or primary pulmonary hypertension (PPH). In other embodiments of this aspect, the disease is asthma, allergic rhinitis, pulmonary arterial hypertension (PAH), pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), uticaria, dermatosis, type I diabetes or type II diabetes.

Another aspect provided herein are medicaments for treating a disease mediated by c-kit or PDGFR kinase activity, or c-kit and PDGFR kinase activity, in a patient in need thereof, and such medicaments include a therapeutically effective amount of a compound of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), and the disease is a mast-cell associated disease, a respiratory disease, an inflammatory disorder, irritable bowel syndrome (IBS),

inflammatory bowel disease (IBD), an autoimmune disorder, a metabolic disease, a fibrosis disease, a dermatological disease, pulmonary arterial hypertension (PAH) or primary pulmonary hypertension (PPH).

In certain embodiments of this aspect, the disease is asthma, allergic rhinitis, pulmonary arterial hypertension (PAH), pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), uticaria, dermatosis, type I diabetes or type II diabetes.

Another aspect provided herein is the use of a compound of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf) in the manufacture of a medicament for treating a disease or disorder in a patient where c-kit or PDGFR kinase activity, or c-kit and PDGFR kinase activity is implicated.

Another aspect provided herein includes methods for treating a disease or disorder where c-kit or PDGFR kinase activity, or c-kit and PDGFR kinase activity is implicated, wherein the method includes administering to a system or subject in need of such treatment an effective amount of a compound of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, thereby treating the disease or disorder. In certain embodiments of such methods, the methods include administering the compound to a cell or tissue system or to a human or animal subject. In certain embodiments of such methods, the disease or condition is a metabolic disease, a fibrotic disease, a respiratory disease, an inflammatory disease or disorder, a dermatological disease or an autoimmune disease. In certain embodiments of such methods, the disease or condition is asthma, allergic rhinitis, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), pulmonary arterial hypertension (PAH), pulmonary fibrosis, liver fibrosis, cardiac fibrosis, scleroderma, urticaria, dermatoses, atopic dermatitis, type I diabetes or type II diabetes.

Another aspect provided herein is a compound of Formula (I), Formula (II), Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf) for use in treating a disease mediated by c-kit, PDGFRα, PDGFRβ or combination thereof, wherein the disease is selected from a mast-cell associated disease, a respiratory disease, an inflammatory disorder, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), an autoimmune disorder, a metabolic disease, a fibrosis disease, a dermatological disease, pulmonary arterial hypertension (PAH) and primary pulmonary hypertension (PPH). In certain embodiments of this aspect, the disease is selected from a mast-cell

associated disease, a respiratory disease, an inflammatory disorder, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), an autoimmune disorder, a metabolic disease, a fibrosis disease, a dermatological disease, pulmonary arterial hypertension (PAH) and primary pulmonary hypertension (PPH). In other embodiments the disease is asthma, allergic rhinitis, pulmonary arterial hypertension (PAH), pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), uticaria, dermatosis, type I diabetes or type II diabetes.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

The term “alkyl,” as used herein, refers to a saturated branched or straight chain hydrocarbon. In certain embodiments such alkyl groups are optionally substituted. As used herein, the terms "C_1-C_3alkyl", "C_1-C_4alkyl", "C_1-C_5alkyl", "C_1-C_6alkyl", "C_1-C_7alkyl" and "C_1-C_8alkyl" refer to an alkyl group containing at least 1, and at most 3, 4, 5, 6, 7 or 8 carbon atoms, respectively. If not otherwise specified, an alkyl group generally is a C_1-C_6 alkyl. Non-limiting examples of alkyl groups as used herein include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, hexyl, heptyl, octyl, nonyl, decyl and the like.

The term “alkoxy,” as used herein, refers to the group –OR_a, where R_a is an alkyl group as defined herein. As used herein, the terms "C_1-C_3alkoxy", "C_1-C_4alkoxy", "C_1-C_5alkoxy", "C_1-C_6alkoxy", "C_1-C_7alkoxy" and "C_1-C_8alkoxy" refer to an alkoxy group wherein the alkyl moiety contains at least 1, and at most 3, 4, 5, 6, 7 or 8, carbon atoms. Non-limiting examples of alkoxy groups, as used herein, include methoxy, ethoxy, n-propoxy, isopropoxy, n-butyloxy, t-butyloxy, pentyloxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, decyloxy and the like.

The term “cycloalkyl,” as used herein, refers to a saturated, monocyclic, fused bicyclic, fused tricyclic, spirocyclic or bridged polycyclic ring assembly. As used herein, the terms "C_3-C_5cycloalkyl", "C_3-C_6cycloalkyl", "C_3-C_7cycloalkyl", "C_3-C_8cycloalkyl, "C_3-C_9cycloalkyl and "C_3-C_{10}cycloalkyl refer to a cycloalkyl group wherein the saturated monocyclic, fused bicyclic or bridged polycyclic ring assembly contain at least 3, and at most 5, 6, 7, 8, 9 or 10, carbon atoms. Non-limiting examples of cycloalkyl groups, as used herein, include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, and the like.

The term "halo," as used herein, refers to fluorine (F), chlorine (Cl), bromine (Br), or iodine (I) substituents.

The terms “haloalkyl” or “halo-substituted alkyl,” as used herein, refers to an alkyl

group as defined herein, substituted with one or more halo groups as defined herein. The halo groups are the same or different. The haloalkyl can be monohaloalkyl, dihaloalkyl or polyhaloalkyl, including perhaloalkyl. A perhalo-alkyl refers to an alkyl having all hydrogen atoms replaced with halo atoms. A monohaloalkyl can have one iodo, bromo, chloro or fluoro within the alkyl group. Dihaloalky and polyhaloalkyl groups can have two or more of the same halo atoms or a combination of different halo groups within the alkyl. Such haloalkyl groups are also refered to herein as "C_1-C_3haloalkyl", "C_1-C_4haloalkyl", "C_1-C_5haloalkyl", "C_1-C_6haloalkyl", "C_1-C_7haloalkyl" and "C_1-C_8haloalkyl" wherein the alkyl group contains at least 1, and at most 3, 4, 5, 6, 7 or 8 carbon atoms, respectively. Non-limiting examples of such branched or straight chained haloalkyl groups, as used herein, include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. In certain embodiments, a haloalkyl group is trifluoromethyl.

The term “heteroaryl,” as used herein, refers to a 5-6 membered heteroaromatic monocyclic ring having 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur, an 8-10 membered fused bicyclic ring having 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur and where at least one of the rings is aromatic, or a 12-14 membered fused tricyclic ring having 1 to 4 heteroatoms independently selected from nitrogen, oxygen and sulfur and where at least one of the rings is aromatic. Such fused bicyclic and tricyclic ring systems may be fused to one or more aryl, cycloalkyl, or heterocycloalkyl rings. Non-limiting examples of heteroaryl groups, as used herein, include 2- or 3-furyl; 1-, 2-, 4-, or 5-imidazolyl; 3-, 4-, or 5-isothiazolyl; 3-, 4-, or 5-isoxazolyl; 2-, 4-, or 5-oxazolyl; 4- or 5-1,2,3-oxadiazolyl; 2- or 3-pyrazinyl; 1-, 3-, 4-, or 5- pyrazolyl; 3-, 4-, 5- or 6-pyridazinyl; 2-, 3-, or 4-pyridyl; 2-, 4-, 5- or 6-pyrimidinyl; 1-, 2- or 3-pyrrolyl; 1- or 5-tetrazolyl; 2- or 5-1,3,4-thiadiazolyl; 2-, 4-, or 5-thiazolyl; 2- or 3-thienyl; 2-, 4- or 6-1,3,5-triazinyl; 1-, 3- or 5-1,2,4-triazolyl; 1-, 4- or 5-1,2,3-triazolyl; 1- , 2-, 3-, 4-, 5-, 6-, 7-, 8-, or 9-acridinyl; 1-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-benzo[g]isoquinoline; 2-, 4-, 5- , 6-, or 7-benzoxazolyl; 1-, 2-, 4-, 5-, 6-, or 7-benzimidazolyl; 2-, 4-, 5-, 6-, or 7-benzothiazolyl; 2-, 3-, 4-, 5-, 6-, 7-benzo[b]thienyl; 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-benzo[b]oxepine; 2-, 4-, 5-, 6-, 7-, or 8-benzoxazinyl; 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8, or 9-carbazolyl; 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl; 2-, 4-, or 5-4H-imidazo[4,5-d] thiazolyl; 2-, 3-, 5-, or 6- imidazo[2,1-b] thiazolyl; 2-, 3-, 6-, or 7-imidazo[1,2-b][1,2,4]triazinyl; 1-, 3-, 4-, 5-, 6-, or 7-indazolyl; 1-, 2-, 3-, 5-, 6-, 7-, or 8-indolizinyl; 1-, 2-, 3-, 4-, 5-, 6-, or 7-indolyl; 1-, 2-, 3-, 4-, 5-, 6-, or 7-isoindolyl; 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinoliyl; 2-, 3-, 4-, 5-, 6-, or 7-naphthyridinyl; 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9-perimidinyl; 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenanthridinyl; 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-

phenathrolinyl; 1-, 2- , 3-, 4-, 6-, 7-, 8-, or 9-phenazinyl; 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenothiazinyl; 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9-, or 10-phenoxazinyl; 1-, 4-, 5-, 6-, 7-, or 8-phthalazinyl; 2-, 4-, 6-, or 7-pteridinyl; 2-, 6-, 7-, or 8- purinyl; 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10 -, or 11-7H-pyrazino[2,3-c]carbazolyl; 2-, 3-, 5-, 6-, or 7-furo[3,2-b]-pyranyl; 1-, 3-, or 5-1H-pyrazolo[4,3-d]-oxazolyl; 2-, 3-, 5-, or 8-pyrazino[2,3-d]pyridazinyl; 1-, 2-, 3-, 4-, 5-, or 8-5H-pyrido[2,3-d]-o-oxazinyl; 1-, 2-, 3-, 4-, 6-, 7-, 8-, or 9-quinolizinyl; 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl; 2-, 3- , 4-, 5-, 6-, 7-, or 8-quinazolinyl; 2-, 3-, 4-, or 5-thieno[2,3-b]furanyl, and 1-, 3-, 6-, 7-, 8-, or 9-furo[3,4-c]cinnolinyl.

The term “hetero atoms,” as used herein, refers to nitrogen (N), oxygen (O) or sulfur (S) atoms.

The term “heterocycloalkyl,” as used herein refers to a to saturated 3-6 membered monocyclic hydrocarbon ring structure, a saturated 6-9 membered fused bicyclic hydrocarbon ring structure, or a saturated 10-14 membered fused tricyclic hydrocarbon ring structure, wherein one to four of the ring carbons of the hydrocarbon ring structure are replaced by one to four groups independently selected from -O-, -NR-, or -S-, wherein R is hydrogen, C_1-C_4alkyl or an amino protecting group.

Non-limiting examples of heterocycloalkyl groups, as used herein, include aziridinyl, aziridin-1-yl, aziridin-2-yl, aziridin-3-yl, oxiranyl, oxiran-2-yl, oxiran-3-yl, thiiranyl, thiiran-2-yl, thiiran-3-yl, azetadinyl, azetadin-1-yl, azetadin-2-yl, azetadin-3-yl, oxetanyl, oxetan-2-yl, oxetan-3-yl, oxetan-4-yl, thietanyl, thietan-2-yl, thietan-3-yl, thietan-4-yl, pyrrolidinyl, pyrrolidin-1-yl, pyrrolidin-2-yl, pyrrolidin-3-yl, pyrrolidin-4-yl, pyrrolidin-5-yl, tetrahydrofuranyl, tetrahydrofuran-2-yl, tetrahydrofuran-3-yl, tetrahydrofuran-4-yl, tetrahydrofuran-5-yl, tetrahydrothienyl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, tetrahydrothien-4-yl, tetrahydrothien-5-yl, piperidinyl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperidin-5-yl, piperidin-6-yl, tetrahydropyranyl, tetrahydropyran-2-yl, tetrahydropyran-3-yl, tetrahydropyran-4-yl, tetrahydropyran-5-yl, tetrahydropyran-6-yl, tetrahydrothiopyranyl, tetrahydrothiopyran-2-yl, tetrahydrothiopyran-3-yl, tetrahydrothiopyran-4-yl, tetrahydrothiopyran-5-yl, tetrahydrothiopyran-6-yl, piperazinyl, piperazin-1-yl, piperazin-2-yl, piperazin-3-yl, piperazin-4-yl, piperazin-5-yl, piperazin-6-yl, morpholinyl, morpholin-2-yl, morpholin-3-yl, morpholin-4-yl, morpholin-5-yl, morpholin-6-yl, thiomorpholinyl, thiomorpholin-2-yl, thiomorpholin-3-yl, thiomorpholin-4-yl, thiomorpholin-5-yl, thiomorpholin-6-yl, oxathianyl, oxathian-2-yl, oxathian-3-yl, oxathian-5-yl, oxathian-6-yl, dithianyl, dithian-2-yl, dithian-3-yl, dithian-5-yl, dithian-6-yl, azepanyl, azepan-1-yl, azepan-2-yl, azepan-3-yl, azepan-4-yl, azepan-5-yl, azepan-6-yl, azepan-7-yl, oxepanyl, oxepan-2-yl, oxepan-3-yl, oxepan-4-yl, oxepan-5-yl, oxepan-6-yl, oxepan-7-yl, thiepanyl, thiepan-2-yl, thiepan-3-yl, thiepan-4-yl, thiepan-5-yl, thiepan-6-yl, thiepan-7-yl, dioxolanyl, dioxolan-2-yl, dioxolan-4-yl,

dioxolan-5-yl, thioxanyl, thioxan-2-yl, thioxan-3-yl, thioxan-4-yl, thioxan-5-yl, dithiolanyl, dithiolan-2-yl, dithiolan-4-yl, dithiolan-5-yl, pyrrolinyl, pyrrolin-1-yl, pyrrolin-2-yl, pyrrolin-3-yl, pyrrolin-4-yl, pyrrolin-5-yl, imidazolinyl, imidazolin-1-yl, imidazolin-3-yl, imidazolin-4-yl, imidazolin-5-yl, imidazolidinyl, imidazolidin-1-yl, imidazolidin-2-yl, imidazolidin-3-yl, imidazolidin-4-yl, imidazolidin-4-yl, pyrazolinyl, pyrazolin-1-yl, pyrazolin-3-yl, pyrazolin-4-yl, pyrazolin-5-yl, pyrazolidinyl, pyrazolidin-1-yl, pyrazolidin-2-yl, pyrazolidin-3-yl, pyrazolidin-4-yl, pyrazolidin-5-yl, hexahydro-1,4-diazepinyl, dihydrofuranyldihydropyranyl, 1,2,3,6-tetrahydropyridinyl, 2H-pyranyl, 4H-pyranyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, pyrrolidinyl-2-one, piperidinyl-3-one piperidinyl-2-one, piperidinyl-4-one, and 2H-pyrrolyl.

The term “acceptable” with respect to a compound, formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

The term “administration” or “administering” of the subject compound means providing a compound of Formula (I) or Formula (II), a pharmaceutically acceptable salt, a pharmaceutically acceptable solvate, or solvate thereof to a subject in need of treatment.

The term “autoimmune disease,” or “autoimmune disorder,” as used herein, refers diseases wherein cells uncontrollably attack the body's own tissues and organs (autoimmunity), producing inflammatory reactions and other serious symptoms and diseases. Non-limiting examples of autoimmune diseases include idiopathic thrombocytopenic purpura, hemolytic anemia, systemic lupus erythematosus, rheumatoid arthritis (RA), multiple sclerosis (MS), immune-mediated or type 1 diabetes mellitus, immune mediated glomerulonephritis, scleroderma, pernicious anemia, alopecia, pemphigus, pemphigus vulgaris, myasthenia gravis, inflammatory bowel diseases, Crohn's disease, psoriasis, autoimmune thyroid diseases, and Hashimoto's disease, Hashimoto's thyroiditis, dermatomyositis, goodpasture syndrome, myasthenia gravis pseudoparalytica, ophtalmia sympatica, phakogene uveitis, chronical aggressive hepatitis, primary billiary cirrhosis, autoimmune hemolytic anemy, Werlof disease, vitiligo vulgaris, Behcet's disease, collagen disease, uveitis, Sjogren's syndrome, autoimmune myocarditis, autoimmune hepatic diseases, autoimmune gastritis, pemphigus, Guillain-Barre syndrome, and HTLV-1-associated myelopathy.

The term “carrier,” as used herein, refers to chemical compounds or agents that facilitate the incorporation of a compound described herein into cells or tissues.

The terms “co-administration” or “combined administration” or the like as used herein are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are not

necessarily administered by the same route of administration or at the same time.

The term “dermatological disease” or “dermatological disorder,” as used herein refers to a skin disorder. Such dermatological disorders include, but are not limited to, proliferative or inflammatory disorders of the skin such as, atopic dermatitis, bullous disorders, collagenoses, contact dermatitis eczema, Kawasaki Disease, rosacea, Sjogren-Larsso Syndrome, actinic keratosis, basal cell carcinoma and urticaria.

The term “diluent,” as used herein, refers to chemical compounds that are used to dilute a compound described herein prior to delivery. Diluents can also be used to stabilize compounds described herein.

The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of a compound described herein being administered which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result can be reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate "effective" amount in any individual case may be determined using techniques, such as a dose escalation study.

The terms “enhance” or “enhancing,” as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term "enhancing" refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An "enhancing-effective amount," as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

The terms “fibrosis” or “fibrosis disease,” as used herein, refers to conditions that follow acute or chronic inflammation and are associated with the abnormal accumulation of cells and/or collagen and include but are not limited to fibrosis of individual organs or tissues such as the heart, kidney, joints, lung, or skin, and includes such disorders as idiopathic pulmonary fibrosis and cryptogenic fibrosing alveolitis.

The term “inflammatory disease or disorders,” as used herein, refers to those diseases or conditions that are characterized by one or more of the signs of pain (dolor, from the generation of noxious substances and the stimulation of nerves), heat (calor, from vasodilatation), redness (rubor, from vasodilatation and increased blood flow), swelling (tumor, from excessive inflow or restricted outflow of fluid), and loss of function (functio laesa, which may be partial or complete, temporary or permanent). Inflammation takes many forms and includes, but is not limited to, inflammation that is one or more of the following: acute, adhesive, atrophic, catarrhal, chronic, cirrhotic, diffuse,

disseminated, exudative, fibrinous, fibrosing, focal, granulomatous, hyperplastic, hypertrophic, interstitial, metastatic, necrotic, obliterative, parenchymatous, plastic, productive, proliferous, pseudomembranous, purulent, sclerosing, seroplastic, serous, simple, specific, subacute, suppurative, toxic, traumatic, and/or ulcerative. Inflammatory disorders further include, without being limited to those affecting the blood vessels (polyarteritis, temporal arthritis); joints (arthritis: crystalline, osteo-, psoriatic, reactive, rheumatoid, Reiter's); gastrointestinal tract (Disease,); skin (dermatitis); or multiple organs and tissues (systemic lupus erythematosus).

As used herein, the term “inhibit”, "inhibition" or “inhibiting” refers to the reduction or suppression of a given condition, symptom, or disorder, or disease, or a significant decrease in the baseline activity of a biological activity or process.

The term “pharmaceutically acceptable,” as used herein, refers to a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compounds described herein. Such materials are administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

The term "pharmaceutically acceptable carrier", as used herein, includes any and all solvents, dispersion media, coatings, surfactants, antioxidants, preservatives (e.g., antibacterial agents, antifungal agents), isotonic agents, absorption delaying agents, salts, preservatives, drug stabilizers, binders, excipients, disintegration agents, lubricants, sweetening agents, flavoring agents, dyes, and the like and combinations thereof, as would be known to those skilled in the art (see, for example, Remington's Pharmaceutical Sciences, 18th Ed. Mack Printing Company, 1990, pp. 1289- 1329). Except insofar as any conventional carrier is incompatible with the active ingredient, its use in the therapeutic or pharmaceutical compositions is contemplated.

The term “pharmaceutically acceptable salt,” as used herein, refers to a formulation of a compound that does not cause significant irritation to an organism to which it is administered and does not abrogate the biological activity and properties of the compounds described herein.

The terms “combination” or “pharmaceutical combination,” as used herein mean a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, by way of example, a compound of Formula (I) or Formula (II) and an additional therapeutic agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, by way of example, a compound of Formula (I) or Formula (II) and an additional therapeutic agent, are both administered to

a patient as separate entities either simultaneously, concurrently or sequentially with no specific time limits, wherein such administration provides therapeutically effective levels of the 2 compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of 3 or more active ingredients.

The terms "composition" or "pharmaceutical composition," as used herein, refers to a mixture of at least one compound, such as the compounds of Formula (I) or Formula (II) provided herein, with at least one and optionally more than one other pharmaceutically acceptable chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients.

The term "respiratory disease," as used herein, refers to diseases affecting the organs that are involved in breathing, such as the nose, throat, larynx, trachea, bronchi, and lungs. Respiratory diseases include, but are not limited to, asthma, adult respiratory distress syndrome and allergic (extrinsic) asthma, non-allergic (intrinsic) asthma, acute severe asthma, chronic asthma, clinical asthma, nocturnal asthma, allergen-induced asthma, aspirin-sensitive asthma, exercise-induced asthma, isocapnic hyperventilation, child-onset asthma, adult-onset asthma, cough-variant asthma, occupational asthma, steroid-resistant asthma, seasonal asthma, seasonal allergic rhinitis, perennial allergic rhinitis, chronic obstructive pulmonary disease, including chronic bronchitis or emphysema, pulmonary hypertension, interstitial lung fibrosis and/or airway inflammation and cystic fibrosis, and hypoxia.

The term "subject" or "patient," as used herein, encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, humans, chimpanzees, apes, monkeys, cattle, horses, sheep, goats, swine; rabbits, dogs, cats, rats, mice, guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish and the like. Frequently the subject is a human, and may be a human who has been diagnosed as in need of treatment for a disease or disorder disclosed herein.

As used herein, a subject is "in need of" a treatment if such subject would benefit biologically, medically or in quality of life from such treatment.

The term "c-kit inhibitor," as used herein, refers to a compound which inhibits c-kit kinase.

The term "disease or disorder associated with c-kit activity," as used herein, refers to any disease state associated with a c-kit kinase. Such diseases or disorders include, but are not limited to, a mast-cell associated disease, inflammatory diseases, respiratory diseases, fibrosis diseases, a dermatological disease, metabolic diseases and autoimmune diseases, such as, by way of example only, asthma, dermatitis, allergic rhinitis, pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), urticaria, rheumatoid arthritis,

multiple sclerosis, uticaria, pulmonary arterial hypertension (PAH), primary pulmonary hypertension (PPH), dermatosis, diabetes, type I diabetes and type II diabetes.

The term “PDGFR inhibitor,” as used herein, refers to a compound which inhibits PDGFR kinase.

The term “disease or disorder associated with PDGFR activity,” as used herein, refers to any disease state associated with a PDGFR kinase. Such diseases or disorders include, but are not limited to, inflammatory diseases, respiratory diseases, fibrosis diseases, metabolic diseases and autoimmune diseases, such as, by way of example only, asthma, dermatitis, allergic rhinitis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), urticaria, rheumatoid arthritis, multiple sclerosis, pulmonary arterial hypertension and diabetes.

The term “an optical isomer” or “a stereoisomer”, as used herein, refers to any of the various stereo isomeric configurations which may exist for a given compound of the present invention and includes geometric isomers. It is understood that a substituent may be attached at a chiral center of a carbon atom. The term "chiral" refers to molecules which have the property of non-superimposability on their mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner. Therefore, the invention includes enantiomers, diastereomers or racemates of the compound. “Enantiomers” are a pair of stereoisomers that are non-superimposable mirror images of each other. A 1:1 mixture of a pair of enantiomers is a "racemic” mixture. The term is used to designate a racemic mixture where appropriate. "Diastereoisomers” are stereoisomers that have at least two asymmetric atoms, but which are not mirror-images of each other. The absolute stereochemistry is specified according to the Cahn- Ingold- Prelog R-S system. When a compound is a pure enantiomer the stereochemistry at each chiral carbon may be specified by either R or S. Resolved compounds whose absolute configuration is unknown can be designated (+) or (-) depending on the direction (dextro- or levorotatory) which they rotate plane polarized light at the wavelength of the sodium D line. Certain compounds described herein contain one or more asymmetric centers or axes and may thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that may be defined, in terms of absolute stereochemistry, as (R)- or (S)-.

The term "a therapeutically effective amount" of a compound of the present invention, as used herein, refers to an amount of the compound of the present invention that will elicit the biological or medical response of a subject, for example, reduction or inhibition of an enzyme or a protein activity, or ameliorate symptoms, alleviate conditions, slow or delay disease progression, or prevent a disease, etc. In one non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the

present invention that, when administered to a subject, is effective to (1) at least partially alleviating, inhibiting, preventing and/or ameliorating a condition, or a disorder or a disease (i) mediated by c-kit kinase or c-kit and PDGFR kinases, or (ii) associated with c-kit kinase or c-kit and PDGFR kinase activity, or (iii) characterized by activity (normal or abnormal) of c-kit kinase or c-kit and PDGFR kinases; or (2) reducing or inhibiting the activity of c-kit kinase or c-kit and PDGFR kinases; or (3) reducing or inhibiting the expression of c-kit kinase or c-kit and PDGFR kinases. In another non-limiting embodiment, the term “a therapeutically effective amount” refers to the amount of the compound of the present invention that, when administered to a cell, or a tissue, or a non-cellular biological material, or a medium, is effective to at least partially reducing or inhibiting the activity of c-kit kinase or c-kit and PDGFR kinases; or at least partially reducing or inhibiting the expression of c-kit kinase or c-kit and PDGFR kinases.

The terms “treat,” “treating” or “treatment,” as used herein, refers to methods of alleviating, abating or ameliorating a disease or condition symptoms, preventing additional symptoms, ameliorating or preventing the underlying metabolic causes of symptoms, inhibiting the disease or condition, arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

In addition, as used herein, the term “treat”, “treating" or "treatment" of any disease or disorder refers in one embodiment, to ameliorating the disease or disorder (i.e., slowing or arresting or reducing the development of the disease or at least one of the clinical symptoms thereof). In another embodiment “treat”, "treating" or "treatment" refers to alleviating or ameliorating at least one physical parameter including those which may not be discernible by the patient. In yet another embodiment, “treat”, "treating" or "treatment" refers to modulating the disease or disorder, either physically, (e.g., stabilization of a discernible symptom), physiologically, (e.g., stabilization of a physical parameter), or both. In yet another embodiment, “treat”, "treating" or "treatment" refers to preventing or delaying the onset or development or progression of the disease or disorder.

The compound names provided herein were obtained using ChemDraw Ultra 10.0 (CambridgeSoft®) or JChem version 5.3.1 (ChemAxon).

Unless specified otherwise, the term “compounds of the present invention” or “compounds provided herein” refers to compounds of Fomula (I) and Formula (II), and subformulae thereof (such as Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) and Formula (IIf)), and pharmaceutically acceptable salts, hydrates or solvates, stereoisomers (including diastereoisomers and enantiomers), tautomers and

isotopically labeled compounds (including deuterium substitutions) thereof. Compounds of the present invention further comprise polymorphs of compounds of Fomula (I) and Formula (II) (or subformulae thereof) and salts thereof.

As used herein, the term "a," "an," "the" and similar terms used in the context of the present invention (especially in the context of the claims) are to be construed to cover both the singular and plural unless otherwise indicated herein or clearly contradicted by the context.

All methods described herein can be performed in any suitable order unless otherwise indicated herein or otherwise clearly contradicted by context. The use of any and all examples, or exemplary language (e.g. "such as") provided herein is intended merely to better illuminate the invention and does not pose a limitation on the scope of the invention otherwise claimed.

Various enumerated embodiments of the invention are described herein. It will be recognized that features specified in each embodiment may be combined with other specified features to provide further embodiments of the present invention.

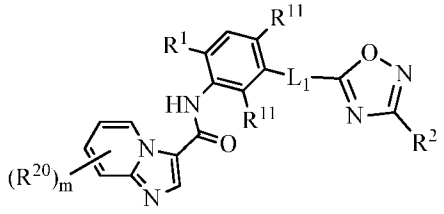
Description of the Preferred Embodiments

Provided herein are compounds, pharmaceutically acceptable salts, solvates, N-oxides and isomers thereof, that are inhibitors of c-kit kinase or c-kit and PDGFR kinases. Certain embodiments of compounds provided herein have an IC_{50} for PDGFR inhibition to IC_{50} for c-kit inhibition ratio ($IC_{50\ PDGFR}/IC_{50\ c\text{-}kit}$) in the range of 750 to 1000. Certain embodiments of compounds provided herein have an IC_{50} for PDGFR inhibition to IC_{50} for c-kit inhibition ratio ($IC_{50\ PDGFR}/IC_{50\ c\text{-}kit}$) in the range of 500 to 750. Certain embodiments of compounds provided herein have an IC_{50} for PDGFR inhibition to IC_{50} for c-kit inhibition ratio ($IC_{50\ PDGFR}/IC_{50\ c\text{-}kit}$) in the range of 250 to 500. Certain embodiments of compounds provided herein have an IC_{50} for PDGFR inhibition to IC_{50} for c-kit inhibition ratio ($IC_{50\ PDGFR}/IC_{50\ c\text{-}kit}$) in the range of 100 to 250. Certain embodiments of compounds provided herein have an IC_{50} for PDGFR inhibition to IC_{50} for c-kit inhibition ratio ($IC_{50\ PDGFR}/IC_{50\ c\text{-}kit}$) in the range of 75 to 100. Certain embodiments of compounds provided herein have an IC_{50} for PDGFR inhibition to IC_{50} for c-kit inhibition ratio ($IC_{50\ PDGFR}/IC_{50\ c\text{-}kit}$) in the range of 50 to 75. Certain embodiments of compounds provided herein have an IC_{50} for PDGFR inhibition to IC_{50} for c-kit inhibition ratio ($IC_{50\ PDGFR}/IC_{50\ c\text{-}kit}$) in the range of 25 to 50. Certain embodiments of compounds provided herein have an IC_{50} for PDGFR inhibition to IC_{50} for c-kit inhibition ratio ($IC_{50\ PDGFR}/IC_{50\ c\text{-}kit}$) in the range of 10 to 25. Certain embodiments of compounds provided herein have an IC_{50} for PDGFR inhibition to IC_{50} for c-kit inhibition ratio ($IC_{50\ PDGFR}/IC_{50\ c\text{-}kit}$) in the range of 7.5 to 10. Certain embodiments of compounds provided herein have an IC_{50} for PDGFR inhibition to IC_{50} for

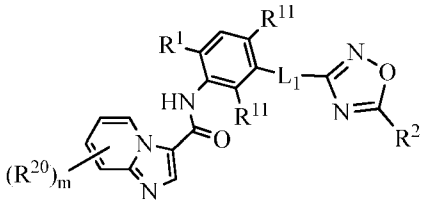
c-kit inhibition ratio ($IC_{50\ PDGFR}/IC_{50\ c\text{-}kit}$) in the range of 5 to 7.5. Certain embodiments of compounds provided herein have an IC_{50} for PDGFR inhibition to IC_{50} for c-kit inhibition ratio ($IC_{50\ PDGFR}/IC_{50\ c\text{-}kit}$) in the range of 2.5 to 5. Certain embodiments of compounds provided herein have an IC_{50} for PDGFR inhibition to IC_{50} for c-kit inhibition ratio ($IC_{50\ PDGFR}/IC_{50\ c\text{-}kit}$) in the range of 1 to 2.5. Certain embodiments of compounds provided herein have an IC_{50} for IC_{50} for PDGFR inhibition to c-kit inhibition ratio ($IC_{50\ PDGFR}/IC_{50\ c\text{-}kit}$) in the range of 0.95 to 2.5.

Also provided herein are pharmaceutical compositions that include such compounds. Further provided herein are methods for the treatment of diseases and/or disorders associated with c-kit kinase or c-kit and PDGFR kinases using such compounds and pharmaceutical compositions.

The c-kit kinase, or c-kit and PDGFR kinase, inhibitors of the present invention are compounds having the structure of Formula (I) or Formula (II), and pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof:



Formula (I)



Formula (II)

wherein:

m is 1 and R^{20} is selected from H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, deuterium, deuterated C_1-C_6alkyl, -CN, $-(CR^9_2)_nOR^4$, $-C(O)R^4$, $-(CR^9_2)_nC(=O)OR^4$, R^{10}, $-(CR^9_2)_nR^{10}$, $-((CR^9_2)_nO)_tR^4$, $-(CR^9_2)_nO(CR^9_2)_nR^7$, $-(CR^9_2)_nC(=O)R^4$, $-C(=O)N(R^4)_2$, $-OR^4$ and $-(CR^9_2)_nCN$;

or m is 4 and R^{20} is deuterium;

R^1 is selected from C_1-C_6alkyl and halo;

each R^{11} is independently selected from H, halo, and C_1-C_6alkyl;

L_1 is a bond, –NH- or -C(=O)NH-;

L_2 is $-(CR^9_2)_n$-, $-CHR^6$-, $-(CR^9_2)_nO$-, -NH-, $-(CR^9_2)_nC(=O)$-, $-C(=O)O(CR^9_2)_n$-, $-(CR^9_2)_nOC(=O)NR^4$-, $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_n$ -, $-(CR^9_2)_nNR^4C(=O)$- or $-(CR^9_2)_nNR^4C(=O)O$- ;

R^2 is R^3 or L_2R^3;

R^3 is selected from an unsubstituted C_3-C_8cycloalkyl, a cyclobutanone, a cyclopentanone and a substituted C_3-C_8cycloalkyl,

wherein the substituted C_3-C_8cycloalkyl of R^2 is substituted with 1-4 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, $-OR^4$, -CN, $-C(=O)OR^4$, $-C(=O)R^4$, $-C(=O)R^7$, $-C(=O)OR^5$, $-(CR^9_2)_nOR^4$, $-O(CR^9_2)_nOR^4$, $-C(=O)O(CR^9_2)_nOR^4$, $-N(R^4)_2$, $=N-OR^4$, $=N-O-(CR^9_2)_nR^5$, $-C(=O)NR^4_2$, $-NR^4C(=O)OR^4$, $-NR^4C(=O)(CR^9_2)_nOR^4$, $-NR^4(CR^9_2)_nOR^4$, $-NR^4S(=O)_2R^4$, $-N(C(=O)OR^4)_2$, $=CH_2$, $=CH(CR^9_2)_nOR^4$, R^8, $-(CR^9_2)_nR^8$, deuterated C_1-C_6alkoxy, $-S(=O)_2R^4$, $-S(=O)_2R^7$, $-S(=O)_2R^8$, $-S(=O)_2N(R^4)_2$, $-S(=O)_2NHC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nOR^4$, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with C_1-C_6alkyl, a spiro attached dioxane, a spiro attached tetrahyrofuranly, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a C_1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S, a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S substituted with 1-3 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, $-OR^4$ and R^8;

each R^4 is independently selected from H and C_1-C_6alkyl;

R^5 is an unsubstituted C_3-C_8cycloalkyl , an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N or O or a C_3-C_8cycloalkyl substituted with 1-3 substituents independently selected from C_1-C_6alkyl;

each R^6 is independently selected from $-NHC(O)OR^4$, $-OR^4$ and $-(CR^9_2)_nOR^4$;

each R^7 is independently selected from C_1-C_6haloalkyl;

R^8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted

C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$, $-C(O)OR^4$ and $-S(O)_2R^4$;

each R^9 is independently selected from H and C_1-C_6alkyl;

R^{10} is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

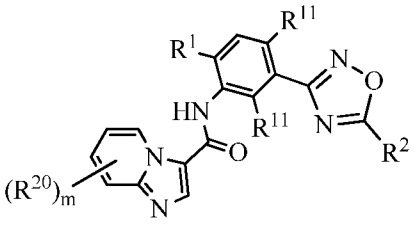
wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$ and $-S(O)_2R^4$;

t is 1, 2 or 3, and

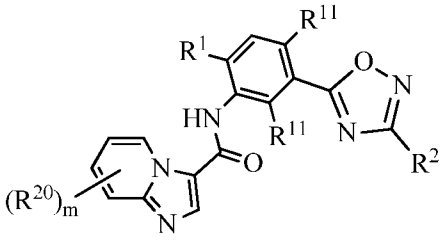
each n is independently selected from 1, 2, 3 and 4.

In certain embodiments of compounds of Formula (I) or Formula (II), and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, the compound of Formula (I) or Formula (II) is a compound having a structure of

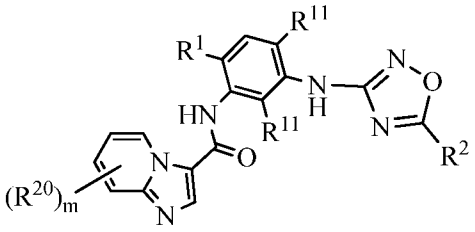
Formula (Ia), Formula (IIa), Formula (Ib) or Formula (IIb)



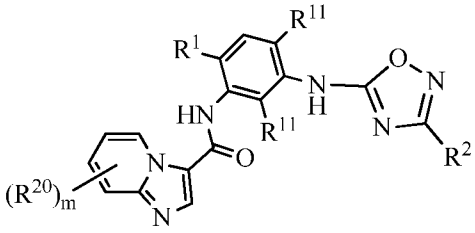
Formula (Ia)



Formula (IIa)



Formula (Ib)



Formula (IIb)

wherein:

m is 1 and R^{20} is selected from H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, deuterium, deuterated C_1-C_6alkyl, -CN, $-(CR^9_2)_nOR^4$, $-C(O)R^4$, $-(CR^9_2)_nC(=O)OR^4$, R^{10}, $-(CR^9_2)_nR^{10}$, $-((CR^9_2)_nO)_tR^4$, $-(CR^9_2)_nO(CR^9_2)_nR^7$, $-(CR^9_2)_nC(=O)R^4$, $-C(=O)N(R^4)_2$, $-OR^4$ and $-(CR^9_2)_nCN$;

or m is 4 and R^{20} is deuterium;

R^1 is selected from C_1-C_6alkyl and halo;

each R^{11} is independently selected from H, halo, and C_1-C_6alkyl;

L_2 is $-(CR^9_2)_n-$, $-CHR^6-$, $-(CR^9_2)_nO-$, -NH-, $-(CR^9_2)_nC(=O)-$, $-C(=O)O(CR^9_2)_n-$, $-(CR^9_2)_nOC(=O)NR^4-$, $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_n-$, $-(CR^9_2)_nNR^4C(=O)-$ or $-(CR^9_2)_nNR^4C(=O)O-$;

R^2 is R^3 or L_2R^3;

R^3 is selected from an unsubstituted C_3-C_8cycloalkyl, a cyclobutanone, a cyclopentanone and a substituted C_3-C_8cycloalkyl,

wherein the substituted C_3-C_8cycloalkyl of R^2 is substituted with 1-4 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, $-OR^4$, -CN, $-C(=O)OR^4$, $-C(=O)R^4$, $-C(=O)R^7$, $-C(=O)OR^5$, $-(CR^9_2)_nOR^4$, $-O(CR^9_2)_nOR^4$, $-C(=O)O(CR^9_2)_nOR^4$, $-N(R^4)_2$, $=N-OR^4$, $=N-O-(CR^9_2)_nR^5$, $-C(=O)NR^4_2$, $-NR^4C(=O)OR^4$, $-NR^4C(=O)(CR^9_2)_nOR^4$, $-NR^4(CR^9_2)_nOR^4$, $-NR^4S(=O)_2R^4$, $-N(C(=O)OR^4)_2$, $=CH_2$, $=CH(CR^9_2)_nOR^4$, R^8, $-(CR^9_2)_nR^8$, deuterated C_1-C_6alkoxy, $-S(=O)_2R^4$, $-S(=O)_2R^7$, $-S(=O)_2R^8$, $-S(=O)_2N(R^4)_2$, $-S(=O)_2NHC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nOR^4$, a spiro attached dioxolane, a spiro attached dioxolane which is substituted

with C_1-C_6alkyl, a spiro attached dioxane, a spiro attached tetrahyrofuranly, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a C_1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S, a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S substituted with 1-3 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, $-OR^4$ and R^8;

each R^4 is independently selected from H and C_1-C_6alkyl;

R^5 is an unsubstituted C_3-C_8cycloalkyl , an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N or O or a C_3-C_8cycloalkyl substituted with 1-3 substituents independently selected from C_1-C_6alkyl;

each R^6 is independently selected from $-NHC(O)OR^4$, $-OR^4$ and $-(CR^9_2)_nOR^4$;

each R^7 is independently selected from C_1-C_6haloalkyl;

R^8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$, $-C(O)OR^4$ and $-S(O)_2R^4$;

each R^9 is independently selected from H and C_1-C_6alkyl;

R^{10} is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl

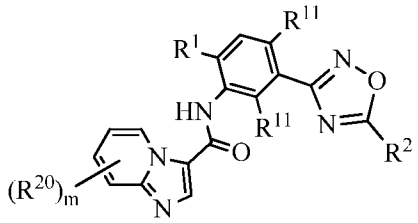
with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$ and $-S(O)_2R^4$;

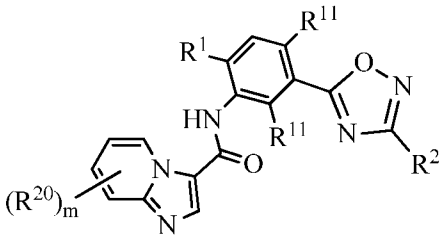
t is 1, 2 or 3, and

each n is independently selected from 1, 2, 3 and 4.

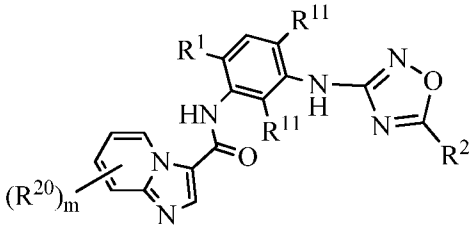
In certain embodiments of compounds of Formula (I) or Formula (II), and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, the compound of Formula (I) or Formula (II), is a compound having a structure of Formula (Ia), Formula (IIa), Formula (Ib), Formula (IIb), Formula (Ic), Formula (IIc), Formula (Id), Formula (IId), Formula (Ie), Formula (IIe), Formula (If) or Formula (IIf):



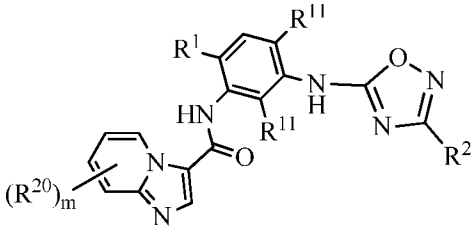
Formula (Ia)



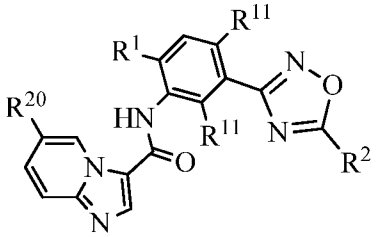
Formula (IIa)



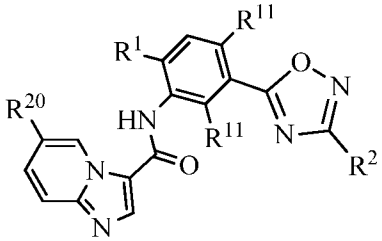
Formula (Ib)



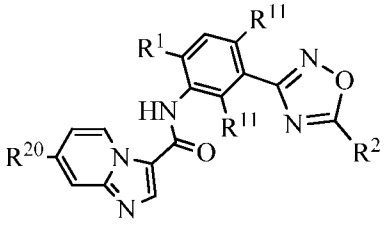
Formula (IIb)



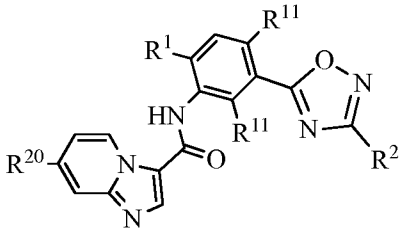
Formula (Ic)



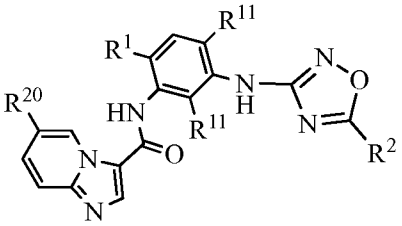
Formula (IIc)



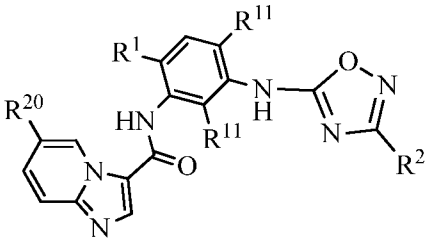
Formula (Id)



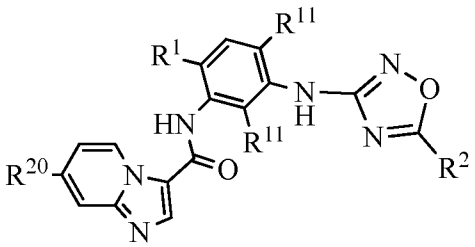
Formula (IId)



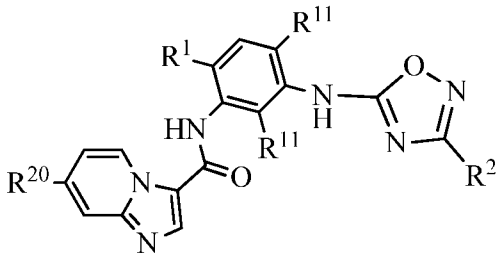
Formula (Ie)



Formula (IIe)



Formula (If)



Formula (IIf)

wherein:

m is 1 and R^{20} is selected from H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, deuterium, deuterated C_1-C_6alkyl, -CN, $-(CR^9_2)_nOR^4$, $-C(O)R^4$, $-(CR^9_2)_nC(=O)OR^4$, R^{10}, $-(CR^9_2)_nR^{10}$, $-((CR^9_2)_nO)_tR^4$, $-(CR^9_2)_nO(CR^9_2)_nR^7$, $-(CR^9_2)_nC(=O)R^4$, $-C(=O)N(R^4)_2$, $-OR^4$ and $-(CR^9_2)_nCN$;

or m is 4 and R^{20} is deuterium;

R^1 is selected from C_1-C_6alkyl and halo;

each R^{11} is independently selected from H, halo, and C_1-C_6alkyl;

L_2 is $-(CR^9_2)_n-$, $-CHR^6-$, $-(CR^9_2)_nO-$, -NH-, $-(CR^9_2)_nC(=O)-$, $-C(=O)O(CR^9_2)_n-$, $-(CR^9_2)_nOC(=O)NR^4-$, $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_n-$, $-(CR^9_2)_nNR^4C(=O)-$ or $-(CR^9_2)_nNR^4C(=O)O-$;

R^2 is R^3 or L_2R^3;

R^3 is selected from an unsubstituted C_3-C_8cycloalkyl, a cyclobutanone, a cyclopentanone and a substituted C_3-C_8cycloalkyl,

wherein the substituted C_3-C_8cycloalkyl of R^2 is substituted with 1-4 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, $-OR^4$, -CN, $-C(=O)OR^4$, $-C(=O)R^4$, $-C(=O)R^7$, $-C(=O)OR^5$, $-(CR^9_2)_nOR^4$, $-O(CR^9_2)_nOR^4$, $-C(=O)O(CR^9_2)_nOR^4$, $-N(R^4)_2$, $=N-OR^4$, $=N-O-(CR^9_2)_nR^5$, $-C(=O)NR^4_2$, $-NR^4C(=O)OR^4$, $-NR^4C(=O)(CR^9_2)_nOR^4$, $-NR^4(CR^9_2)_nOR^4$, $-NR^4S(=O)_2R^4$, $-N(C(=O)OR^4)_2$, $=CH_2$, $=CH(CR^9_2)_nOR^4$, R^8, $-(CR^9_2)_nR^8$, deuterated C_1-C_6alkoxy, $-S(=O)_2R^4$, $-S(=O)_2R^7$, $-S(=O)_2R^8$, $-S(=O)_2N(R^4)_2$, $-S(=O)_2NHC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nOR^4$, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with C_1-C_6alkyl, a spiro attached dioxane, a spiro attached tetrahyrofuranly, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a C_1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S, a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O

and S substituted with 1-3 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, -OR^4 and R^8;

each R^4 is independently selected from H and C_1-C_6alkyl;

R^5 is an unsubstituted C_3-C_8cycloalkyl , an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N or O or a C_3-C_8cycloalkyl substituted with 1-3 substituents independently selected from C_1-C_6alkyl;

each R^6 is independently selected from -$NHC(O)OR^4$, -OR^4 and -$(CR^9{}_2)_nOR^4$;

each R^7 is independently selected from C_1-C_6haloalkyl;

R^8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, -$(C(R^9)_2)_nOR^4$, -$(C(R^9)_2)_nR^5$, -$(C(R^9)_2)_nC(O)OR^4$, -$C(O)OR^4$ and -$S(O)_2R^4$;

each R^9 is independently selected from H and C_1-C_6alkyl;

R^{10} is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$ and $-S(O)_2R^4$;

t is 1, 2 or 3, and

each n is independently selected from 1, 2, 3 and 4.

The compounds of Formula (I) or Formula (II), pharmaceutically acceptable salts, solvates, N-oxides and isomers thereof, and pharmaceutical compositions provided herein also includes all suitable isotopic variations of such compounds, and pharmaceutically acceptable salts, solvates, N-oxides and isomers thereof, and pharmaceutical compositions. Therefore, any formula given herein is also intended to represent unlabeled forms as well as isotopically labeled forms of the compounds. Isotopically labeled compounds have structures depicted by the formulas given herein except that one or more atoms are replaced by an atom having a selected atomic mass or mass number. Examples of isotopes that can be incorporated into compounds of the invention include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine, and chlorine, such as ^{2}H, ^{3}H, ^{11}C, ^{13}C, ^{14}C, ^{15}N, ^{18}F ^{31}P, ^{32}P, ^{35}S, ^{36}Cl, ^{125}I respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as ^{3}H and ^{14}C, or those into which non-radioactive isotopes, such as ^{2}H and ^{13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with ^{14}C), reaction kinetic studies (with, for example ^{2}H or ^{3}H), detection or imaging techniques, such as positron emission tomography (PET) or single-photon emission computed tomography (SPECT) including drug or substrate tissue distribution assays, or in radioactive treatment of patients. In particular, an ^{18}F or labeled compound may be particularly desirable for PET or SPECT studies. Isotopically-labeled compounds of formula (I) can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagents in place of the non-labeled reagent previously employed.

Further, substitution with heavier isotopes, particularly deuterium (i.e., ^{2}H or D) may afford certain therapeutic advantages resulting from greater metabolic stability, for example increased in vivo half-life or reduced dosage requirements or an improvement in therapeutic index. It is understood that deuterium in this context is regarded as a substituent of a compound of the formula (I). The concentration of such a heavier isotope, specifically deuterium, may be defined by the isotopic enrichment factor. The

term "isotopic enrichment factor" as used herein means the ratio between the isotopic abundance and the natural abundance of a specified isotope. If a substituent in a compound of this invention is denoted deuterium, such compound has an isotopic enrichment factor for each designated deuterium atom of at least 3500 (52.5% deuterium incorporation at each designated deuterium atom), at least 4000 (60% deuterium incorporation), at least 4500 (67.5% deuterium incorporation), at least 5000 (75% deuterium incorporation), at least 5500 (82.5% deuterium incorporation), at least 6000 (90% deuterium incorporation), at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation).

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallization may be isotopically substituted, *e.g.* D_2O, d_6-acetone, d_6-DMSO.

Compounds of the invention, i.e. compounds of Formula (I) and Formula (II) that contain groups capable of acting as donors and/or acceptors for hydrogen bonds may be capable of forming co-crystals with suitable co-crystal formers. These co-crystals may be prepared from compounds of formula (I) by known co-crystal forming procedures. Such procedures include grinding, heating, co-subliming, co-melting, or contacting in solution compounds of formula (I) with the co-crystal former under crystallization conditions and isolating co-crystals thereby formed. Suitable co-crystal formers include those described in WO 2004/078163. Hence the invention further provides co-crystals comprising a compound of Formula (I) and Formula (II).

Processes for Making Compounds of Formula (I) or Formula (II)

General procedures for preparing compounds of Formula (I) or Formula (II) are described in the Examples, *infra*. In the reactions described, reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these are desired in the final product, may be protected to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice (see e.g., T.W. Greene and P. G. M. Wuts in “Protective Groups in Organic Chemistry,” John Wiley and Sons, 1991).

In certain embodiments, the compounds of Formula (I) or Formula (II) provided herein are prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound of Formula (I) or Formula (II) with a stoichiometric amount of an appropriate pharmaceutically acceptable organic acid or inorganic acid or a suitable anion exchange reagent. In other embodiments, a pharmaceutically acceptable

base addition salt of compounds of Formula (I) or Formula (II) is prepared by reacting the free acid form of the compound of Formula (I) or Formula (II) with a stoichiometric amount of an appropriate pharmaceutically acceptable organic base or inorganic base or a suitable ion exchange reagent. Such reactions are typically carried out in water or in an organic solvent, or in a mixture of the two. Generally, use of non-aqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile is desirable, where practicable.

Alternatively, the salt forms of the compounds of Formula (I) or Formula (II) are prepared using salts of the starting materials or intermediates. In certain embodiments, the compounds of Formula (I) or Formula (II) are in the form of other salts including, but not limited to, oxalates and trifluoroacetates. In certain embodiments, hemisalts of acids and bases are formed, for example, hemisulphate and hemicalcium salts.

Such pharmaceutically acceptable acid addition salts of compounds of Formula (I) or Formula (II) include, but are not limited to, a hydrobromide, hydrochloride, sulfate, nitrate, succinate, maleate, formate, acetate, adipate, besylatye, bicarbonate/carbonate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluenesulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, ethanedisulfonate, camphorsulfonate, chlortheophyllonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate), hexanoate salt, bisulphate/sulphate, borate, camsylate, cyclamate, edisylate, esylate, gluceptate, gluconate, glucuronate, hexafluorophosphate, hibenzate, hippurate, hydrochloride/chloride, hydrobromide/bromide, hydroiodide/iodide, isethionate, lactobionate, laurylsulphate, malate, malonate, mandelate, mesylate, methylsulphate, naphthoate, napsylate, naphthylate, 2-napsylate, nicotinate, octadecanoate, oleate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, polygalacturonate, pyroglutamate, saccharate, stearate, sulfosalicylate, tannate, tosylate, trifluoroacetate and xinofoate salts.

The organic acid or inorganic acids used to form certain pharmaceutically acceptable acid addition salts of compounds of Formula (I) or Formula (II) include, but are not limited to, hydrobromic acid, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, succinic acid, maleic acid, malonic acid, mandelic acid, formic acid, acetic acid, propionic acid, glycolic acid, oxalic acid, fumaric acid, citric acid, tartaric acid, lactic acid, benzoic acid, salicylic acid, glutamic acid, aspartic acid, toluenesulfonic acid, sulfosalicylic acid, benzenesulfonic acid, methanesulfonic acid, ethanesulfonic acid, naphthalenesulfonic acid, such as 2-naphthalenesulfonic acid, or hexanoic acid.

Such pharmaceutically acceptable base addition salt of compounds of Formula (I) or Formula (II) include, but are not limited to, ammonium, aluminium, arginine, benzathine, calcium, choline, copper, diethylamine, diolamine, glycine, isopropylamine, cholinate, diethanolamine, piperazine, iron, lysine, magnesium, meglumine, olamine, potassium,

silver, sodium, tromethamine and zinc salts.

The organic or inorganic bases used to form certain pharmaceutically acceptable base addition salt of compounds of Formula (I) or Formula (II) include, but are not limited to, salts derived from ammonium salts and metals from columns I to XII of the periodic table, or salts derived from primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines, basic ion exchange resins, and the like.

In certain embodiments, the free acid or free base forms of the compounds of Formula (I) or Formula (II) provided herein are prepared from the corresponding base addition salt or acid addition salt from, respectively. For example a compound Formula (I) in an acid addition salt form is converted to the corresponding free base by treating with a suitable base (by way of example only, an ammonium hydroxide solution, a sodium hydroxide, and the like). For example, a compound of Formula (I) in a base addition salt form is converted to the corresponding free acid by treating with a suitable acid (by way of example only, hydrochloric acid).

Lists of additional suitable salts can be found, e.g., in "Remington's Pharmaceutical Sciences", 20th ed., Mack Publishing Company, Easton, Pa., (1985); and in "Handbook of Pharmaceutical Salts: Properties, Selection, and Use" by Stahl and Wermuth (Wiley-VCH, Weinheim, Germany, 2002.

In certain embodiments, compounds of Formula (I) or Formula (II) in unoxidized form are prepared from N-oxides of compounds Formula (I) or Formula (II) by treating with a reducing agent (by way of example only, sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in a suitable inert organic solvent (by way of example only, acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

In certain embodiments, compounds of Formula (I) or Formula (II) are prepared as protected derivatives using methods known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T. W. Greene, "Protecting Groups in Organic Chemistry," 3rd edition, John Wiley and Sons, Inc., 1999.

In certain embodiments, compounds of Formula (I) or Formula (II) are prepared or formed, as solvates (e.g., hydrates). In certain embodiments, hydrates of compounds of Formula (I) or Formula (II) are prepared by recrystallization from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

Furthermore, the compounds of the present invention, including their salts, can also be obtained in the form of their hydrates, or include other solvents used for their crystallization. The compounds of the present invention may inherently or by design

form solvates with pharmaceutically acceptable solvents (including water); therefore, it is intended that the invention embrace both solvated and unsolvated forms. The term "solvate" refers to a molecular complex of a compound of the present invention (including pharmaceutically acceptable salts thereof) with one or more solvent molecules. Such solvent molecules are those commonly used in the pharmaceutical art, which are known to be innocuous to the recipient, e.g., water, ethanol, and the like. The term "hydrate" refers to the complex where the solvent molecule is water.

The compounds of the present invention, including salts, hydrates and solvates thereof, may inherently or by design form polymorphs.

Any asymmetric atom (e.g., carbon or the like) of the compound(s) of the present invention can be present in racemic or enantiomerically enriched, for example the (*R*)-, (*S*)- or (*R,S*)- configuration. In certain embodiments, each asymmetric atom has at least 50 % enantiomeric excess, at least 60 % enantiomeric excess, at least 70 % enantiomeric excess, at least 80 % enantiomeric excess, at least 90 % enantiomeric excess, at least 95 % enantiomeric excess, or at least 99 % enantiomeric excess in the (*R*)- or (*S*)- configuration. Substituents at atoms with unsaturated double bonds may, if possible, be present in *cis*- (*Z*)- or *trans*- (*E*)- form.

Accordingly, as used herein a compound of the present invention can be in the form of one of the possible isomers, rotamers, atropisomers, tautomers or mixtures thereof, for example, as substantially pure geometric (*cis* or *trans*) isomers, diastereomers, optical isomers (antipodes), racemates or mixtures thereof.

Any resulting mixtures of isomers can be separated on the basis of the physicochemical differences of the constituents, into the pure or substantially pure geometric or optical isomers, diastereomers, racemates, for example, by chromatography and/or fractional crystallization.

Any resulting racemates of final products or intermediates can be resolved into the optical antipodes by known methods, *e.g.*, by separation of the diastereomeric salts thereof, obtained with an optically active acid or base, and liberating the optically active acidic or basic compound. In particular, a basic moiety may thus be employed to resolve the compounds of the present invention into their optical antipodes, *e.g.*, by fractional crystallization of a salt formed with an optically active acid, *e.g.*, tartaric acid, dibenzoyl tartaric acid, diacetyl tartaric acid, di-*O,O'*-*p*-toluoyl tartaric acid, mandelic acid, malic acid or camphor-10-sulfonic acid. Racemic products can also be resolved by chiral chromatography, *e.g.*, high pressure liquid chromatography (HPLC) using a chiral adsorbent.

In certain embodiments, compounds of Formula (I) or Formula (II) are prepared as their individual stereoisomers. In other embodiments, the compounds of Formula (I) or

Formula (II) provided herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomers. In certain embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds of Formula (I) or Formula (II), or by using dissociable complexes (e.g., crystalline diastereomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubility, reactivity, etc.) and are readily separated by taking advantage of these dissimilarities. In certain embodiments, the diastereomers are separated by chromatography, or by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixture can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions," John Wiley And Sons, Inc., 1981.

Mixtures of isomers obtainable according to the invention can be separated in a manner known to those skilled in the art into the individual isomers; diastereoisomers can be separated, for example, by partitioning between polyphasic solvent mixtures, recrystallisation and/or chromatographic separation, for example over silica gel or by *e.g.* medium pressure liquid chromatography over a reversed phase column, and racemates can be separated, for example, by the formation of salts with optically pure salt-forming reagents and separation of the mixture of diastereoisomers so obtainable, for example by means of fractional crystallisation, or by chromatography over optically active column materials.

Depending on the choice of the starting materials and procedures, certain embodiments of the compounds of the present invention are present in the form of one of the possible isomers or as mixtures thereof, for example as pure optical isomers, or as isomer mixtures, such as racemates and diastereoisomer mixtures, depending on the number of asymmetric carbon atoms. The present invention is meant to include all such possible isomers, including racemic mixtures, diasteriomeric mixtures and optically pure forms. Optically active (R)- and (S)- isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. If the compound contains a double bond, the substituent may be E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans-configuration. All tautomeric forms are also intended to be included.

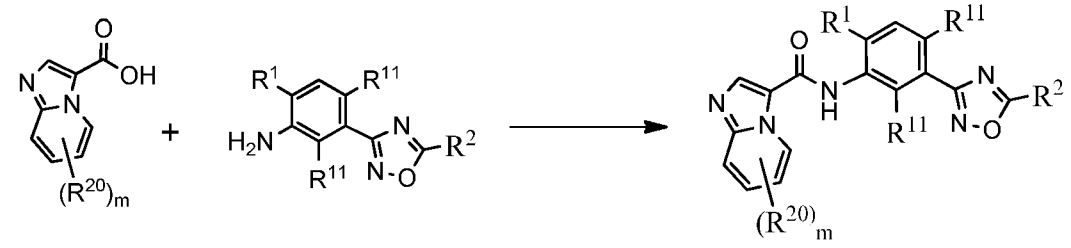
Compounds of Formula (I) or Formula (II) are made by processes described herein and as illustrated in the Examples.Intermediates and final products can be worked up

and/or purified according to standard methods, *e.g.* using chromatographic methods, distribution methods, (re-) crystallization, and the like. The invention relates also to those forms of the process in which a compound obtainable as an intermediate at any stage of the process is used as starting material and the remaining process steps are carried out, or in which a starting material is formed under the reaction conditions or is used in the form of a derivative, for example in a protected form or in the form of a salt, or a compound obtainable by the process according to the invention is produced under the process conditions and processed further in situ. All starting materials, building blocks, reagents, acids, bases, dehydrating agents, solvents and catalysts utilized to synthesize the compounds of the present invention are either commercially available or can be produced by organic synthesis methods known to one of ordinary skill in the art.

Non-limiting examples of synthetic schemes used to make compounds of the invention are illustrated in reaction schemes (I)-(IV). The R_1, R_{20}, R_{11} and R_2 groups as defined herein.

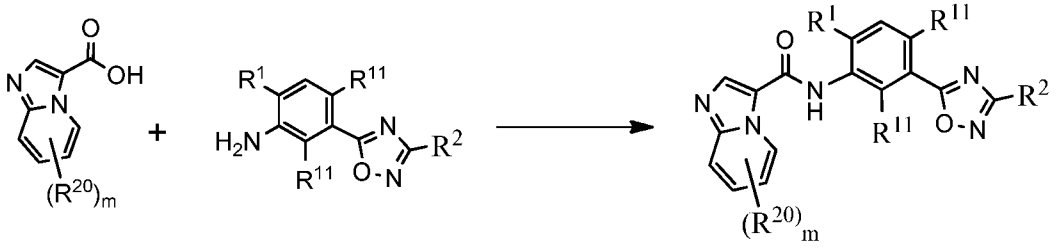
Scheme (I) illustrates the synthesis of compounds of Formula (I) by coupling the amine with the carboxylic acid in the presence of a base and a coupling reagent. By way of example only, the coupling reagent is HATU and the base is diisopropylethylamine.

Scheme (I)



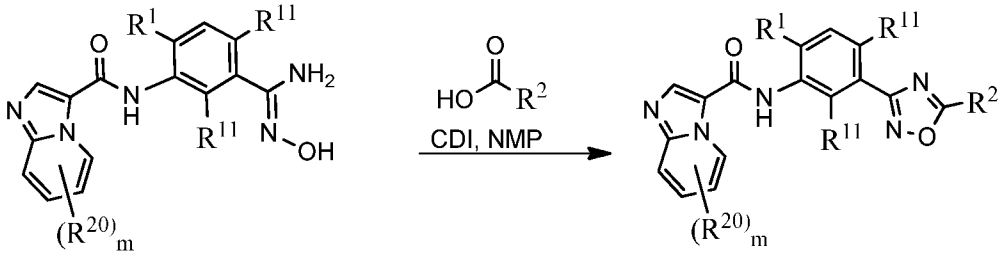
Scheme (II) illustrates the synthesis of compounds of Formula (II) by coupling the amine with the carboxylic acid in the presence of a base and a coupling reagent. By way of example only, the coupling reagent is HATU and the base is diisopropylethylamine.

Scheme (II)



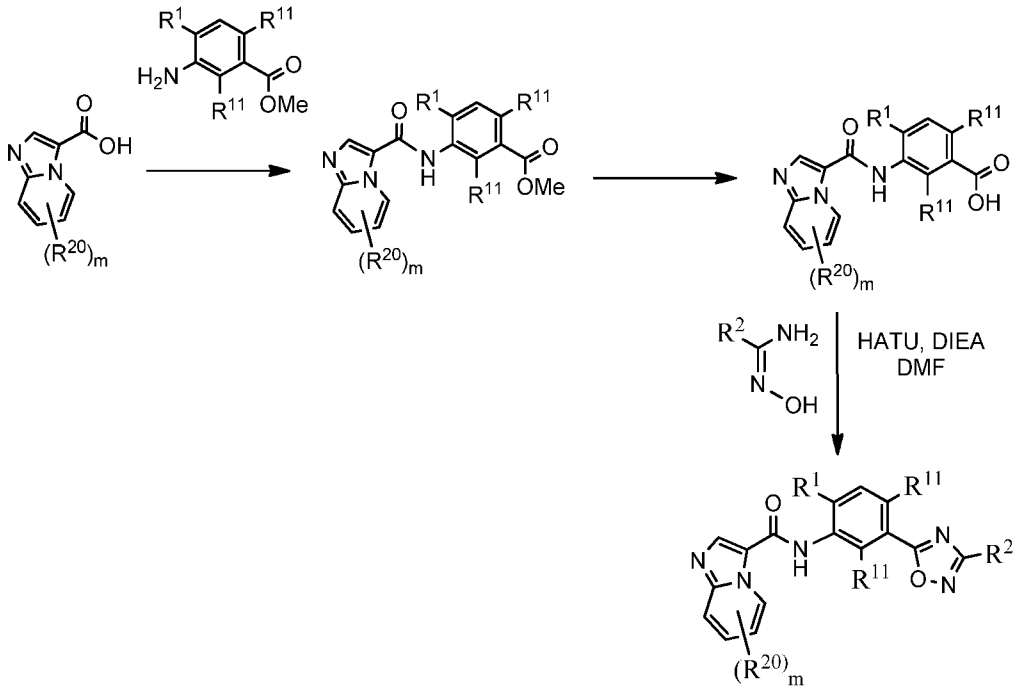
Scheme (III) illustrates the synthesis of compounds of Formula (I) by formation of the oxadiazole from the corresponding N'-hydroxyformimidamide and carboxylic acid.

Scheme (III)



Scheme (IV) illustrates the synthesis of compounds of Formula (II) by formation of the oxadiazole from the corresponding N'-hydroxyformimidamide and carboxylic acid.

Scheme (IV)



The examples provided herein are offered to illustrate, but not to limit, the compounds of Formula (I) or Formula (II) provided herein, and the preparation of such compounds.

Pharmacology and Utility

Protein tyrosine kinases (PTK) play a central role in the regulation of a wide variety of cellular processes and maintaining control over cellular function. Protein kinases catalyze and regulate the process of phosphorylation, whereby the kinases covalently attach phosphate groups to proteins or lipid targets in response to a variety of extracellular signals. Examples of such stimuli include hormones, neurotransmitters,

growth and differentiation factors, cell cycle events, environmental stresses and nutritional stresses. An extracellular stimulus may affect one or more cellular responses related to cell growth, migration, differentiation, secretion of hormones, activation of transcription factors, muscle contraction, glucose metabolism, control of protein synthesis, and regulation of the cell cycle.

Many diseases are associated with abnormal cellular responses triggered by protein kinase-mediated events. These diseases include, but are not limited to, autoimmune diseases, inflammatory diseases, bone diseases, metabolic diseases, neurological and neurodegenerative diseases, cancer, cardiovascular diseases, respiratory diseases, allergies and asthma, Alzheimer's disease, and hormone-related diseases.

Examples of protein-tyrosine kinases include, but are not limited to,

(a) tyrosine kinases such as Irk, IGFR-1, Zap-70, Bmx, Btk, CHK (Csk homologous kinase), CSK (C-terminal Src Kinase), Itk-1, Src (c-Src, Lyn, Fyn, Lck, Syk, Hck, Yes, Blk, Fgr and Frk), Tec, Txk/Rlk, Abl, EGFR (EGFR-1/ErbB-1, ErbB-2/NEU/HER-2, ErbB-3 and ErbB-4), FAK, FGF1R (also FGFR1 or FGR-1), FGF2R (also FGR-2), MET (also Met-I or c-MET), PDGFR (α and β), Tie-1, Tie-2 (also Tek-1 or Tek), VEGFR1 (also FLT-1), VEGFR2 (also KDR), FLT-3, FLT-4, c-KIT, JAK1, JAK2, JAK3, TYK2, LOK, RET, TRKA, PYK2, ALK (Anaplastic Lymphoma Kinase), EPHA (1-8), EPHB (1-6), RON, Fes, Fer or EPHB4 (also EPHB4-1), and

(b) and serine/threonine kinases such as Aurora, c-RAF, SGK, MAP kinases (e.g., MKK4, MKK6, etc.), SAPK2α, SAPK2β, Ark, ATM (1-3), CamK (1-IV), CamKK, Chk1 and 2 (Checkpoint kinases), CKI, CK2, Erk, IKK-I (also IKK-α or CHUK), IKK-2 (also IKK-β), Ilk, Jnk (1-3), LimK (1 and 2), MLK3Raf (A, B, and C), CDK (1-10), PKC (including all PKC subtypes), Plk (1-3), NIK, Pak (1-3), PDK1, PKR, RhoK, RIP, RIP-2, GSK3 (α and β), PKA, P38, Erk (1-3), PKB (including all PKB subtypes) (also AKT-1, AKT-2, AKT-3 or AKT3-1), IRAK1, FRK, SGK, TAK1 and Tp1-2 (also COT).

Phosphorylation modulates or regulates a variety of cellular processes such as proliferation, growth, differentiation, metabolism, apoptosis, motility, transcription, translation and other signaling processes. Aberrant or excessive PTK activity has been observed in many disease states including, but not limited to, benign and malignant proliferative disorders, diseases resulting from inappropriate activation of the immune system and diseases resulting from inappropriate activation of the nervous systems. Specific diseases and disease conditions include, but are not limited to, autoimmune

disorders, allograft rejection, graft vs. host disease, diabetic retinopathy, choroidal neovascularization due to age-related macular degeneration, psoriasis, arthritis, osteoarthritis, rheumatoid arthritis, synovial pannus invasion in arthritis, multiple sclerosis, myasthenia gravis, diabetes mellitus, diabetic angiopathy, retinopathy of prematurity, infantile hemangiomas, non-small cell lung, bladder and head and neck cancers, prostate cancer, breast cancer, ovarian cancer, gastric and pancreatic cancer, psoriasis, fibrosis, rheumatoid arthritis, atherosclerosis, restenosis, auto-immune disease, allergy, respiratory diseases, asthma, transplantation rejection, inflammation, thrombosis, retinal vessel proliferation, inflammatory bowel disease, Crohn's disease, ulcerative colitis, bone diseases, transplant or bone marrow transplant rejection, lupus, chronic pancreatitis, cachexia, septic shock, fibroproliferative and differentiative skin diseases or disorders, central nervous system diseases, neurodegenerative diseases, disorders or conditions related to nerve damage and axon degeneration subsequent to a brain or spinal cord injury, acute or chronic cancer, ocular diseases, viral infections, heart disease, lung or pulmonary diseases or kidney or renal diseases and bronchitis.

Tyrosine kinases can be broadly classified as receptor-type (having extracellular, transmembrane and intracellular domains) or the non-receptor type (being wholly intracellular) protein tyrosine kinases. Tyrosine kinases transfer the terminal phosphate of ATP to tyrosine residues of proteins thereby activating or inactivating signal transduction pathways. Inappropriate or uncontrolled activation of many of these kinase (aberrant protein tyrosine kinase activity), for example by over-expression or mutation, results in uncontrolled cell growth. Many of the protein tyrosine kinases, whether a receptor or non-receptor tyrosine kinase have been found to be involved in cellular signaling pathways involved in numerous pathogenic conditions, including, but not limited to, immunomodulation, inflammation, or proliferative disorders such as cancer.

c–Kit

Mast cells are tissue elements derived from a particular subset of hematopoietic stem cells that express CD34, c-kit and CD13 antigens. Mast cells are characterized by their heterogeneity, not only regarding tissue location and structure but also at the functional and histochemical levels. Immature mast cell progenitors circulate in the bloodstream and differentiate into various tissues. These differentiation and proliferation processes are under the influence of cytokines, one of importance being Stem Cell Factor (SCF), also termed c-Kit ligand, Steel factor or Mast Cell Growth Factor. The Stem Cell Factor receptor is encoded by the protooncogene, c-kit, which is expressed in hematopoietic progenitor cells, mast cells, germ cells, interstitial cells of Cajal (ICC), and some human tumors, and is also expressed by non hematopoietic cells.

Stem cell factor (SCF), also known as *c-kit* ligand, is the primary regulating factor for

human mast cell growth and function. The SCF receptor, c-kit receptor, is a Type III transmembrane receptor protein tyrosine kinase which initiates cell growth and proliferation signal transduction cascades in response to SCF binding. Ligation of c-kit receptor by SCF induces its dimerization followed by its transphorylation, leading to the recruitment and activation of various intracytoplasmic substrates. These activated substrates induce multiple intracellular signaling pathways responsible for cell proliferation and activation. These proteins are known to be involved in many cellular mechanisms, which in case of disruption, lead to disorders such as abnormal cell proliferation and migration, as well as inflammation.

The relationship between mast cells, SCF and c-kit receptor is discussed in the following references: Huang, E. et al., "The hematopoietic growth factor KL is encoded by the Sl locus and is the ligand of the c-kit receptor, the gene product of the W locus", *Cell*, 63, 225–233, 1990; Zsebo, K.M. et al., "Stem cell factor is encoded at the Sl locus of the mouse and is the ligand for the c-kit tyrosine kinase receptor", *Cell*, 63, 213–224, 1990; Zhang, S. et al.," Cytokine production by cell cultures from bronchial subepithelial myofibroblasts", *J. Pathol.*, 180, 95–10, 1996; Zhang, S. et al., "Human mast cells express stem cell factor", *J. Pathol.*, 186, 59–66, 1998; Kassel, O. et al., "Up and down-regulation by glucocorticoids of the constitutive expression of the mast cell growth factor stem cell factor by human lung fibroblasts in culture", *Mol. Pharmacol.*, 54, 1073–1079, 1998; Kassel, O. et al., "Human bronchial smooth muscle cells in culture produce Stem Cell Factor", *Eur. Respir.* J., 13, 951–954, 1999; Kassel, O. et al., "The Stem Cell Factor, Stem cell factor, its Properties and Potential Role in the Airways", *Pulmonary Pharmacology & Therapeutics*", 14, 227–288, 2001; de Paulis, A. et al, "Stem cell factor is localized in, released from, and cleaved by human mast cells", *J. Immunol.*, 163, 2799–2808, 1999; Mol, C.D. et al., "Structure of a c-kit product complex reveals the basis for kinase transactivation", *J. Biol. Chem.*, 278, 31461–31464, 2003; Iemura, A. et al., "The c-kit ligand, stem cell factor, promotes mast cell survival by suppressing apoptosis", *Am. J. Pathol.*, 144, 321–328, 1994; Nilsson, G. et al., "Stem cell factor is a chemotactic factor for human mast cells", *J. Immunol.*, 153, 3717–3723, 1994; Meininger, C.J. et al., "The c-kit receptor ligand functions as a mast cell chemoattractant", *Blood*, 79, 958–963, 1992, and Kinashi, T. et al., "Steel factor and c-kit regulate cell-matrix adhesion", *Blood*, 83, 1033–1038, 1994.

The following references discuss the c-kit signaling pathway and its relationship with various downstream pathways and the relationship with diseases associated with mast cells: Thommes, K. et al., "Identification of Tyr-703 and Tyr-936 as the primary association sites for Grb2 and Grb7 in the c-Kit/stem cell factor receptor", *Biochem., J.* 341, 211–216, 1999; Ishizuka, T. et al., "Stem cell factor augments Fc epsilon RI-

mediated TNF-alpha production and stimulates MAP kinases via a different pathway in MC/9 mast cells", *J. Immunol.*, 161, 3624–3630, 1998; Timokhina, I. et al., "Kit signaling through PI 3-kinase and Src kinase pathways: an essential role for Rac1 and JNK activation in mast cell proliferation", *EMBO J.*, 17, 6250–6262, 1998; Tang, B. et al., "Tec kinase associates with c-kit and is tyrosine phosphorylated and activated following stem cell factor binding", *Mol. Cell. Biol.*, 14, 8432–8437, 1994, and Ueda, S. et al., "Critical roles of c-Kit tyrosine residues 567 and 719 in stem cell factor-induced chemotaxis: contribution of src family kinase and PI3-kinase on calcium mobilization and cell migration", *Blood*, 99, 3342–3349, 2002.

Mast cells are the primary effector cells in allergic inflammation. Mast cells are also involved in other pathogenic processes such as acute inflammation and fibrosis.Mast cells present in tissues of patients are implicated in or contribute to the genesis of diseases such as autoimmune diseases (multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases (IBD)), allergic diseases (allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis and insect bite skin inflammation and bronchial asthma), tumor angiogenesis, germ cell tumors, mast cell tumors, gastrointestinal stromal tumors, small-cell lung cancer, melanoma, breast cancer, acute myelogenous leukemia, glioblastoma, neuroblastoma and mastocytosis, inflammatory diseases, diabetes, type I diabetes, type II diabetes, irritable bowel syndrome (IBS), CNS disorders and interstitial cystitis. In these diseases, mast cells participate in the destruction of tissues by releasing a cocktail of different proteases and mediators categorized into three groups: preformed granule-associated mediators (histamine, proteoglycans, and neutral proteases), lipid-derived mediators (prostaglandins, thromboxanes and leucotrienes), and various cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, TNF-α, GM-CSF, MIP-Lα, MIP-Iβ, MIP-2 and IFN- γ). The liberation by activated mast cells of mediators (TNF-α, histamine, leukotrienes, prostaglandins etc.) as well as proteases may i) induce inflammation and vasodilatation and ii) participate in the tissue destruction process.

In addition, mast cell activation induces diverse effector responses, such as secretion of allergic mediators, proteases, chemokines such as MCP-1 and RANTES, leukotrienes, prostaglandins and neurotrophins; and induction of cytokine gene transcription (IL-4, IL-5, IL-6, IL-13, TNF–α and GM-CSF). These mediators contribute to creating the asthmatic phenotype by their effects on endothelial cells, smooth muscle cells and fibroblasts and on extracellular matrix, and by recruiting other inflammatory cells.

Asthma is characterized by airflow obstruction, bronchial hyper responsiveness and

airway inflammation. Airway inflammation is the major factor in the development and perpetuation of asthma. In allergic asthma, allergens are thought to initiate the inflammatory process by inducing a T-lymphocyte mediated response (TH2) that results in the production of allergen-specific IgE. IgE binds to its high-affinity receptor FcεRI on pulmonary mast cells, triggering a type I (IgE-mediated) immediate allergic response. Thus, mast cells play a role in asthma.

The activation of mast cells by different stimuli such as stress, trauma, infection and neurotransmitters, also participate in the exacerbation of the chemical imbalance causing CNS disorders. More specifically, mast cell degranulation is stimulated by common neurotransmitters such as neurotensin, somatostatin, substance P and acetylcholine, by growth or survival factors, notably such as NGF. Mast cells involved in the response to such stimulus can be brain mast cells but also other mast cells releasing the content of their granules in the blood stream that ultimately reach sensory, motor or brain neurons. Following mast cells activation, released granules liberate various factors capable of modulating and altering neurotransmission and neurons survival. Among such factors, serotonin is important since an increase of the level of free serotonin has been observed in depressed patients. Alternatively, the sudden burst of serotonin may be followed by a period of serotonin shortage, leading to pain and migraine. As a consequence, it is believed that mast cells exacerbate in autocrine or paracrine manner the deregulation of neurotransmission. For example, anxiety or stress-induced release of neurotransmitters such as serotonin activates mast cells, which in turn release the content of their granules, further contributing to the chemical imbalance in the brain leading to CNS disorders.

Other mediators released by mast cells can be categorized into vasoactive, nociceptive, proinflammatory and other neurotransmitters. Taken together, these factors are able to induce disturbance in the activity of neurons, whether they are sensory, motor, or CNS neurons. In addition, patients afflicted with mastocytosis are more inclined to develop CNS disorders than the normal population. This can be explained by the presence of activating mutations in the c-kit receptor, which induce degranulation of mast cells and a burst of factors contributing to chemical imbalance and neurotransmission alteration.

The activation of mast cells by different drugs, including, but not limited to, salicylic derivatives, morphine derivatives, opioids, heroin, amphetamines, alcohol, nicotine, analgesics, anesthetics, and anxyolitics results in the degranulation of mast cells, which participate in the exacerbation of the chemical imbalance responsible for drug habituation and withdrawal syndrome. Following mast cells activation, released granules liberate various factors capable of modulating and altering neurotransmission. Among

such factors is morphine which is bound or stored in mast cells granules. Tobacco smoke also induces the release of mediators from canine mast cells and modulates prostaglandin production leading to asthma. In addition, patients afflicted with mastocytosis are more incline to develop substance use disorders than the normal population. This can be explained by the presence of activating mutations in the c-kit receptor, which induce degranulation of mast cells and a burst of factors contributing to chemical imbalance and neurotransmission alteration.

Mast cells have also been identified to be involved in or to contribute to drug dependence and withdrawal symptoms.

The relationship between mast cells, SCF and c-kit kinase in various diseases is discussed in the following fereferences: Oliveira et al., "Stem Cell Factor: A Hemopoietic Cytokine with Important Targets in Asthma", *Current Drug Targets*, 2: 313-318, 2003; Puxeddu et al., "Mast cells in allergy and beyond", *The International Journal of Biochemistry & Cell Biology*, 35: 1601-1607, 2003; Rottem et al., "Mast cells and autoimmunity", *Autoimmunity Reviews*, 4: 21-27, 2005; Woolley, D.E. et al., "The mast cell in inflammatory arthritis", *N. Engl. J. Med.*, 348:1709–1711, 2003; Benoist, C. et al., "Mast cells in autoimmune disease", *Nature*, 420:875–878, 2002; Nigrovic, P.A. et al., "Mast cells in inflammatory arthritis", *Arthritis Res. Ther.*, 7:1–11, 2005; Wang, H.W. et al., "Mast cell accumulation and cytokine expression in the tight skin mouse model of scleroderma", *Exp. Dermatol.*, 14, 295–302, 2005; Olsson, N. et al., "Demonstration of mast cell chemotactic activity in bronchoalveolar lavage fluid collected from asthmatic patients before and during pollen season", *J. Allergy Clin. Immunol.*, 105, 455–461, 2000; Ma, Y. et al., "Indolinone derivatives inhibit constitutively activated KIT mutants and kill neoplastic mast cells", *J. Invest. Dermatol.*, 114, 392–394, 2000; Kobayashi, Y. et al., "Mst Cells as a Target of Rheumatoid Arthritis Treatment", *Jpn. J.* Pharmacol., 7-11, 2002, and Al-Muhsen, S.Z. et al., "The expression of stem cell factor and c-kit receptor in human asthmatic airways", *Clin. Exp. Allergy*, 34, 911–916, 2004.

In addition, the treatment of asthma and arthritis with administration of a c-kit inhibitor is presented in the following references: Takeuchi et al., "STI571 inhibits growth and adhesion of human mast cells in culture", Journal of Leukocyte Biology, 74: 1026-1034, 2003; Berlin et al., "Treatment of Cockroach Allergen Asthma Model with Imatinib Attenuates Airway Responses", American Journal of Respiratory and Critical care Medicine, 171: 35-39, 2005; Ekland et al., "Treatment of rheumatoid arthritis with imatinib mesylate: clinical improvement in three refractory cases", *Annals of Medicine*, 35: 362-367, 2003; Miyachi et al., "Efficacy of imatinib mesylate (STI571) treatment for a patient with rheumatoid arthritis developing chronic myelogenous leukemia", *Clinical Rheumatology*, 22: 329-332, 2003; Juurikivi et al., "Inhibition of c-kit tyrosine kinase by

imatinib mesylate induces apoptosis in mast cells in rheumatoid synovial: a potential approach to the treatment of arthritis", *Ann. Rheum. Dis.*, 64: 1126-1131, 2005; Wolf, A.M., et al., "The kinase inhibitor imatinib mesylate inhibits TNF-alpha production in vitro and prevents TNF-dependent acute hepatic inflammation", *Proc. Natl. Acad. Sci.* U. S. A. 102:13622--13627, 2005; Leath et al., "Novel and emerging therapies for asthma", *Drug Discovery Today*, 10(23/24): 1647-1655, 2005; Berlin et al., "Inhibition of SCF attenuates peribronchial remodeling in chronic cockroach allergen-induced asthma", *Laboratory Investigations*, 86: 557-565, 2006; Paniagua et al., "Selective tyrosine kinase inhibition by imatinib mesylate for the treatment of autoimmune arthritis", *The Journal of Clinical Investigation*, 116(10): 2633-2642, 2006; Wenzel et al., "Update in Asthma", *American Journal of Respiratory and Critical care Medicine*, 173: 698-706, 2006; Chaudhary et al., "Pharmacological Differentiation of Inflammation and Fibrosis in the Bleomycin Model", *American Journal of Respiratory and Critical care Medicine*, 173: 769-776, 2006, and Reber et al., "Review: Stem cell factor and its receptor c-Kit as targets for inflammatory diseases", *European Journal of Pharmacology*, 533: 327-340, 2006.

The activity of the c-kit receptor is regulated in normal cells, and the normal functional activity of this c-kit gene product is important for the maintenance of normal hematopoeisis, melanogenesis, genetogensis, and growth and differentiation of mast cells. Inhibition of c-kit kinase activity reduces the growth and differentiation of mast cells and thereby mediates the diseases and/or conditions associated with mast cells, such as autoimmune diseases, multiple sclerosis, rheumatoid arthritis, inflammatory bowel diseases (IBD), respiratory diseases, allergic diseases, allergic rhinitis, allergic sinusitis, anaphylactic syndrome, urticaria, angioedema, atopic dermatitis, allergic contact dermatitis, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis and insect bite skin inflammation, bronchial asthma, tumor angiogenesis, germ cell tumors, mast cell tumors, gastrointestinal stromal tumors, small-cell lung cancer, melanoma, breast cancer, acute myelogenous leukemia, glioblastoma, neuroblastoma and mastocytosis, inflammatory diseases, diabetes, type I diabetes, type II diabetes, irritable bowel syndrome (IBS), CNS disorders and interstitial cystitis

In addition to its importance in normal cellular physiologic activities, c-kit kinase plays a role in the biological aspects of certain human cancers, and unregulated c-kit kinase activity is implicated in the pathogenesis of human cancers, and in certain tumors types. Proliferation of tumor cell growth mediated by c-kit can occur by a specific mutation of the c-kit polypeptide that results in ligand independent activation or by autocrine stimulation of the receptor. In the former case, mutations that cause constitutive activation of c-kit kinase activity in the absence of SCF binding are implicated in malignant human cancers, including germ cell tumors, mast cell tumors, gastrointestinal

stromal tumors, small-cell lung cancer, melanoma, breast cancer, acute myelogenous leukemia, glioblastoma, neuroblastoma and mastocytosis.

A proliferation assay for the evaluation of the efficacy of c-kit inhibitors and PDGFR inhibitors is given in Kuriu et al., "Proliferation of human myeloid leukemia cell line associated with the tyrosine-phosphorylation and activation of the proto-oncogene c-kit product", Blood, 78(11): 2834-2840 , 1991; Heinrich et al., "Inhibition of c-kit receptor tyrosine kinase activity by STI571, a selective tyrosine kinase inhibitor", Blood, 96(3): 925-932, 2000; Buchdunger et al., "Abl Protein-Tyrosine Kinase Inhibitor STI571 Inhibits In Vitro Signal Transduction Mediated by c-Kit and Platelet-Derived Growth Factor Receptors", The Journal of Pharmacology and Experimental Therapeutics, 295(1): 139-145, 2000; and Smolich et al., "The antiangiogenic protein kinase inhibitors SU5416 and SU6668 inhibit the SCF receptor (c-kit) in a human myeloid leukemia cell line and in acute myeloid leukemia blasts", Blood, 97(5): 1413-1421, 2001. This assay use MO7e cells, which are a human promegakaryocytic leukemia cell line that depend on SCF for proliferation. These references in combination with Berlin et al., Ekland et al., and Miyachi et al., (cited above) show that that a c-kit kinase inhibitor screened via this proliferation assay was later found to treat rheumatoid arthritis and asthma.

In addition, a compound that was initially evaluated for its efficacy as a c-kit inhibitor using a proliferation assay based on Ba/F3 cells and Ba/F3-derived cells (see WO 2004/01903) was later found to be effective in the treatment of mast cell tumours and asthma (see Bellamy F. et al., " Pharmacokinetics of masitinib in cats", Vet. Res. Commun., June 16 (epub) 2009; Hahn K.A. et al., "Mastinib is safe and effective for treatment of canine mact cell tumours', J. Vet. Intern. Med., 22, 1301-1309, 2008 and Humbert M. et al., " Mastinib, a c-kit/PDGF receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics", 64, 1194-1201, 2009.

c-kit receptor has a substantial homology to the PDGF receptor and to the CSF-1 receptor (c-Fms).

Platelet-derived Growth Factor (PDGF) receptor family

PDGF (Platelet-derived Growth Factor) is commonly occurring growth factor which plays an important role both in normal growth and in pathological cell proliferation. By way of example, such as that observed in carcinogenesis and in diseases of the smooth-muscle cells of blood vessels, for example in atherosclerosis and thrombosis. The PDGF growth factor family consists of PDGF-A, PDGF-B, PDGF-C and PDGF-D, which form either homo- or heterodimers (AA, AB, BB, CC, DD) that bind to the protein tyrosine kinase receptors PDGFR-α and PDGFR-β. Dimerization of the growth factors is a prerequisite for activation of the kinase, as the monomeric forms are inactive. The two

receptor isoforms dimerize upon binding resulting in three possible receptor combinations, PDGFR-αα, PDGFR-ββ and PDGFR–αβ. Growth factor AA binds only to -αα, growth factor BB can bind with -αα, -ββ and -αβ, growth factors CC and AB specifically interact with -αα and -αβ, and growth factor DD binds to -ββ. The PDGF-receptor plays an important role in the maintenance, growth and development of hematopoietic and non-hematopoietic cells.

Key downstream mediators of PDGFR signaling are Ras/mitogen-activated protein kinase (MAPK), PI-3 kinase and phospholipase-γ (PLCγ) pathways. MAPK family members regulate various biological functions by phosphorylation of target molecules (transcription factors and other kinases) and thus contribute to regulation of cellular processes such as proliferation, differentiation, apoptosis and immunoresponses. PI-3 kinase activation generated PIP3 which functions as a second messenger to activate downstream tyrosine kinases Btk and Itk, the Ser/Thr kinases PDK1 and Akt (PKB). Akt activation is involved in survival, proliferation and cell growth. After activation PLC hydolyses its substrate, PtdIns(4,5)P2, and forms two secondary messengers, diacylglycerol and Ins(1,4,5)P3 which stimulates intracellular processes such as proliferation, angiogenesis and cell motility.

PDGFR is expressed on early stem cells, mast cells, myeloid cells, mesenchymal cells and smooth muscle cells. Only PDGFR-β is implicated in myeloid leukemias-usually as a translocation partner with Tel, Huntingtin interacting protein (HIP1) or Rabaptin5. Activation mutations in PDGFR-α kinase domain are associated with gastrointestinal stromal tumors (GIST).

Certain embodiments of compounds of Formula (I) and Formula (II) provided herein inhibit PDGF receptor (PDGFRα and PDGFRβ) activity and c-kit kinase activity, and are useful for the treatment of diseases, which respond to an inhibition of the PDGF receptor kinase. Therefore, certain compounds of Formula (I) and Formula (II) provided herein are useful for the treatment of tumor diseases, such as gliomas, sarcomas, prostate tumors, small cell lung cancer and tumors of the colon, breast, and ovary. In addition certain embodiments of compounds of Formula (I) and Formula (II) provided herein are useful to treat disorders, such as thrombosis, psoriasis, scleroderma, fibrosis, asthma, metabolic diseases and hypereosinophilia. Compounds of Formula (I) and Formula (II) provided herein are also effective against diseases associated with vascular smooth-muscle cell migration and proliferation, such as restenosis and atherosclerosis.

Patients with obliterative bronchiolitis (OB), a chronic rejection of allogenic lung transplants, often show an elevated PDGF concentration in bronchoalveolar lavage fluids. In certain embodiments, compounds of Formula (I) and Formula (II) provided

herein exhibit useful effects in the treatment of disorders arising as a result of transplantation, for example, allogenic transplantation, especially tissue rejection, such as obliterative bronchiolitis (OB).

In certain embodiments, compounds of Formula (I) and Formula (II) provided herein are useful for the protection of stem cells, for example to combat the hemotoxic effect of chemotherapeutic agents, such as 5-fluorouracil.

The compounds of Formula (I) and Formula (II) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are inhibitors of c-kit kinase activity or are inhibitors of c-kit kinase activity and PDGFR (α and β) kinase activity. In certain embodiments, the compounds of Formula (I) and Formula (II) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are inhibitors of c-kit kinase activity and PDGFR (α and β) kinase activity. In other embodiments, the compounds of Formula (I) and Formula (II) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are inhibitors of either c-kit kinase activity. Such compounds of Formula (I) and Formula (II) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are useful for treating diseases or disorders in which c-kit kinase, or c-kit and PDGFR (α and/or β) kinase, contributes to the pathology and/or symptomology of a disease or disorder. Such diseases or disorders include, but are not limited to, a mast cell associated disease, inflammatory diseases, respiratory diseases, an allergy disorder, fibrosis diseases, metabolic diseases, autoimmune diseases, a CNS related disorder, a neurodegenerative disorder, neurological diseases, dermatoligical diseases, a graft-versus-host disease, a pain condition, a neoplastic disorder, a cardiovascular disease and cancer.

Non-limiting examples of such diseases include asthma, allergic rhinitis, allergic sinusitis, bronchial asthma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), pulmonary arterial hypertension (PAH), idiopathic arterial hypertension (IPAH), primary pulmonary hypertension (PPH), pulmonary fibrosis, liver fibrosis, cardiac fibrosis, scleroderma, urticaria, dermatoses, atopic dermatitis, allergic contact dermatitis, diabetes, type I diabetes, type II diabetes, rheumatoid arthritis, multiple scherosis, cytopenias (by way of example only, anemia, leucopenia, neutropenia, thrombocytopenia, granuloctopenia, pancytoia and idiopathic thrombocytopenic

purpura), systemic lupus erythematosus, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohns disease, psoriasis, lymphomas (by way of example only, B and T cell lymphomas), myelodysplasic syndrome, breast cancer, pancreatic cancer, papillary thyroid carcinoma, ovarian carcinoma, human adenoid cystic carcinoma, non small cell lung cancer, secretory breast carcinoma, congenital fibrosarcoma, congenital mesoblastic nephroma, acute myelogenous leukemia, chronic myeloid leukemia metastasis, cancer-related pain, neuroblastoma, osteosarcoma, melanoma, bone metastases, a tumor of breast, renal, lung, prostate, pancreas, colon, ovary, thyroid, colorectal tumors, neuronal tumors, uterine tumors, gastrointestinal stromal tumors (GIST), gliomas, sarcomas, tumor angiogenesis, germ cell tumors, mast cell tumors, glioblastoma, neuroblastoma, mastocytosis, osteoporosis, hypereosinophilia, restenosis, atherosclerosis, anaphylactic syndrome, angioedema, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation, CNS disorders and interstitial cystitis.

In certain embodiments, the compounds of Formula (I) and Formula (II) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are useful for treating diseases or disorders in which c-kit kinase contributes to the pathology and/or symptomology of a disease or disorder. Non-limiting examples of such diseases include asthma, allergic rhinitis, allergic sinusitis, bronchial asthma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), pulmonary arterial hypertension (PAH), pulmonary fibrosis, liver fibrosis, cardiac fibrosis, scleroderma, urticaria, dermatoses, atopic dermatitis, allergic contact dermatitis, diabetes, type I diabetes, type II diabetes, rheumatoid arthritis, multiple scherosis, cytopenias (by way of example only, anemia, leucopenia, neutropenia, thrombocytopenia, granuloctopenia, pancytoia and idiopathic thrombocytopenic purpura), systemic lupus erythematosus, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohns disease, psoriasis, lymphomas (by way of example only, B and T cell lymphomas), myelodysplasic syndrome, breast cancer, pancreatic cancer, papillary thyroid carcinoma, ovarian carcinoma, human adenoid cystic carcinoma, non small cell lung cancer, secretory breast carcinoma, congenital fibrosarcoma, congenital mesoblastic nephroma, acute myelogenous leukemia, chronic myeloid leukemia metastasis, cancer-related pain, neuroblastoma, osteosarcoma, melanoma, bone metastases, a tumor of breast, renal, lung, prostate, pancreas, colon, ovary, thyroid, colorectal tumors, neuronal tumors, uterine tumors, gastrointestinal stromal tumors (GIST), gliomas, sarcomas, tumor angiogenesis, germ cell tumors, mast cell tumors, glioblastoma, neuroblastoma,

mastocytosis, osteoporosis, hypereosinophilia, restenosis, atherosclerosis, anaphylactic syndrome, angioedema, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation, CNS disorders and interstitial cystitis.

In certain embodiments, the compounds of Formula (I) and Formula (II) provided herein, and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are useful for treating diseases or disorders in which c-kit kinase and PDGFR (α and/or β) kinase contribute to the pathology and/or symptomology of a disease or disorder. Non-limiting examples of such diseases include asthma, allergic rhinitis, allergic sinusitis, bronchial asthma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), pulmonary arterial hypertension (PAH), pulmonary fibrosis, liver fibrosis, cardiac fibrosis, scleroderma, urticaria, dermatoses, atopic dermatitis, allergic contact dermatitis, diabetes, type I diabetes, type II diabetes, rheumatoid arthritis, multiple scherosis, cytopenias (by way of example only, anemia, leucopenia, neutropenia, thrombocytopenia, granuloctopenia, pancytoia and idiopathic thrombocytopenic purpura), systemic lupus erythematosus, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohns disease, psoriasis, lymphomas (by way of example only, B and T cell lymphomas), myelodysplasic syndrome, breast cancer, pancreatic cancer, papillary thyroid carcinoma, ovarian carcinoma, human adenoid cystic carcinoma, non small cell lung cancer, secretory breast carcinoma, congenital fibrosarcoma, congenital mesoblastic nephroma, acute myelogenous leukemia, chronic myeloid leukemia metastasis, cancer-related pain, neuroblastoma, osteosarcoma, melanoma, bone metastases, a tumor of breast, renal, lung, prostate, pancreas, colon, ovary, thyroid, colorectal tumors, neuronal tumors, uterine tumors, gastrointestinal stromal tumors (GIST), gliomas, sarcomas, tumor angiogenesis, germ cell tumors, mast cell tumors, glioblastoma, neuroblastoma, mastocytosis, osteoporosis, hypereosinophilia, restenosis, atherosclerosis, anaphylactic syndrome, angioedema, erythema nodosum, erythema multiforme, cutaneous necrotizing venulitis, insect bite skin inflammation, CNS disorders and interstitial cystitis.

Another aspect provided herein includes methods for treating a cell-proliferative disease, comprising administering to a system or subject in need of such treatment an effective amount of a compound of Formula (I) and Formula (II), or pharmaceutically acceptable salts or pharmaceutical compositions thereof; wherein the cell-proliferative disease is lymphoma, osteosarcoma, melanoma, or a tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, neuronal, lung, uterine or gastrointestinal tumor.

In certain embodiments, the compounds of Formula (I) and Formula (II),

pharmaceutically acceptable salts, solvates, N-oxides and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment diseases and/or disorders including, but not limited to, asthma, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma, exercise-induced asthma, drug-induced asthma (including aspirin and NSAID-induced) and dust-induced asthma, chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiectasis; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus.

In certain embodiments, the compounds of Formula (I) and Formula (II), pharmaceutically acceptable salts, solvates, N-oxides and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of dermatological disorders including, but not limited to, psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoid, basal cell carcinoma, actinic keratosis, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis;cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions.

In certain embodiments, the compounds of Formula (I) and Formula (II), pharmaceutically acceptable salts, solvates, N-oxides and isomers thereof, pharmaceutical compositions, and/or combinations provided herein are used in the treatment of rheumatoid arthritis, irritable bowel syndrome, systemic lupus erythematosus, multiple sclerosis, Hashimoto's thyroiditis, Crohns disease, inflammatory bowel disease (IBD), Graves' disease, Addison's disease, diabetes mellitus, idiopathic

thrombocytopaenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome and Sazary syndrome.

In certain embodiments, the compounds of Formula (I) and Formula (II), pharmaceutically acceptable salts, solvates, N-oxides and isomers thereof, and pharmaceutical compositions provided herein are used in the treatment of cancer including, but not limited to, prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumor recurrences, and paraneoplastic syndromes.

Provided herein are compounds of Formula (I) and Formula (II), pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers or mixture of isomers thereof, for use in activating c-kit kinase activity, or c-kit kinase and PDGFR (α and/or β) kinase activity, and thereby are used to in the prevention or treatment of diseases and/or disorders associated with c-kit kinase activity, or c-kit kinase and PDGFR (α and/or β) kinase activity.

Also provided herein are methods for the treatment of a subject suffering from a disease and/or disorder associated with c-kit kinase activity, wherein the method includes administering to the subject in need thereof, an effective amount of a compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers or mixture of isomers thereof, either alone or as part of a pharmaceutical composition as described herein.

Also provided herein are methods for the treatment of a subject suffering from a disease and/or disorder associated with c-kit kinase activity and PDGFR (α and/or β) kinase activity, wherein the method includes administering to the subject in need thereof, an effective amount of a compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers or mixture of isomers thereof, either alone or as part of a pharmaceutical composition as described herein.

Provided herein is the use of a compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers or mixture of isomers

thereof, in the manufacture of a medicament for the treatment of a disease or disorder associated with c-kit kinase activity. Also provided herein is the use of a compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers or mixture of isomers thereof, in the manufacture of a medicament for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR (α and/or β) kinase activity.

Furthermore, provided herein is the use of a compound having Formula (I) or Formula (II), or pharmaceutically acceptable salts or pharmaceutical compositions thereof, and optionally in combination with a therapeutically effective amount of a second agent, in the manufacture of a medicament for treating a disease or condition modulated by kinase activity, particularly c-kit, or c-kit and PDGFR (α and β).

In accordance with the foregoing, the present invention further provides a method for preventing or treating any of the diseases or disorders described above in a subject in need of such treatment, which method comprises administering to said subject a therapeutically effective amount of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof. For any of the above uses, the required dosage will vary depending on the mode of administration, the particular condition to be treated and the effect desired. (See, "Administration and Pharmaceutical Compositions," infra).

Administration and Pharmaceutical Compositions

For the therapeutic uses of compounds of Formula (I) and Formula (II), or pharmaceutically acceptable salts, solvates, N-oxides or isomers thereof, described herein, such compounds are administered in therapeutically effective amounts either alone or as part of a pharmaceutical composition. Accordingly, provided herein are pharmaceutical compositions, which comprise at least one compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts solvates, N-oxides or isomers thereof, and one or more pharmaceutically acceptable carriers, diluents, or excipients. In addition, such compounds and compositions are administered singly or in combination with one or more additional therapeutic agents. The method of administration of such compounds and compositions include, but are not limited to, oral administration, rectal administration, transdermal administration, parenteral, intravenous administration, intravitreal administration, intramuscular administration, pulmonary administration, inhalation administration, intranasal administration, topical administration, ophthalmic administration or otic administration. In certain embodiments the method of administration of such compounds and compositions is oral administration. In other

embodiments the method of administration of such compounds and compositions is pulmonary administration, inhalation administration or intranasal administration.

The therapeutically effective amount will vary depending on, among others, the disease indicated, the severity of the disease, the age and relative health of the subject, the potency of the compound administered, the mode of administration and the treatment desired. In certain embodiments, the daily dosage of a compound of Formula (I) and Formula (II), satisfactory results are indicated to be obtained systemically at daily dosages of from about 0.03 to 2.5mg/kg per body weight. In certain embodiments, the daily dosage of a compound of Formula (I) and Formula (II), administered by inhalation, is in the range from 0.05 micrograms per kilogram body weight (μg/kg) to 100 micrograms per kilogram body weight (μg/kg). In other embodiments, the daily dosage of a compound of Formula (I) and Formula (II), administered orally, is in the range from 0.01 micrograms per kilogram body weight (μg/kg) to 100 milligrams per kilogram body weight (mg/kg). An indicated daily dosage in the larger mammal, e.g. humans, is in the range from about 0.5mg to about 100mg of a compound of Formula (I) and Formula (II), conveniently administered, e.g. in divided doses up to four times a day or in controlled release form. In certain embodiment, unit dosage forms for oral administration comprise from about 1 to 50 mg of a compound of Formula (I) and Formula (II).

Other aspects provided herein are processes for the preparation of pharmaceutical composition which comprise at least one compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts, solvates, N-oxides or isomers thereof. In certain embodiments, such processes include admixing a compound of the Formula (I) or Formula (II), or pharmaceutically acceptable salts, solvates, N-oxides or isomers thereof, with one or more pharmaceutically acceptable carriers, diluents or excipients. In certain embodiments, the pharmaceutical compositions comprising a compound of Formula (I) or Formula (II) in free form, or in a pharmaceutically acceptable salt, solvate, N-oxide or isomeric form, in association with at least one pharmaceutically acceptable carrier, diluent or excipient are manufactured by mixing, granulating and/or coating methods. In other embodiments, such compositionsoptionally contain excipients, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure and/or buffers. In other embodiments, such compositions are sterilized.

In certain embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for oral administration for the treatment of diseases and/or disorders associated with c-kit kinase activity. In other embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for oral administration for the treatment of diseases and/or disorders associated with c-kit kinase and PDGFR (α and/or β) kinase

activity.

In certain embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for inhalation adminitsation, including pulmonary administration, inhalation administration or intranasal administration, for the treatment of diseases and/or disorders associated with c-kit kinase activity. In other embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for inhalation adminitsation, including pulmonary administration, inhalation administration or intranasal administration,for the treatment of diseases and/or disorders associated with c-kit kinase and PDGFR (α and/or β) kinase activity.

In certain embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for inhalation adminitsation, including pulmonary administration, inhalation administration or intranasal administration, for the treatment of respiratory diseases with c-kit kinase activity. In certain embodiments, the respiratory disease is allergic rhinitis or asthma. In other embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for inhalation adminitsation, including pulmonary administration, inhalation administration or intranasal administration,for the treatment of respiratory diseases associated with c-kit kinase and PDGFR (α and/or β) kinase activity. In certain embodiments, the respiratory disease is allergic rhinitis or asthma.

In certain embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for parenteral or intravenous administration, for the treatment of diseases and/or disorders associated with c-kit kinase activity. In other embodiments, the pharmaceutical compositions comprising at least one compound of Formula (I) or Formula (II) are adapted for parenteral or intravenous administration,for the treatment of diseases and/or disorders associated with c-kit kinase and PDGFR (α and/or β) kinase activity.

Oral Dosage Forms

In certain embodiments, the pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered orally as discrete dosage forms, wherein such dosage forms include, but are not limited to, capsules, gelatin capsules, caplets, tablets, chewable tablets, powders, granules, syrups, flavored syrups, solutions or suspensions in aqueous or non-aqueous liquids, edible foams or whips, and oil-in-water liquid emulsions or water-in-oil liquid emulsions.

The capsules, gelatin capsules, caplets, tablets, chewable tablets, powders or granules, used for the oral administration of at least one compound of Formula (I) and

Formula (II) are prepared by admixing at least one compound of Formula (I) and Formula (II) (active ingredient) together with at least one excipient using conventional pharmaceutical compounding techniques. Non-limiting examples of excipients used in oral dosage forms described herein include, but are not limited to, binders, fillers, disintegrants, lubricants, absorbents, colorants, flavors, preservatives and sweeteners.

Non-limiting examples of such binders include, but are not limited to, corn starch, potato starch, starch paste, pre-gelatinized starch, or other starches, sugars, gelatin, natural and synthetic gums such as acacia, sodium alginate, alginic acid, other alginates, tragacanth, guar gum, cellulose and its derivatives (by way of example only, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethylcellulose, methyl cellulose, hydroxypropyl methylcellulose and microcrystalline cellulose), magnesium aluminum silicate, polyvinyl pyrrolidone and combinations thereof.

Non-limiting examples of such fillers include, but are not limited to, talc, calcium carbonate (e.g., granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, and mixtures thereof. In certain embodiments, the binder or filler in pharmaceutical compositions provided herein are present in from about 50 to about 99 weight percent of the pharmaceutical composition or dosage form.

Non-limiting examples of such disintegrants include, but are not limited to, agar-agar, alginic acid, sodium alginate, calcium carbonate, sodium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, pre-gelatinized starch, other starches, clays, other algins, other celluloses, gums, and combinations thereof. In certain embodiments, the amount of disintegrant used in the pharmaceutical compositions provided herein is from about 0.5 to about 15 weight percent of disintegrant, while in other embodiments the amount is from about 1 to about 5 weight percent of disintegrant.

Non-limiting examples of such lubricants include, but are not limited to, sodium stearate, calcium stearate, magnesium stearate, stearic acid, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, sodium lauryl sulfate, talc, hydrogenated vegetable oil (by way of example only, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, sodium oleate, ethyl oleate, ethyl laureate, agar, silica, a syloid silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic silica (marketed by Degussa Co. of Plano, Tex.), CAB-O-SIL (a pyrogenic silicon dioxide product sold by Cabot Co. of Boston, Mass.) and combinations thereof. In certain embodiments, the amount of lubricants used in the pharmaceutical compositions

provided herein is in an amount of less than about 1 weight percent of the pharmaceutical compositions or dosage forms.

Non-limiting examples of such diluents include, but are not limited to, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, glycine or combinations thereof.

In certain embodiments, tablets and capsules are prepared by uniformly admixing at least one compound of Formula (I) or Formula (II) (active ingredients) with liquid carriers, finely divided solid carriers, or both, and then shaping the product into the desired presentation if necessary. In certain embodiments, tablets are prepared by compression. In other embodiments, tablets are prepared by molding.

In certain embodiments, at least one compound of Formula (I) or Formula (II) is orally administered as a controlled release dosage form. Such dosage forms are used to provide slow or controlled-release of one or more compounds of Formula (I) or Formula (II). Controlled release is obtained using, for example, hydroxypropylmethyl cellulose, other polymer matrices, gels, permeable membranes, osmotic systems, multilayer coatings, microparticles, liposomes, microspheres, or a combination thereof. In certain embodiments, controlled-release dosage forms are used to extend activity of the compound of Formula (I) or Formula (II), reduce dosage frequency, and increase patient compliance.

Administration of compounds of Formula (I) or Formula (II) as oral fluids such as solution, syrups and elixirs are prepared in unit dosage forms such that a given quantity of solution, syrups or elixirs contains a predetermined amount of a compound of Formula (I) or Formula (II). Syrups are prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions are formulated by dispersing the compound in a non-toxic vehicle. Non-limiting examples of excipients used in as oral fluids for oral administration include, but are not limited to, solubilizers, emulsifiers, flavoring agents, preservatives, and coloring agents. Non-limiting examples of solubilizers and emulsifiers include, but are not limited to, water, glycols, oils, alcohols, ethoxylated isostearyl alcohols and polyoxy ethylene sorbitol ethers. Non-limiting examples of preservatives include, but are not limited to, sodium benzoate. Non-limiting examples of flavoring agents include, but are not limited to, peppermint oil or natural sweeteners or saccharin or other artificial sweeteners.

Parenteral Dosage Forms

In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered parenterally by various routes including, but not limited to, subcutaneous, intravenous (including bolus injection), intramuscular, and intraarterial.

Such parenteral dosage forms are administered in the form of sterile or sterilizable injectable solutions, suspensions, dry and/or lyophylized products ready to be dissolved or suspended in a pharmaceutically acceptable vehicle for injection (reconstitutable powders) and emulsions. Vehicles used in such dosage forms include, but are not limited to, Water for Injection USP; aqueous vehicles such as, but not limited to, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles such as, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles such as, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

Transdermal Dosage Forms

In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered transdemally. Such transdermal dosage forms include "reservoir type" or "matrix type" patches, which are applied to the skin and worn for a specific period of time to permit the penetration of a desired amount of a compound of Formula (I) or Formula (II). By way of example only, such transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin. In other embodiments, matrix transdermal formulations are used.

Formulations for transdermal delivery of a compound of Formula (I) orFormula (II) include an effective amount of a compound of Formula (I) or Formula (II), a carrier and an optional diluent. A carrier includes, but is not limited to, absorbable pharmacologically acceptable solvents to assist passage through the skin of the host, such as water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and combinations thereof.

In certain embodiments, such transdermal delivery systems include penetration enhancers to assist in delivering one or more compounds of Formula (I) or Formula (II) to the tissue. Such penetration enhancers include, but are not limited to, acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

In other embodiments, the pH of such a transdermal pharmaceutical composition or dosage form, or of the tissue to which the pharmaceutical composition or dosage form is

applied, is adjusted to improve delivery of one or more compounds of Formula (I) or Formula (II). In other embodiments, the polarity of a solvent carrier, its ionic strength, or tonicity are adjusted to improve delivery. In other embodiments, compounds such as stearates are added to advantageously alter the hydrophilicity or lipophilicity of one or more compounds of Formula (I) or Formula (II) so as to improve delivery. In certain embodiments, such stearates serve as a lipid vehicle for the formulation, as an emulsifying agent or surfactant, and as a delivery-enhancing or penetration-enhancing agent. In other embodiments, different salts, hydrates or solvates of the compounds of Formula (I) or Formula (II) are used to further adjust the properties of the resulting composition.

In certain embodiments compounds of Formula (I) or Formula (II) are transderrmally delivered from a patch by iontophoresis.

Topical Dosage Forms

In certain embodiments at least one compound of Formula (I) or Formula (II) is administered by topical application of pharmaceutical composition containing at least one compound of Formula (I) or Formula (II) in the form of lotions, gels, ointments solutions, emulsions, suspensions or creams. Suitable formulations for topical application to the skin are aqueous solutions, ointments, creams or gels, while formulations for ophthalmic administration are aqueous solutions. Such formulations optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

Such topical formulations include at least one carrier, and optionally at least one diluent. Such carriers and diluents include, but are not limited to, water, acetone, ethanol, ethylene glycol, propylene glycol, butane-1,3-diol, isopropyl myristate, isopropyl palmitate, mineral oil, and combinations thereof.

In certain embodiments, such topical formulations include penetration enhancers to assist in delivering one or more compounds of Formula (I) or Formula (II) to the tissue. Such penetration enhancers include, but are not limited to, acetone; various alcohols such as ethanol, oleyl, and tetrahydrofuryl; alkyl sulfoxides such as dimethyl sulfoxide; dimethyl acetamide; dimethyl formamide; polyethylene glycol; pyrrolidones such as polyvinylpyrrolidone; Kollidon grades (Povidone, Polyvidone); urea; and various water-soluble or insoluble sugar esters such as Tween 80 (polysorbate 80) and Span 60 (sorbitan monostearate).

Inhalation Administration

In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered by inhalation. Inhalation refers to administration into the patient's lungs whether inhaled through the mouth or through the nasal passages. Dosage forms for inhaled administration are formulated as aerosols,

dry powders, suspensions, or solution compositions. Dry powder compositions contain at least one compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof as a finely divided powder together with one or more pharmaceutically-acceptable excipients as finely divided powders. Such pharmaceutically-acceptable excipients used in dry powders include, but are not limited to, lactose, starch, mannitol, and mono-, di-, and polysaccharides. In certain embodiments, the finely divided powder is prepared by micronisation and milling, wherein the size-reduced (micronised) compound is defined by a D_{50} value of about 1 to about 10 microns.

Aerosol formulations for inhalation administration comprise a solution or fine suspension of at least one compound of Formula (I) or Formula (II) in a pharmaceutically acceptable aqueous or non-aqueous solvent/propellant. Suitable propellants include halocarbons, hydrocarbons, and other liquified gases. Representative propellants include: trichlorofluoromethane (propellant 1 1), dichlorofluoromethane (propellant 12), dichlorotetrafluoroethane (propellant 1 14), tetrafluoroethane (HFA-134a), 1 ,1 -difluoroethane (HFA-152a), difluoromethane (HFA-32), pentafluoroethane (HFA-12), heptafluoropropane (HFA-227a), perfluoropropane, perfluorobutane, perfluoropentane, butane, isobutane, and pentane. In addition, such pharmaceutical compositions optionally comprise a powder base such as lactose, glucose, trehalose, mannitol or starch, and optionally a performance modifier such as L-leucine or another amino acid, and/or metals salts of stearic acid such as magnesium or calcium stearate. Aerosol also optionally contain additional pharmaceutically-acceptable excipients such as surfactants, lubricants, cosolvents and other excipients to improve the physical stability of the formulation, to improve solubility, or to improve taste.

The particle size of a micronized compound of Formula (I) or Formula (II) contained in an aerosol formulation is less than 100 microns, while in other embodiments less than 20 microns. In certain embodiments the particle size is in the range of from 1 to 10 microns, in other embodiments from 1 to 5 microns, while in still other embodiments from 2 to 3 microns.

Thus provided herein is a pharmaceutical aerosol formulation comprising at least one compound of Formula (I) or Formula (II) or a pharmaceutically acceptable salt thereof and a fluorocarbon or hydrogen-containing chlorofluorocarbon as propellant, optionally in combination with a surfactant and/or a cosolvent. In certain embodiments, in such pharmaceutical aerosol formulation the propellant is selected from 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane and mixtures thereof.

In certain embodiments, suspensions and solutions comprising at least one compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salt thereof, formulated for inhalation administration are administered via a nebulizer. The solvent or

suspension agent utilized for nebulization is any pharmaceutically-acceptable liquid such as water, aqueous saline, alcohols or glycols, (by way of example only, ethanol, isopropylalcohol, glycerol, propylene glycol, polyethylene glycol or mixtures thereof). Saline solutions utilize salts which display little or no pharmacological activity after administration. Such salt include, but are not limited to, alkali metal or ammonium halogen salts or organic acids (by way of example only, ascorbic acid, citric acid, acetic acid and tartaric acid). Such suspensions optionally contain other pharmaceutically-acceptable excipients provided herein.

In certain embodiments, compounds of Formula (I) or Formula (II) are administered directly to the lung by inhalation using a Metered Dose Inhaler ("MDI"), which utilizes canisters that contain a suitable low boiling propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas, or a Dry Powder Inhaler (DPI) device which uses a burst of gas to create a cloud of dry powder inside a container, which is then be inhaled by the patient. In certain embodiments, capsules and cartridges of gelatin for use in an inhaler or insufflator are formulated containing a powder mixture of a compound of Formula (I) or Formula (II) and a powder base such as lactose or starch. In certain embodiments, compounds of Formula (I) or Formula (II) are delivered to the lung using a liquid spray device, wherein such devices use extremely small nozzle holes to aerosolize liquid drug formulations that can then be directly inhaled into the lung. In other embodiments, compounds of Formula (I) or Formula (II) are delivered to the lung using a nebulizer device, wherein a nebulizers creates an aerosols of liquid drug formulations by using ultrasonic energy to form fine particles that can be readily inhaled. In other embodiments, compounds of Formula (I) or Formula (II) are delivered to the lung using an electrohydrodynamic ("EHD") aerosol device wherein such EHD aerosol devices use electrical energy to aerosolize liquid drug solutions or suspensions.

In certain embodiments, the proportion of Formula (I) or Formula (II) or pharmaceutically acceptable salt thereof used in powders for inhalation or insufflation is within the range of from 0.1 to 10%. In other embodiments, the proportion of Formula (I) or Formula (II) or pharmaceutically acceptable salt thereof used in powders for inhalation or insufflation is within the range of from 0.1 to 5%. In certain embodiments, aerosol formulations contain from 20μg to 10mg of a compound of Formula (I) or Formula (II), while in other embodiments, aerosol formulations contain from 20μg to 2000μg of a compound of Formula (I) or Formula (II). In certain embodiments, aerosol formulations contain from 20μg to 500μg of a compound of Formula (I) or Formula (II). In certain embodiments, a compound of Formula (I) or Formula (II) is administered once daily by inhalation administration, while in other embodiments a compound of Formula (I) or

Formula (II) is administered several times daily by inhalation administration, By way of example only, such multiple daily dosages occur 2, 3, 4 or 8 times daily, giving for example 1 , 2 or 3 doses each time.

In certain embodiments, the pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), or pharmaceutically acceptable salts and solvates thereof, described herein, also contain one or more absorption enhancers. In certain embodiments, such absorption enhancers include, but are not limited to, sodium glycocholate, sodium caprate, N-lauryl-β-D-maltopyranoside, EDTA, and mixed micelles.

In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered intranasally. The dosage forms for nasal administration are formulated as aerosols, solutions, drops, gels or dry powders. Aqueous formulations for administration to the lung or nose optionally include conventional excipients as provided herein, such as buffering agents, tonicity modifying agents and the like.

Rectal Administration

In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered rectally in the form of suppositories, enemas, ointment, creams rectal foams or rectal gels. In certain embodiments such suppositories are prepared from fatty emulsions or suspensions, cocoa butter or other glycerides.

In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered opthamically as eye drops. Such formulations are aqueous solutions that optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

Otic Administration

In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are administered otically as ear drops. Such formulations are aqueous solutions that optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

Depot Administration

In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) or Formula (II) are formulated as a depot preparation. Such formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. In certain embodiments, such formulations include polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Combination Treatment

In certain embodiments, a compound of Formula (I) or Formula (II) of the present invention, or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II) provided herein, is administered alone (without an additional therapeutic agent) for the treatment of a disease or disorder associated with c-kit kinase activity.

In certain embodiments, a compound of Formula (I) or Formula (II) of the present invention, or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II) provided herein, is administered alone (without an additional therapeutic agent) for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR (α and/or β) kinase activity.

In other embodiments, a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), is administered in combination with one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity.

In other embodiments, a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), is administered in combination with one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR (α and/or β) kinase activity.

In other embodiments, a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), is formulated in combination with one or more additional therapeutic agents and administered for the treatment of a disease or disorder associated with c-kit kinase activity.

In other embodiments, a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates),

the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), is formulated in combination with one or more additional therapeutic agents and administered for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR (α and/or β) kinase activity.

In other embodiments, a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), is administered sequentially with one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity.

In other embodiments, a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), is administered sequentially with one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR (α and/or β) kinase activity.

In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), prior to administration of one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity.

In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), prior to administration of one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR (α and/or β) kinase activity.

In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a

pharmaceutical composition containing at least one compound of Formula (I) or Formula (II) , subsequent to administration of one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity.

In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), subsequent to administration of one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR (α and/or β) kinase activity.

In certain embodiments, the combination treatments provided herein include administration of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), concurrently with one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity.

In certain embodiments, the combination treatments provided herein include administration of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a pharmaceutical composition containing at least one compound of Formula (I) or Formula (II), concurrently with one or more additional therapeutic agents, for the treatment of a disease or disorder associated with c-kit kinase activity and PDGFR (α and/or β) kinase activity.

In certain embodiments of the combination therapies described herein, the compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the additional therapeutics agent(s) act additively. In certain embodiments of the combination therapies described herein, the compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, and the additional therapeutics agent(s) act synergistically.

The additional therapeutic agents used in combination with at least one compound of Formula (I) or Formula (II) of the present invention, or a pharmaceutically acceptable

salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to antiemetic agents, anti-inflammatory agents, immunomodulatory agents, cytokines, antidepressants, hormones, alkylating agents, antimetabolites, antitumour antibiotics, antimitotic agents, topoisomerase inhibitors, cytostatic agents, anti-invasion agents, antiangiogenic agents, inhibitors of growth factor function, anticancer agents and toll-like receptor modulators.

In some embodiments, the compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, are used in combination with a second therapeutic agent for treating asthma. In certain combinations, the second therapeutic agent is a bronchodilator, an anti-inflammatory agent, a leukotriene antagonist, or an IgE blocker.

The antiemetic agents used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, metoclopromide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acethylleucine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxyperndyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinols, thiethylperazine, thioproperazine, tropisetron, and combinations thereof.

The anti-inflammatory agents used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, non-steroidal anti-inflammatory drugs such as salicylic acid, acetylsalicylic acid, methyl salicylate, diflunisal, salsalate, olsalazine, sulfasalazine, acetaminophen, indomethacin, sulindac, etodolac, mefenamic acid, meclofenamate sodium, tolmetin, ketorolac, dichlofenac, ibuprofen, naproxen, naproxen sodium, fenoprofen, ketoprofen, flurbinprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, nabumetome, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone and nimesulide, leukotriene antagonists including, but not limited to, zileuton, aurothioglucose, gold sodium thiomalate and auranofin, steroids including, but not limited to, alclometasone diproprionate, amcinonide, beclomethasone dipropionate, betametasone, betamethasone benzoate, betamethasone diproprionate, betamethasone sodium

phosphate, betamethasone valerate, clobetasol proprionate, clocortolone pivalate, hydrocortisone, hydrocortisone derivatives, desonide, desoximatasone, dexamethasone, flunisolide, flucoxinolide, flurandrenolide, halcinocide, medrysone, methylprednisolone, methprednisolone acetate, methylprednisolone sodium succinate, mometasone furoate, paramethasone acetate, prednisolone, prednisolone acetate, prednisolone sodium phosphate, prednisolone tebuatate, prednisone, triamcinolone, triamcinolone acetonide, triamcinolone diacetate, and triamcinolone hexacetonide and other anti-inflammatory agents including, but not limited to, methotrexate, colchicine, allopurinol, probenecid, thalidomide or a derivative thereof, 5-aminosalicylic acid, retinoid, dithranol or calcipotriol, sulfinpyrazone and benzbromarone.

The immunomodulatory agents used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, azathioprine, tacrolimus, cyclosporin methothrexate, leflunomide, corticosteroids, cyclophosphamide, cyclosporine A, cyclosporin G, mycophenolate mofetil, ascomycin, rapamycin (sirolimus), FK-506, mizoribine, deoxyspergualin, brequinar, mycophenolic acid, malononitriloamindes (such as, by way of example only, leflunamide), T cell receptor modulators, and cytokine receptor modulators, peptide mimetics, and antibodies (such as, by way of example only, human, humanized, chimeric, monoclonal, polyclonal, Fvs, ScFvs, Fab or F(ab)2 fragments or epitope binding fragments), nucleic acid molecules (such as, by way of example only, antisense nucleic acid molecules and triple helices), small molecules, organic compounds, and inorganic compounds. Examples of T cell receptor modulators include, but are not limited to, anti-T cell receptor antibodies (such as, by way of example only, anti-CD4 antibodies (such as, by way of example only, cM-T412 (Boehringer), IDEC-CE9.1™ (IDEC and SKB), mAB 4162W94, Orthoclone and OKTcdr4a (Janssen-Cilag)), anti-CD3 antibodies (such as, by way of example only, Nuvion (Product Design Labs), OKT3 (Johnson & Johnson), or Rituxan (IDEC)), anti-CD5 antibodies (such as, by way of example only, an anti-CD5 ricin-linked immunoconjugate), anti-CD7 antibodies (such as, by way of example only, CHH-380 (Novartis)), anti-CD8 antibodies, anti-CD40 ligand monoclonal antibodies (such as, by way of example only, IDEC-131 (IDEC)), anti-CD52 antibodies (such as, by way of example only, CAMPATH 1H (Ilex)), anti-CD2 antibodies, anti-CD11a antibodies (such as, by way of example only, Xanelim (Genentech)), anti-B7 antibodies (such as, by way of example only, IDEC-114 (IDEC)), CTLA4-immunoglobulin, and toll receptor-like (TLR) modulators. Examples of cytokine receptor modulators include, but are not limited to, soluble cytokine receptors (such as, by way of example only, the extracellular domain of

a TNF-α receptor or a fragment thereof, the extracellular domain of an IL-1β receptor or a fragment thereof, and the extracellular domain of an IL-6 receptor or a fragment thereof), cytokines or fragments thereof (such as, by way of example only, interleukin (IL)-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-15, TNF-α, interferon (IFN)-α, IFN-β, IFN-γ, and GM-CSF), anti-cytokine receptor antibodies (such as, by way of example only, anti-IFN receptor antibodies, anti-IL-2 receptor antibodies (such as, by way of example only, Zenapax (Protein Design Labs)), anti-IL-4 receptor antibodies, anti-IL-6 receptor antibodies, anti-IL-10 receptor antibodies, and anti-IL-12 receptor antibodies), anti-cytokine antibodies (such as, by way of example only, anti-IFN antibodies, anti-TNF-α antibodies, anti-IL-1β antibodies, anti-IL-6 antibodies, anti-IL-8 antibodies (such as, by way of example only, ABX-IL-8 (Abgenix)), and anti-IL-12 antibodies).

The alkylating agents used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, nitrogen mustards, ethylenimines, methylmelamines, alkyl sulfonates, nitrosoureas, carmustine, lomustine, triazenes, melphalan, mechlorethamine, cis-platin, oxaliplatin, carboplatin, cyclophosphamide, ifosfamide, melphalan, chlorambucil, hexamethylmelaine, thiotepa, busulfan, carmustine, streptozocin, dacarbazine and temozolomide.

The antimetabolites used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, cytarabile, gemcitabine and antifolates such as, by way of example only, fluoropyrimidines (by way of example only, 5-fluorouracil and tegafur), raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea.

The antitumour antibiotics used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, anthracyclines, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycin-C, dactinomycin and mithramycin.

The antimitotic agents used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, vinca alkaloids (by

way of example only, vincristine, vinblastine, vindesine and vinorelbine), taxoids (by way of example only, taxol, paclitaxel and taxotere) and polokinase inhibitors.

The topoisomerase inhibitors used in combination with compounds of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, include, but are not limited to, epipodophyllotoxins by way of example only, etoposide and teniposide, amsacrine, topotecan, irinotecan and camptothecin.

In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a leukotriene biosynthesis inhibitor, 5-lipoxygenase (5-LO) inhibitor or 5-lipoxygenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleuton; tepoxalin; Abbott-79175; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrazones; a methoxytetrahydropyrans such as Zeneca ZD-2138; the compound SB-210661; a pyridinyl-substituted 2-cyanonaphthalene compound such as L-739,010; a 2- cyanoquinoline compound such as L-746,530; or an indole or quinoline compound such as MK-591, MK-886, and BAYx1005.

In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a receptor antagonist for leukotrienes (LTB4, LTC4, LTD4, and LTE4) selected from the group consisting of the phenothiazin-3-ls such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzenecarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, SINGULAIR™, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, iralukast (CGP 45715A), and BAYx7195.

In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a phosphodiesterase (PDE) inhibitor such as a methylxanthanine including theophylline and aminophylline; a selective PDE isoenzyme inhibitor including a PDE4 inhibitor, including, but not limited to, cilomilast or roflumilast, an inhibitor of the isoform PDE4D, or an inhibitor of PDE5.

In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts,

pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a histamine type 1 receptor antagonist such as cetirizine, loratadine, desloratadine, fexofenadine, acrivastine, terfenadine, astemizole, azelastine, levocabastine, chlorpheniramine, promethazine, cyclizine, or mizolastine.

In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a gastroprotective histamine type 2 receptor antagonist. In other embodiments, the combinations described herein include combination of a compound of Formula (I) and Formula (II), or a pharmaceutically acceptable salt or solvate thereof, described herein, with an antagonist of the histamine type 4 receptor.

In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with an alpha-l/alpha-2 adrenoceptor agonist vasoconstrictor sympathomimetic agent, such as propylhexedrine, phenylephrine, phenylpropanolamine, ephedrine, pseudoephedrine, naphazoline hydrochloride, oxymetazoline hydrochloride, tetrahydrozoline hydrochloride, xylometazoline hydrochloride, tramazoline hydrochloride or ethylnorepinephrine hydrochloride.

In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with a glucocorticoid, such as flunisolide, triamcinolone acetonide, beclomethasone dipropionate, budesonide, fluticasone propionate, ciclesonide or mometasone furoate.

In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, with an immunoglobulin (Ig), gamma globulin, Ig preparation or an antagonist or antibody modulating Ig function such as anti-IgE (omalizumab).

In other embodiments, the combinations described herein include combination of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected

derivatives, individual isomers and mixture of isomers thereof, with a chemotherapeutic agent to treat a cell proliferative disorder, including but not limited to, lymphoma, osteosarcoma, melanoma, or a tumor of breast, renal, prostate, colorectal, thyroid, ovarian, pancreatic, neuronal, lung, uterine or gastrointestinal tumor. Non-limiting examples of chemotherapeutic agents used in such combinations are anthracyclines, alkylating agents (e.g., mitomycin C), alkyl sulfonates, aziridines, ethylenimines, methylmelamines, nitrogen mustards, nitrosoureas, antibiotics, antimetabolites, folic acid analogs (e.g., dihydrofolate reductase inhibitors such as methotrexate), purine analogs, pyrimidine analogs, enzymes, podophyllotoxins, platinum-containing agents, interferons, and interleukins. Other non-limiting examples of chemotherapeutic agents used in such combinations are busulfan, improsulfan, piposulfan, benzodepa, carboquone, meturedepa, uredepa, altretamine, triethylenemelamine, triethylenephosphoramide, triethylenethiophosphoramide, trimethylolomelamine, chlorambucil, chlornaphazine, cyclophosphamide, estramustine, ifosfamide, mechlorethamine, mechlorethamine oxide hydrochloride, melphalan, novembichin, phenesterine, prednimustine, trofosfamide, uracil mustard, carmustine, chlorozotocin, fotemustine, lomustine, nimustine, ranimustine, dacarbazine, mannomustine, mitobronitol, mitolactol, pipobroman, aclacinomycins, actinomycin F(1), anthramycin, azaserine, bleomycin, cactinomycin, carubicin, carzinophilin, chromomycin, dactinomycin, daunorubicin, daunomycin, 6-diazo-5-oxo-1-norleucine, doxorubicin, epirubicin, mitomycin C, mycophenolic acid, nogalamycin, olivomycin, peplomycin, plicamycin, porfiromycin, puromycin, streptonigrin, streptozocin, tubercidin, ubenimex, zinostatin, zorubicin, denopterin, methotrexate, pteropterin, trimetrexate, fludarabine, 6-mercaptopurine, thiamiprine, thioguanine, ancitabine, azacitidine, 6-azauridine, carmofur, cytarabine, dideoxyuridine, doxifluridine, enocitabine, floxuridine, fluorouracil, tegafur, L-asparaginase, pulmozyme, aceglatone, aldophosphamide glycoside, aminolevulinic acid, amsacrine, bestrabucil, bisantrene, carboplatin, cisplatin, defofamide, demecolcine, diaziquone, elfornithine, elliptinium acetate, etoglucid, etoposide, flutamide, gallium nitrate, hydroxyurea, interferon-alpha, interferon-beta, interferon-gamma, interleukin-2, lentinan, lonidamine, mitoguazone, mitoxantrone, mopidamol, nitracrine, pentostatin, phenamet, pirarubicin, podophyllinic acid, 2-ethylhydrazide, procarbazine, razoxane, sizofiran, spirogermanium, paclitaxel, tamoxifen, teniposide, tenuazonic acid, triaziquone, 2,2',2"-trichlorotriethylamine, urethane, vinblastine, vincristine, and vindesine.

In certain embodiments, the combination treatments provided herein include administration of a compound of Formula (I) or Formula (II), or a pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, or a

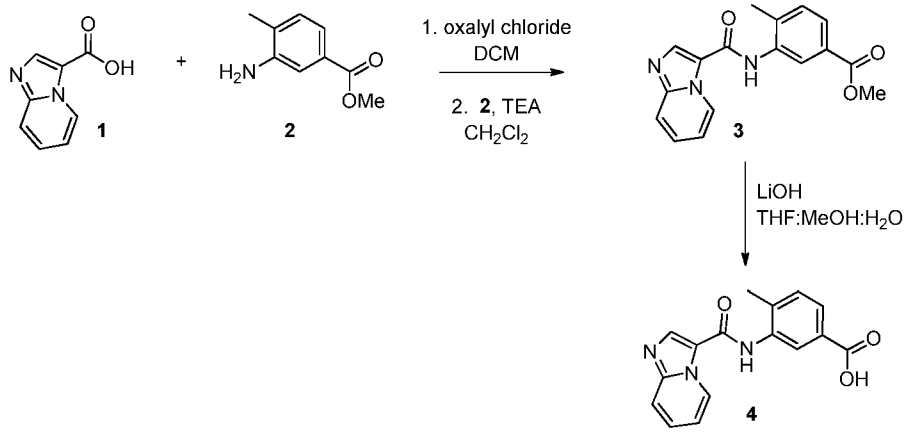
pharmaceutical composition containing a compound of Formula (I) and Formula (II) in combination with one or more additional therapeutic agents, for the treatment of Pulmonary Arterial Hypertension (PAH). Such additional therapeutic agents include phosphodiesterase-5 inhibitors, prostanoids, endothelin receptor antagonists, calcium channel blockers, oxygen therapy, iloprost, sildenafil, tadalifil, digoxin, furosemide, spironolactone, warfarin, epoprostenol, treprostinil, bosentan and ambrisentan.

Examples

The following examples are offered to illustrate, but not to limit, the compounds of Formula (I) or Formula (II) of the present invention, and the preparation of such compounds.

Synthesis of intermediates

Synthesis of 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoic acid (**4**)

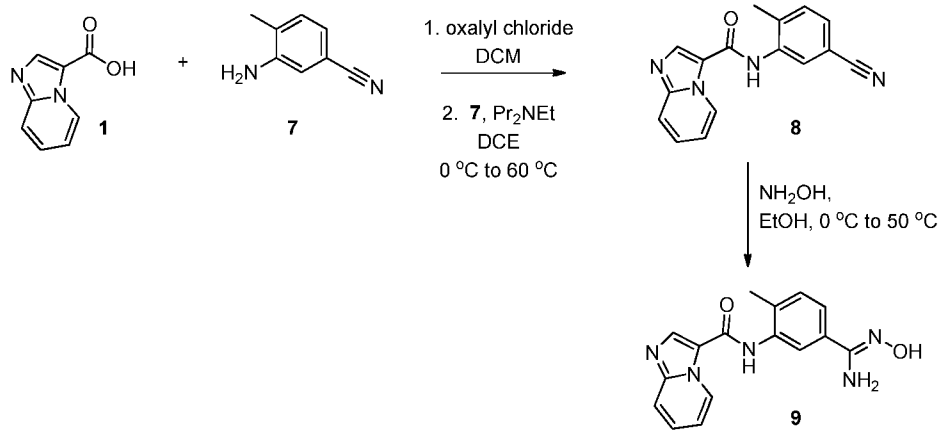


To a suspension of imidazo[1,2-a]pyridine-3-carboxylic acid (**1**) (4.09 g, 25.3 mmol) in dichloromethane (100 mL) and DMF (0.25 mL) at 0 °C was added oxalyl chloride (4.15 mL, 48.0 mmol) dropwise over 10 minutes. The reaction was slowly warmed to room temperature and stirred until complete conversion was detected by LCMS. The reaction was subsequently reduced to dryness and suspended in dichloromethane (100 mL) and was added a solution of methyl 3-amino-4-methylbenzoate (**2**) (4.6 g, 27.9 mmol) in dichloromethane (100 mL) and triethylamine (7.1 mL). Contents were stirred at room temperature for 4 hours and diluted with dichloromethane (100 mL). The reaction was washed with water, saturated $NaHCO_3$, brine, dried over magnesium sulfate, filtered and reduced to dryness. The crude solid was triturated with diethyl ether to remove excess aniline and dried to afford methyl 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoate (**3**) as a white solid. MS *m/z* 310.1 $(M+1)^+$.

To a suspension of 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoate (**3**) (5.43 g, 17.6 mmol) in THF (225 ml) and MeOH (150 mL) was added LiOH 3 M (17.5 mL) and water (50 mL). The reaction was stirred at room temperature for 12 hours then reduced in volume on roto-vap to remove THF and MeOH. The mixture was diluted with

water (75 mL) and neutralized with HCl (17.5 mL of a 3M solution). The resulting precipitate was filtered, washed with water and dried under vacuum to afford 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoic acid (**4**) as a white solid. ^{1}H NMR (400MHz, d_6-DMSO) δ 10.0 (s, 1H), 9.45 (dt, J = 6.8, 1.2 Hz, 1H), 8.58 (s, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.79 (dt, J = 9.2, 1.2 Hz, 1H), 7.76 (dd, J = 8.0, 1.6 Hz, 1H), 7.52 (ddd, J = 9.2, 9.2, 1.2 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.17 (td, J = 6.8, 1.2 Hz, 1H), 2.35 (s, 3H). MS *m/z* 296.1 $(M+1)^+$.

Synthesis of N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**9**)

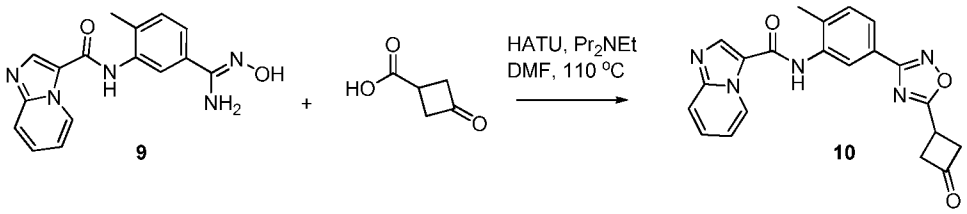


To a suspension of imidazo[1,2-a]pyridine-3-carboxylic acid (**1**) (16.6 g, 102 mmol) in dichloromethane (300 mL) and DMF (0.5 mL) at 0 °C was added oxalyl chloride (45 mL, 510 mmol) dropwise over 10 minutes. The reaction was slowly warmed to room temperature and stirred until complete conversion was detected by LCMS in MeOH. The reaction was subsequently reduced to dryness and suspended in dichloroethane (100 mL) and was added to a solution of 3-amino-4-methylbenzonitrile (**7**) (15 g, 113 mmol) in dichloroethane (200 mL) and Pr_2NEt (55 mL) at 0 °C. After the addition, the cold bath was removed and contents were stirred at room temperature for 1 hour and then heated to 50 °C for another 2 hours. After the completion of the reaction, the mixture was cooled and a white precipitate formed. The mixture was filtered and the solid was washed with cold dichloromethane. About 10 g of the desired N-(5-cyano-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**8**) was obtained. The filtrate was washed with saturated NH_4Cl, saturated $NaHCO_3$, brine, dried over magnesium sulfate, filtered and reduced to dryness. The crude solid was triturated with diethyl ether to remove excess aniline and filtered to afford another crop of N-(5-cyano-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**8**) as a white solid. MS *m/z* 277.1 (M+1).

To a stirred and cooled (0 °C) suspension of N-(5-cyano-2-methylphenyl)imidazo[1,2-

a]pyridine-3-carboxamide (**8**) (10 g, 36.2 mmol) in EtOH (225 ml) was added NH_2OH (6 mL, 50% in water solution). After the addition, the reaction was stirred at room temperature for 2 hours then heated at 50 °C for another 2 hours. After cooling to room temperature, the mixture was stored in the fridge overnight. The resulting precipitate was filtered, washed with cold EtOH and dried under vacuum to afford N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**9**) as a white solid. ^{1}H NMR (400MHz, d_6-DMSO) δ 9.40 (dt, J = 6.8, 1.2 Hz, 1H), 8.15 (s, 1H), 7.88 (d, J = 2.0 Hz, 1H), 7.79 (dt, J = 9.2, 1.2 Hz, 1H), 7.76 (dd, J = 8.0, 1.6 Hz, 1H), 7.52 (ddd, J = 9.2, 9.2, 1.2 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.17 (td, J = 6.8, 1.2 Hz, 1H), 2.49 (s, 3H). MS m/z 310.1 $(M+1)^+$.

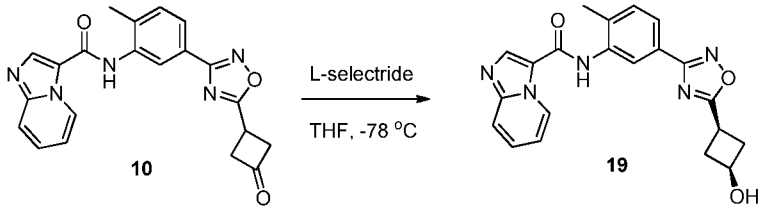
Synthesis of N-(2-methyl-5-(5-(3-oxocyclobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**10**)



9 **10**

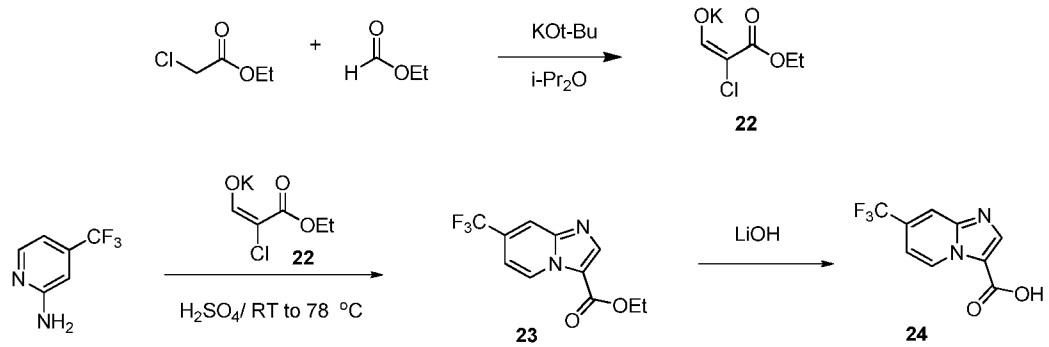
HATU (1.41 g, 3.72 mmol) was added in one portion to a stirred solution of 3-oxocyclobutanecarboxylic acid (0.405 g, 3.55 mmol) and Pr_2NEt (0.62 mL, 3.7 mmol) in dry DMF (5 mL). After 10 minutes, N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**9**) (1.0 g, 3.23 mmol) was added in one portion and continued to stir for another 30 minutes. The resulting solution was heated (110 °C) for 30 minutes and then cooled to room temperature. The solvent was evaporated and the residue was partitioned with saturated NH_4Cl and EtOAc. The organic layer was dried with $MgSO_4$ and filtered. The residue was purified on silica gel using 10% MeOH in dichloromethane to obtain N-(2-methyl-5-(5-(3-oxocyclobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**10**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.20 (s, 1 H), 9.53 – 9.51 (m, 1 H), 8.71 (s, 1 H), 8.08 (d, J = 1.6 Hz, 1 H), 7.91 – 7.88 (m, 1 H), 7.85 (dd, J = 2.0, 8.0 Hz, 1 H), 7.72 – 7.68 (m, 1 H), 7.51 (d, J = 8.4 Hz, 1 H), 7.34 – 7.30 (m, 1 H), 4.12 – 4.04 (m, 1 H), 3.70 – 3.53 (m, 4 H), 2.37 (s, 3 H). MS m/z 388.1 $(M+1)^+$.

Synthesis of N-(5-(5-((1s,3s)-3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**19**)



L-selectride (1.7 mL, 1 M in THF, 1.7 mmol) was added dropwise to a stirred solution of N-(2-methyl-5-(5-(3-oxocyclobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**10**) (0.5 g, 1.29 mmol) in THF at -78 °C. After 30 minutes, the reaction was warmed to 0 °C and quenched with 1N NaOH. The mixture was partitioned with EtOAc and brine. The organic phase was dried over $MgSO_4$ and purified over silica gel using 10% MeOH in dichloromethane to give N-(5-(5-((1s,3s)-3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**19**) as a white solid. ^{1}H NMR (400MHz, d_4-MeOH) δ 10.03 (s, 1H), 9.47 – 9.45 (m, 1H), 8.59 (s, 1H), 8.08 (s, 1H), 7.83 – 7.78 (m, 2H), 7.52 – 7.48 (m, 2H), 7.20 – 7.16 (m, 1H), 5.41 (d, J = 8 Hz, 1H), 4.18 – 4.10 (m, 1H), 2.73 – 2.68 (m, 2H), 2.37 (s, 3H), 2.27 – 2.20 (m, 2H). MS m/z 390.1 $(M+1)^+$.

Synthesis of 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**24**)



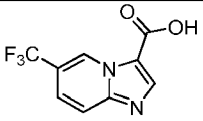
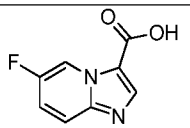
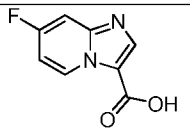
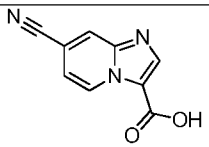
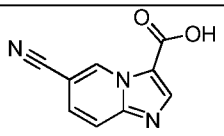
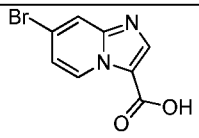
Ethyl 2-chloroacetate (20 mL, 187 mmol) and ethyl formate (15.1 mL, 187 mmol) were added simultaneously to a stirred and cooled suspension of potassium *tert*-butoxide (21.4 g, 188 mmol) in dry diisopropylether (300 mL). After the addition, the reaction was warmed to room temperature and stirred overnight. The yellow suspension was filtered and the solid potassium 2-chloro-3-ethoxy-3-oxoprop-1-en-1-olate (**22**) was vacuum dried and used directly in the following step.

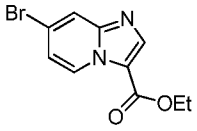
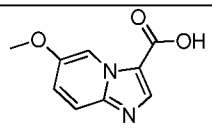
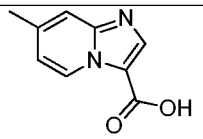
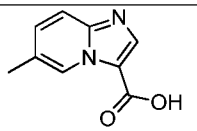
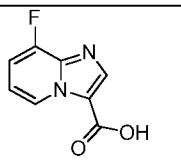
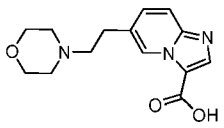
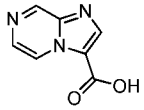
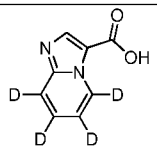
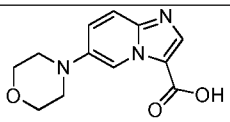
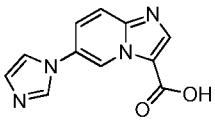
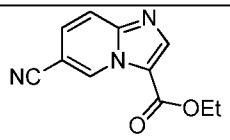
To a stirring suspension of 4-(trifluoromethyl)pyridin-2-amine (128 mg, 0.791 mmol) and potassium 2-chloro-3-ethoxy-3-oxoprop-1-en-1-olate (**22**) (500 mg, 2.64 mmol) in EtOH (5 mL) at room temperature was added sulfuric acid (70 μL, 1.32 mmol) dropwise. The reaction mixture was stirred at room temperature overnight then heated at 78 °C for 3 hours. The reaction was cooled to room temperature and the solvent was concentrated. The residue was taken in water and the pH was adjusted between 6-8 with

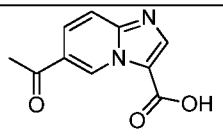
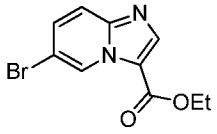
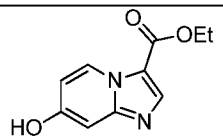
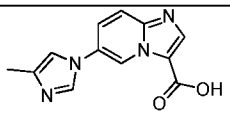
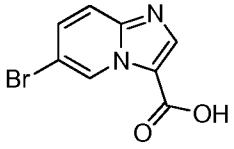
saturated sodium bicarbonate. The crude product was extracted with ethyl acetate. The organic was washed with brine and dried over anhydrous sodium sulfate. The crude product 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylate (**23**) was purified by silica chromatography. MS *m/z* 259.3 $(M+1)^+$.

To a stirring solution of ethyl 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylate (**23**) (100 mg, 0.387 mmol) in THF : MeOH (4:1, 1.5 mL) was added 2N LiOH (0.25 mL). The reaction was heated at 60 °C for 1 hour. Then, cooled to room temperature and the pH was adjusted between 4-5 with 1N HCl. The solvent was partially concentrated and the resulting aqueous layer was lyophilized to give 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylic acid **(24)**. ^{1}H NMR (400MHz, d_6-DMSO) δ 9.44 (d, J = 7.2 Hz, 1 H), 8.40 (s, 1 H), 8.31 – 8.30 (m, 1 H), 7.48 (dd, J = 2.0, 7.6 Hz, 1 H). MS *m/z* 231.2 $(M+1)^+$.

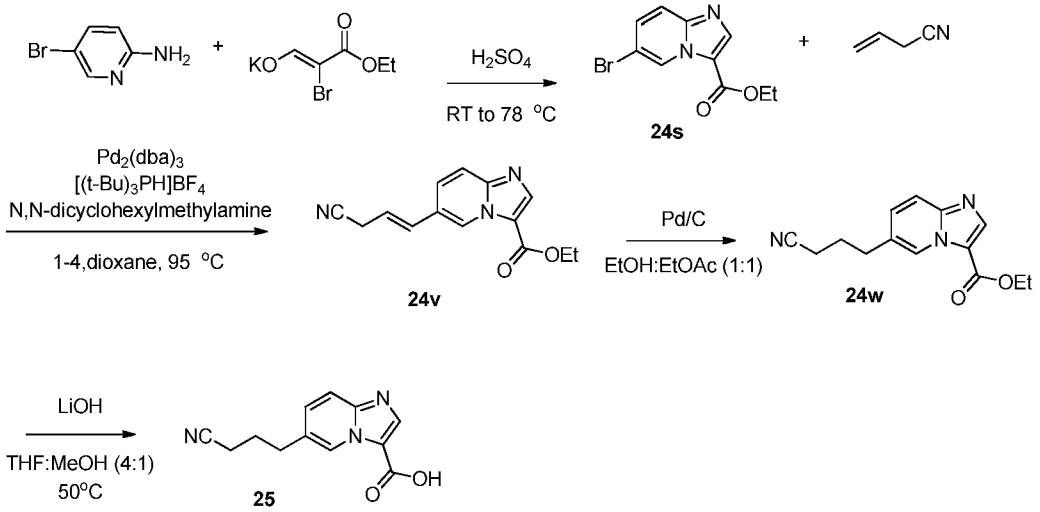
The following compounds were prepared according to the protocol described for 7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**24**).

Intermediate number	Structure	Physical Data
24a		^{1}H NMR (400MHz, d_6-DMSO) δ 9.64 – 9.62 (m, 1 H), 8.39 (s, 1 H), 8.01 (d, J = 9.2 Hz, 1 H), 7.81 (dd, J = 2.0, 9.2 Hz, 1 H). MS *m/z* 231.2 $(M+1)^+$.
24b		MS *m/z* 181.2 $(M+1)^+$.
24c		MS *m/z* 181.2 $(M+1)^+$.
24d		MS *m/z* 188.1 $(M+1)^+$.
24e		MS *m/z* 188.1 $(M+1)^+$.
24f		MS *m/z* 241.0 $(M+1)^+$.

24g		MS *m/z* 270.0 $(M+1)^+$.
24h		^{1}H NMR (400MHz, d_6-DMSO) δ 8.94 (d, *J* = 2.0 Hz, 1H), 8.13 (s, 1 H), 7.70 (d, *J* = 9.6 Hz, 1 H), 7.31 (dd, *J* = 2.8, 9.8 Hz, 1 H), 3.85 (s, 3H). MS *m/z* 193.1 $(M+1)^+$.
24i		MS *m/z* 177.6 $(M+1)^+$.
24j		MS *m/z* 177.6 $(M+1)^+$.
24k		MS *m/z* 209.06 $(M+1)^+$.
24l		^{1}H NMR (400MHz, d_6-DMSO) δ 9.21 (s, 1 H), 8.22 (s, 1 H), 7.76 (d, *J* = 9.2 Hz, 1 H), 7.50 (dd, *J* = 1.6, 9.2 Hz, 1 H), 3.72 – 3.69 (m, 4 H), 3.40 – 3.28 (m, 2 H), 2.99 – 2.92 (m, 4 H), 2.88 – 2.82 (m, 2 H). MS *m/z* 276.13 $(M+1)^+$.
24m		^{1}H NMR (400MHz, d_6-DMSO) δ 9.29 (d, *J* = 1.6 Hz, 1 H), 9.15 (dd, *J* = 1.6, 4.4 Hz, 1 H), 8.4 (s, 1 H), 8.20 (d, *J* = 4.4 Hz, 1 H). MS *m/z* 164.1 $(M+1)^+$.
24n		MS *m/z* 167.0 $(M+1)^+$.
24o		^{1}H NMR (400MHz, d_6-DMSO) δ 8.79 (s, 1 H), 8.49 (s, 1 H), 7.84 (m, 2 H), 3.80 (m, 4 H), 3.16 (m, 4 H). MS *m/z* 248.1 $(M+1)^+$.
24p		^{1}H NMR (400MHz, d_6-DMSO) δ 9.69 (dd, *J* = 0.8, 2.0 Hz, 1 H), 9.54 (s, 1 H), 8.42 (s, 1 H), 8.23 (s, 1 H), 8.09 (dd, *J* = 0.8, 9.6 Hz, 1 H), 7.95 (dd, *J* = 2.0, 9.6 Hz, 1 H), 7.87 (s, 1 H). MS *m/z* 248.1 $(M+1)^+$.
24q		MS *m/z* 216.0 $(M+1)^+$.

24r		MS *m/z* 205.0 (M+1) $^+$.
24s		MS *m/z* 270.0 (M+1) $^+$.
24t		MS *m/z* 207.1 (M+1) $^+$.
24u		MS *m/z* 243.1 (M+1) $^+$.
24v		MS *m/z* 241.0 (M+1) $^+$.

Synthesis of 6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**25**)



To a stirring suspension of 5-bromopyridin-2-amine (1.2 g, 7.05 mmol) and ethyl 2-chloro-3-hydroxyacrylate potassium salt (6.6 g, 28.19 mmol) (prepared in a similar manner as **22**) in EtOH (100 mL) at room temperature was added sulfuric acid (751 µL, 14.10 mmol) dropwise. The reaction mixture was heated at 78 °C overnight. The reaction was cooled to room temperature and the solvent was concentrated. The residue was taken in water and the pH was adjusted between 6-8 with saturated sodium bicarbonate. The crude product was extracted with ethyl acetate. The organic was washed with brine and dried over anhydrous sodium sulfate. The crude product was purified by silica

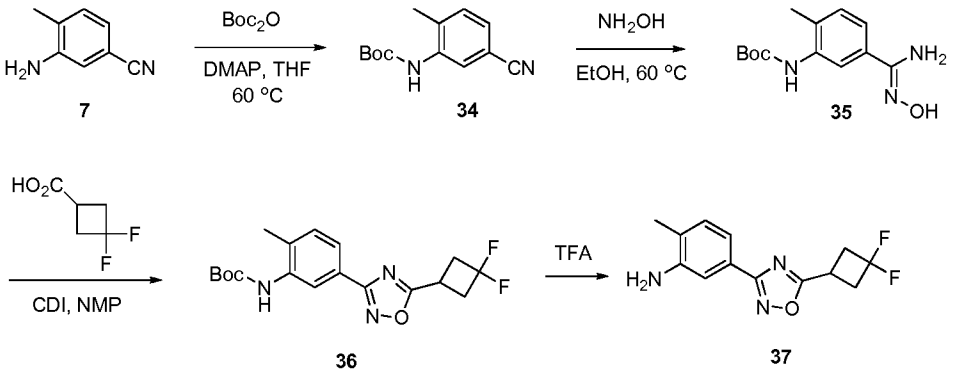
chromatography to yield ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate **(24s)**. MS *m/z* 270.2 $(M+1)^+$.

A stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate **(24s)** (500 mg, 1.86 mmol), allyl cyanide (224 uL, 2.79 mmol), tris(dibenzylideneacetone)dipalladium(0) (26 mg, 0.028 mmol), $[(t\text{-Bu})_3PH]BF_4$ (16 mg, 0.056 mmol), and N,N-dicyclohexylmethylamine (433 μL, 2.04 mmol) in anhydrous 1,4-dioxane (6 mL) was heated at 95 °C overnight. The reaction was cooled to room temperature and filtered. The solvent was concentrated. The crude product was purified by silica chromatography to give ethyl 6-(3-cyanoprop-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate **(24v)**. MS *m/z* 256.4 $(M+1)^+$.

To a stirring solution of ethyl 6-(3-cyanoprop-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate **(24v)** (400 mg, 1.57 mmol) in EtOH : EtOAc (1:1, 10 mL) was added catalytic Pd/C (10 wt%, wet basis). The reaction was hydrogenated by balloon overnight then filtered through celite. The crude product ethyl 6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxylate **(24w)** was used in the next step without further purification. MS *m/z* 258.4 $(M+1)^+$.

To a stirring solution of ethyl 6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxylate **(24w)** (375 mg, 1.46 mmol) in THF : MeOH (4:1, 5 mL) was added 2N LiOH (500 μL). The reaction was heated at 50 °C for 45 minutes then cooled to room temperature and the pH was adjusted between 3-4 with 1N HCl. The solvent was partially concentrated and the remaining aqueous was lyophilized to yield 6-(3-cyanopropyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**25**). ^{1}H NMR (400MHz, d_6-DMSO) δ 9.21 – 9.19 (m, 1 H), 8.45 (s, 1 H), 7.85 (dd, J = 0.8, 9.2 Hz, 1 H), 7.70 (dd, J = 1.6, 9.2 Hz, 1 H), 2.82 (t, J = 7.2 Hz, 2 H), 2.55 (t, J = 7.2 Hz, 2 H), 1.97 – 1.90 (m, 2 H). MS *m/z* 230.3 $(M+1)^+$.

Synthesis of 5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**37**)



$(Boc)_2O$ (50 g, 227 mmol) was added portion-wise to a stirred solution of 3-amino-4-methylbenzonitrile (**7**) (10 g, 75.7 mmol) and DMAP (0.5 g) in THF (250 mL). After 30 minutes, the reaction was heated at 60 °C overnight. The crude reaction mixture was

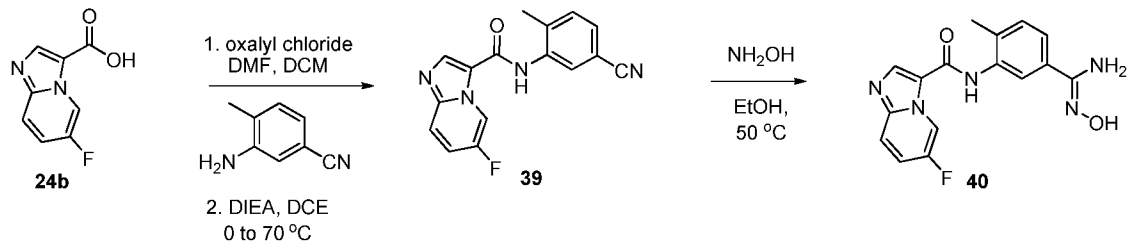
purified over silica gel to obtain a white solid tert-butyl 5-cyano-2-methylphenylcarbamate (**34**) (17.5 g, quantitative yield). MS *m/z* 233.1 $(M+1)^+$.

NH_2OH (20 mL, 50% in water) was added to a stirred solution of tert-butyl 5-cyano-2-methylphenylcarbamate (**34**) (17.5 g, 75.3 mmol) in EtOH (200 mL) and the resulting solution was heated at 50 °C for 10 hours. The solvent was then evaporated and the product was titurated with EtOAc and hexane to obtain a white solid (Z)-tert-butyl 5-(N'-hydroxycarbamimidoyl)-2-methylphenylcarbamate (**35**) in a quantitative yield which was used without further purification. MS *m/z* 266.1 $(M+1)^+$.

CDI (1.2 g, 7.34 mmol) was added portion-wise to a stirred solution 3,3-difluorocyclobutanecarboxylic acid (1 g, 7.34 mmol) in NMP (10 mL). After 30 minutes, (Z)-tert-butyl 5-(N'-hydroxycarbamimidoyl)-2-methylphenylcarbamate (**35**) (1.8 g, 7.34 mmol) was added in one portion and stirred for another hour at room temperature. The solution was then heated via microwave at 120 °C for 20 minutes. The solution was partitioned with EtOAc and water. The organic phase was separated, dried over $MgSO_4$ and purified over silica gel to afford tert-butyl (5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)carbamate (**36**) (1.2 g, 45% yield). MS *m/z* 366.1 $(M+1)^+$.

Tert-butyl (5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)carbamate (**36**) (1.2 g, 3.3 mmol) was dissolved in TFA (10 mL) and stirred at room temperature for 15 minutes. Then TFA was removed under vaccum to give the residue which was neutralized by addition of 2M Na_2CO_3 solution (20 mL). The solution was extracted with EtOAc and the organic phase was dried over Na_2SO_4. Evaporation of solvent gave 5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**37**) as a white solid (0.9 g, 100% yield), which was used without further purification. ^1H NMR (400MHz, d_6-DMSO) δ 7.33 (d, J = 1.2 Hz, 1H), 7.14 (dd, J = 1.2, 7.6 Hz, 1H), 7.09 (d, J = 8.0 Hz, 1H), 5.37 (br, 2H), 3.84 (m, 1H), 2.98-3.24 (m, 4H), 2.12 (s, 3H). MS *m/z* 266.1 $(M+1)^+$.

Synthesis of (Z)-6-fluoro-N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**40**)

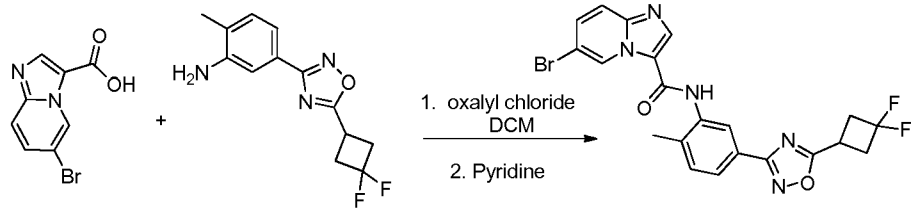


Oxalyl chloride (10 mL, 110 mmol) was added dropwise to a stirred suspension of 6-fluoroimidazo[1,2-a]pyridine-3-carboxylic acid (**24b**) (2 g, 11 mmol) and catalytic

amounts of DMF in dichloromethane (20 mL). After 5 hours, the solvent was evaporated and the solid was suspended in dry DCE (20 mL) and added to a stirred solution of 3-amino-4-methylbenzonitrile (1.45 g, 11 mmol) and DIEA (6 mmol) in DCE (10 mL) at 0 °C. After the addition, the reaction was heated at 60 °C for 5 hours. The mixture was subjected to standard aqueous work and silica purification to give N-(5-cyano-2-methylphenyl)-6-fluoroimidazo[1,2-a]pyridine-3-carboxamide (**39**) as a solid. ^{1}H NMR (400MHz, d_6-DMSO) δ 10.14 (s, 1 H), 9.45 (dd, J = 5.2, 2.0 Hz, 1H), 8.62 (s, 1 H), 7.90 – 7.87 (m, 2 H), 7.68–7.63 (m, 1 H), 7.53 (d, J = 8.0 Hz, 1 H), 2.37 (s, 3H). MS *m/z* 295.1 $(M+1)^+$.

NH_2OH (5 mL, 16.1 mmol) was added in one portion to a stirred suspension of N-(5-cyano-2-methylphenyl)-6-fluoroimidazo[1,2-a]pyridine-3-carboxamide (**39**) (0.95 g, 3.23 mmol). The resulting suspension was heated at 60 °C overnight and then cooled to 0 °C. The product, (Z)-6-fluoro-N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**40**) was collected by filtration. MS *m/z* 328.1 $(M+1)^+$.

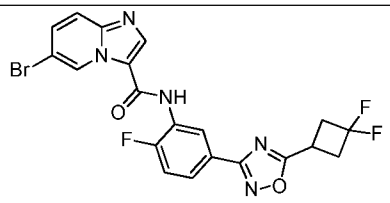
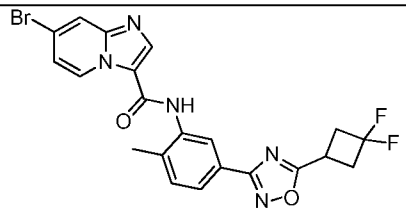
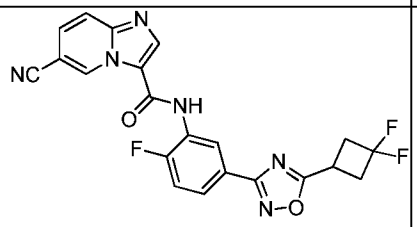
Synthesis of 6-bromo-N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**42**)



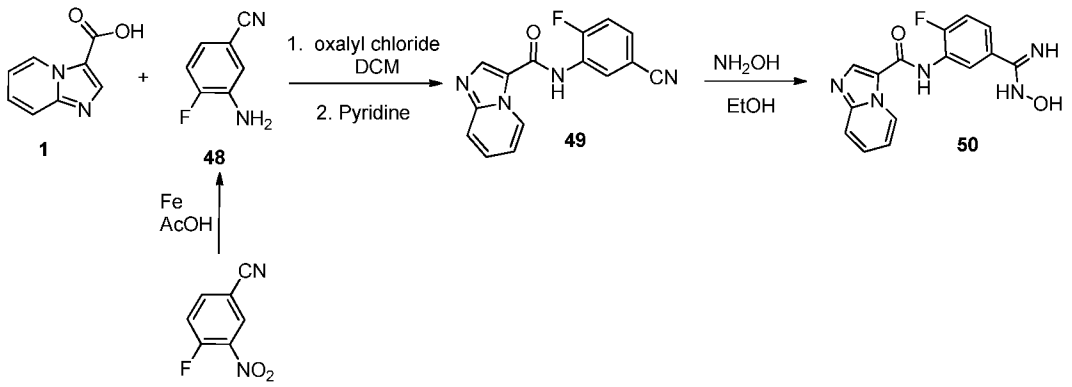
24v **37** **42**

To a stirring suspension of 6-bromoimidazo[1,2-a]pyridine-3-carboxylic acid (**24v**) (300 mg, 1.25 mmol), in anhydrous dichloromethane (10 mL) at 0 °C under Argon was added dropwise oxalyl chloride (116 μL, 1.37 mmol). Then, three drops of anhydrous DMF was added and the reaction mixture was stirred at room temperature for 45 min. The solvent was concentrated and the crude solid was added portion-wise to a stirring solution of methyl 3-(3-(3-amino-4-methylphenyl)-1,2,4-oxadiazol-5-yl)azetidine-1-carboxylate (**31**) (330 mg, 1.25 mmol) in anhydrous pyridine (5 mL) at 0 °C. The reaction was stirred to room temperature under Argon for 2 h. Then, the reaction was quenched with water. The solvent was concentrated and the crude product was purified by silica chromatography to yield 6-bromo-N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (205 mg, 67% yield).

The following compounds were prepared according to the protocol described for 6-bromo-N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**42**).

Intermediate number	Structure	Physical Data
42c		MS *m/z* 492.0, 494.0 $(M+1)^+$.
42f		^{1}H NMR (400MHz, $CDCl_3$) δ 9.44 (dd, *J* = 0.8, 7.6 Hz, 1H), 8.56 (d, *J* = 1.6 Hz, 1H), 8.18 (s, 1H), 7.96 (dd, *J* = 0.8, 2.0 Hz, 1H), 7.89 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.62 (s, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 2.0, 7.2 Hz, 1H), 3.68 (m, 1H), 3.18 (m, 4H), 2.45 (s, 3H). MS *m/z* 488.0, 490.0 $(M+1)^+$.
42h		MS *m/z* 439.0 $(M+1)^+$.

Synthesis of N-(2-fluoro-5-(N'-hydroxycarbamimidoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**50**)

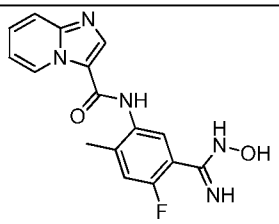
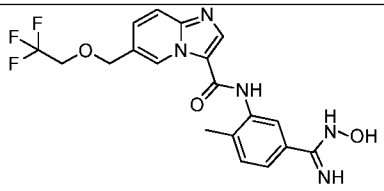


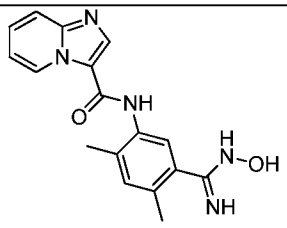
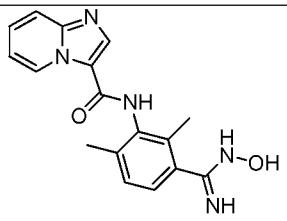
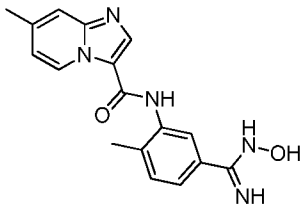
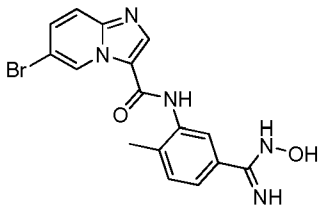
A mixture of 4-fluoro-3-nitrobenzonitrile (5.0 g, 30.1 mmol) and Fe powder (5.05 g, 90.3 mmol) in AcOH (100 mL) was heated at 80 °C for 1 hour under N_2. Then the solvent was removed under vacuum and water (200 mL) was added to the residue. The solution was adjusted to pH 6 by addition of Na_2CO_3 and extracted with DCM (2 x 200 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to yield 3-amino-4-fluorobenzonitrile (**48**), which was used without further purification. MS *m/z* 137.0 $(M+1)^+$.

To a stirring suspension of imidazo[1,2-a]pyridine-3-carboxylic acid (**1**) (3.0 g, 18.5 mmol) in anhydrous dichloromethane (50 mL) at 0 °C was added dropwise oxalyl chloride (4.84 mL, 55.5 mmol). Then, three drops of anhydrous DMF was added and the reaction mixture was stirred at room temperature for 15 minutes. The solvent was concentrated and the crude solid was added to a stirring solution of 3-amino-4-fluorobenzonitrile (**48**) (2.5 g, 18.5 mmol) in anhydrous pyridine (50 mL) at room temperature. The reaction was stirred for 20 minutes and quenched with water (200 mL) with stirring for another 10 minutes. Then the precipitate was filtered and dried in air to yield N-(5-cyano-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide (**49**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.40 (s, 1H), 9.43 (td, J = 1.2, 6.8 Hz, 1H), 8.63 (s, 1H), 8.21 (dd, J = 2.0, 7.2 Hz, 1H), 7.78-7.84 (m, 2H), 7.54-7.63 (m, 2H), 7.22 (dt, J = 1.2, 6.8, 1H). MS m/z 281.1 $(M+1)^+$.

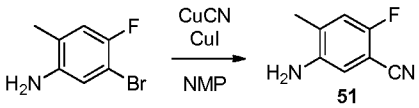
NH_2OH (10 mL, 32.1 mmol) was added in one portion to a stirred suspension of N-(5-cyano-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide (**49**) (3.6 g, 12.85 mmol) in EtOH (100 mL). The resulting suspension was heated at 70 °C for 3 hours and then the solvent was removed to yield N-(2-fluoro-5-(N'-hydroxycarbamimidoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**50**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.21 (s, 1H), 9.70 (s, 1H), 9.45 (td, J = 1.2, 7.2 Hz, 1H), 8.61 (s, 1H), 7.95 (dd, J = 2.4, 7.6 Hz, 1H), 7.79 (td, J = 1.2, 8.8 Hz, 1H), 7.51-7.60 (m, 2H), 7.31-7.37 (m, 1H), 7.19 (dt, J = 1.2, 6.8, 1H), 5.88 (s, 2H). MS m/z 314.1 $(M+1)^+$.

The following compounds were prepared according to the protocol described for N-(2-fluoro-5-(N'-hydroxycarbamimidoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**50**).

Intermediate number	Structure	Physical Data
50a		^{1}H NMR (400MHz, d_6-DMSO) δ 9.96 (s, 1H), 9.65 (s, 1H), 9.44 (td, J = 0.8, 6.8 Hz, 1H), 8.55 (s, 1H), 7.78 (td, J = 1.2, 9.2 Hz, 1H), 7.52 (m, 2H), 7.21 (d, J = 11.6 Hz, 1H), 7.17 (dt, J = 1.2, 6.8, 1H), 5.81 (s, 2H), 2.28 (s, 3H). MS m/z 328.1 $(M+1)^+$.
50b		MS m/z 422.1 $(M+1)^+$.

50c		^{1}H NMR (400MHz, d_6-DMSO) δ 9.89 (s, 1H), 9.44 (dt, J = 6.8, 1.2 Hz, 1H), 9.33 (s, 1H), 8.55 (s, 1H), 7.76 (dt, J = 9.2, 1.2 Hz, 1H), 7.49-7.52 (m, 1H), 7.28 (s, 1H), 7.14-7.18 (m, 2H), 5.72 (s, 2H), 2.34 (s, 3H), 2.24 (s, 3H). MS m/z 324.1 $(M+1)^+$.
50d		^{1}H NMR (400MHz, d_6-DMSO) δ 9.84 (s, 1H), 9.43 (d, J = 6.8 Hz, 1H), 8.59 (s, 1H), 7.78 (d, J = 8.8 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.17 (m, 3H), 5.76 (s, 2H), 2.25 (s, 3H), 2.24 (s, 3H). MS m/z 324.1 $(M+1)^+$.
50e		^{1}H NMR (400MHz, d_6-DMSO) δ 9.90 (s, 1H), 9.60 (s, 1H), 9.32 (d, J = 7.2 Hz, 1H), 8.50 (s, 1H), 7.69 (d, J = 2.0 Hz, 1H), 7.56 (m, 1H), 7.50 (dd, J = 1.6, 8.0 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.02 (dd, J = 1.6, 7.2 Hz, 1H), 5.80 (s, 2H), 2.42 (s, 3H), 2.27 (s, 3H). MS m/z 324.1 $(M+1)^+$.
50f		^{1}H NMR (400MHz, d_6-DMSO) δ 10.09 (s, 1H), 9.63 (m, 1H), 9.60 (s, 1H), 8.58 (s, 1H), 7.78 (dd, J = 0.8, 9.6 Hz, 1H), 7.69 (d, J = 1.6 Hz, 1H), 7.66 (dd, J = 2.0, 9.2 Hz, 1H), 7.52 (dd, J = 1.6, 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 5.81 (s, 2H), 2.27 (s, 3H). MS m/z 388.0, 390.0 $(M+1)^+$.

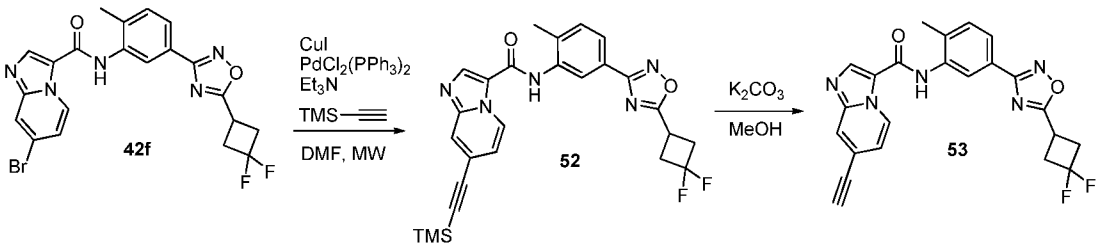
Synthesis of 5-amino-2-fluoro-4-methylbenzonitrile (**51**)



51

A mixture of 5-bromo-4-fluoro-2-methylaniline (2.04 g, 10.0 mmol), CuCN (889 mg, 10.0 mmol) and CuI (1.9 g, 10.0 mmol) in NMP was purged with N_2 for 5 minutes and then sealed and heated at 195 °C for 30 minutes under microwave condition. The mixture was subjected to standard aqueous workup to give a residue which was purified by silica chromatography to yield 5-amino-2-fluoro-4-methylbenzonitrile (**51**) (540 mg, 36% yield). MS m/z 151.0 $(M+1)^+$.

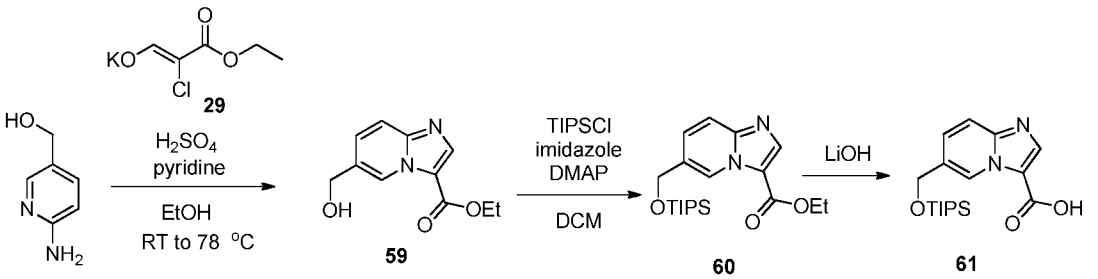
Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-ethynylimidazo[1,2-a]pyridine-3-carboxamide (**53**)



7-Bromo-N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**42f**) (50.0 mg, 0.10 mmol), CuI (3.82 mg, 0.02 mmol), $PdCl_2(PPh_3)_2$ (14.0 mg, 0.02 mmol), triethylamine (20.0 mg, 0.20 mmol) and ethynyltrimethylsilane (20 mg, 0.20 mmol) were mixed in DMF (1 mL) in a 1 mL mircowave vial. The vial was capped and heated at 110 °C for 5 minutes under microwave condition. Once complete, the reaction mixture was diluted and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered, concentrated and purified by silica chromatography to yield N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyridine-3-carboxamide (**52**). MS *m/z* 506.1 $(M+1)^+$.

N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-((trimethylsilyl)ethynyl)imidazo[1,2-a]pyridine-3-carboxamide (**52**) (50 mg, 0.1 mmol) was dissolved in MeOH (1 mL) and K_2CO_3 (42 mg, 0.3 mmol) was added. The resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with water (20 mL). The resulting precipitate was filtered and dried to give N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-ethynylimidazo[1,2-a]pyridine-3-carboxamide (**53**). MS *m/z* 434.1 $(M+1)^+$.

Synthesis of 6-(((triisopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**61**)



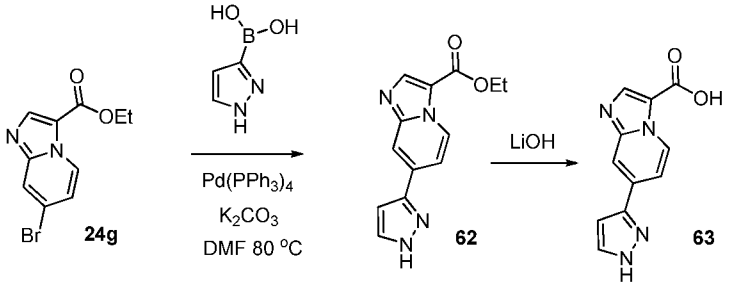
To a stirring suspension of (6-aminopyridin-3-yl)methanol (1.24 mg, 10.0 mmol) and ethyl 2-chloro-3-hydroxyacrylate, potassium salt (**29**) (3.76 g, 20.0mmol) in EtOH (10 mL) at room temperature was added conc sulfuric acid (10.0 mmol) dropwise. The reaction mixture was stirred at room temperature for 15 minutes and pyridine (0.92 g, 12.0 mmol) was added. The resulting mixture was heated at 85 °C overnight. The reaction was

cooled to room temperature and the solvent was concentrated. The residue was taken in water and the solution was adjusted to pH 8 with saturated sodium bicarbonate. The crude product was extracted with ethyl acetate. The organic layer was washed with brine and dried over anhydrous sodium sulfate. The crude product ethyl 6-(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxylate (**59**) was purified by silica chromatography. ^{1}H NMR (400MHz, d_6-DMSO) δ 9.16 (d, J = 6.8 Hz, 1H), 8.26 (s, 1H), 7.67 (s, 1H), 7.19 (dd, J = 1.6, 6.8 Hz, 1H), 5.57 (t, J = 6.4 Hz, 1H), 4.63 (d, J = 6.0, 2H), 4.36 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 6.8 Hz, 3H). MS *m/z* 221.1 $(M+1)^+$.

To a suspension of ethyl 6-(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxylate (**59**) (497.0 mg, 2.26 mmol), DMAP (12.2 mg, 0.1 mmol) and 1H-imidazole (154.0 mg, 2.26 mmol) in dichloromethane (10 mL), was added TIPSCl (523.0 mg, 2.71 mmol). The resulting mixture was stirred overnight at room temperature. The solvent was removed under vacuum to yield crude ethyl 6-(((triisopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxylate (**60**). MS *m/z* 377.2 $(M+1)^+$.

The crude ethyl 6-(((triisopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxylate (**60**) obtained above was dissolved in THF/MeOH/H2O (3:2:1, 5 mL). 6N LiOH (2.27 mL, 13.6 mmol) was added and the reaction mixture was stirred at room temperature for 2 hours. All solvents were removed and 6N HCl was added until pH 5-6. EtOAc (5 mL) was added and the mixture was stirred for 1 hour. The precipitate was filtered and dried to give 6-(((triisopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**61**). ^{1}H NMR (400MHz, d_6-DMSO) δ 9.37 (s, 1H), 8.21 (s, 1H), 7.76 (dd, J = 1.2, 9.2 Hz, 1H), 7.46 (dd, J = 2.0, 9.2 Hz, 1H), 4.94 (s, 2H), 1.20 (m, 3H), 1.08 (d, J = 6.8 Hz, 18H). MS *m/z* 349.2 $(M+1)^+$.

Synthesis of 7-(1H-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (**63**)

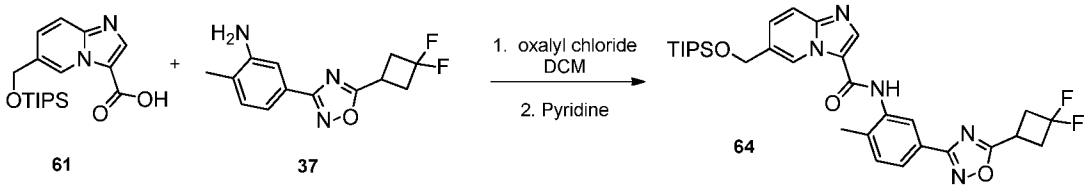


To a solution of 5-ethyl 7-bromoimidazo[1,2-a]pyridine-3-carboxylate **24g** (202 mg, 0.75 mmol) in DMF (2 mL) was added (1H-pyrazol-3-yl)boronic acid (101 mg, 0.903 mmol), 1.8 M K_2CO_3 (1.3 mL, 2.26 mmol) and $Pd(PPh_3)_4$ (87 mg, 0.075 mmol). The reaction was evacuated and backfilled with nitrogen twice then heated at 160 ºC for 10 minutes in a microwave oven. After the reaction mixture was filtered through a pad of Celite, the mixture was diluted with a saturated solution of NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated

to give ethyl 7-(1H-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxylate (**62**). MS (*m/z*) 257.1 $(M+1)^+$.

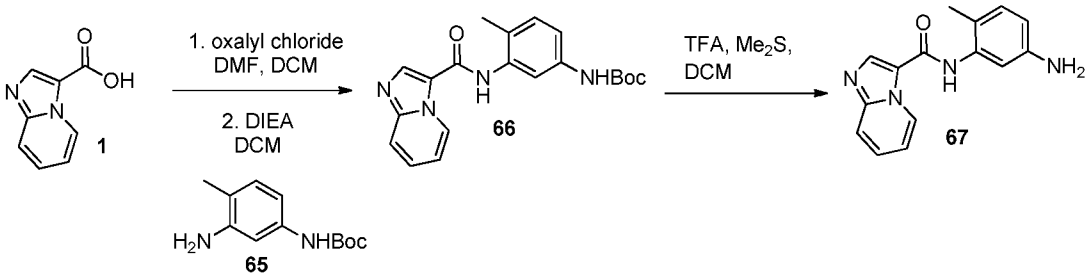
To a stirring solution of ethyl 7-(1H-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxylate (**62**) (103 mg, 0.4 mmol) in THF:MeOH:H_2O (3:2:1, 1.6 mL) was added 6N LiOH (0.035 mL). The reaction was stirred at room temperature for 20 minutes. The pH was adjusted between 4-5 with 3N HCl. The resulting mixture was concentrated to yield 7-(1H-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (**63**). MS (*m/z*) 229.2 $(M+1)^+$.

Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(((triisopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxamide (**64**)



To a stirring suspension of 6-(((triisopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**61**) (260 mg, 0.74 mmol) in anhydrous dichloromethane (5 mL) at room temperature oxalyl chloride was added dropwise (0.19 mL, 2.22 mmol). Then, one drop of anhydrous DMF was added and the reaction mixture was stirred at room temperature for 15 minutes. The solvent was concentrated and the crude solid was added to a stirring solution of 5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**37**) (180 mg, 0.74 mmol) in anhydrous pyridine (5 mL) at room temperature. The reaction was stirred for 20 minutes and the solvent was removed to afford residue. To the above residue was added water (20 mL) and sonicated to give precipitate. Then the precipitate was filtered, dried in air and purified by silica chromatography to afford N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(((triisopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxamide (**64**). MS *m/z* 596.3 $(M+1)^+$.

Synthesis of N-(5-amino-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**67**)

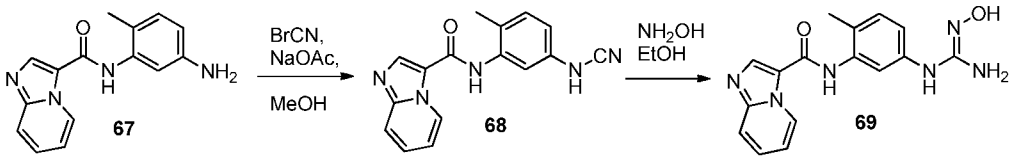


Oxalyl chloride (10 mL) was added dropwise to a stirred solution of imidazo[1,2-a]pyridine-3-carboxylic acid (**1**) (3 g, 18.5 mmol) in dry dichloromethane (100 mL) and a

few drops of DMF. The resulting solution was stirred at room temperature for 5 hours before it was evaporated to dryness and fresh dichloromethane was added to the resulting acid chloride to make a suspension. In a separate flask, tert-butyl 3-amino-4-methylphenylcarbamate (**65**) (4.5 g, 20.3 mmol) and DIEA (10 mL) was dissolved in dichloromethane (100 mL) and the above acid chloride solution was added slowly. The resulting solution was stirred overnight at room temperature. Saturated NH_4Cl was added to the reaction solution and the phases were separated. The organic layer was dried over Na_2SO_4 and filtered. After evaporation, the residue was purified over silica gel column using hexane and EtOAc to give tert-butyl 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenylcarbamate (**66**) as a slightly yellow solid.

TFA (50 mL) was added to a stirred suspension of tert-butyl 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenylcarbamate (**66**) in Me_2S (5 mL) and dichloromethane (10 mL). After 2 hours the solution was evaporated and partitioned with dichloromethane and saturated $NaHCO_3$. The aqueous layer was extracted several times with dichloromethane and the combined organic layers were dried over Na_2SO_4. N-(5-amino-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**67**) was isolated and used without further purification. ^{1}H NMR (400MHz, $CDCl_3$) δ 9.44 (d, J = 6.8 Hz, 1 H), 8.05 (s, 1 H), 7.67 (d, J = 8.8 Hz, 1 H), 7.38 – 7.33 (m, 2 H), 6.98 – 6.94 (m, 2 H), 2.19 (s, 3 H). MS m/z 267.1 $(M+1)^+$.

Synthesis of (E)-N-(5-(2-hydroxyguanidino)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**69**)

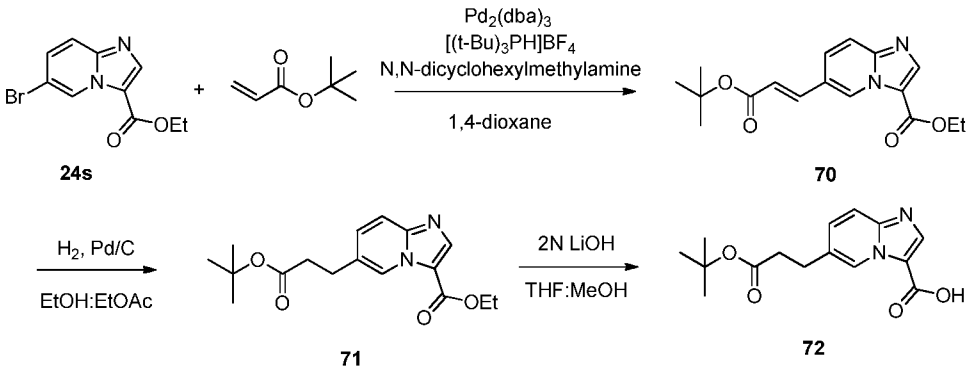


To N-(5-amino-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**67**) (4.53 g, 15 mmol) in MeOH (100 mL) was added KOAc (4.41 g, 45 mmol) and the mixture was stirred at room temperature for 5 minutes then cooled to 0 °C before a solution of BrCN (1.62 g, 15 mmol) in MeOH (30 mL) was added dropwise. The resulting mixture was slowly warmed to room temperature and stirred overnight. The solvent was evaporated and to the residue was added water (150 mL). The mixture was stirred at room temperature for 1 hour, filtered and washed with water (2 x 20 mL), then air dried to give N-(5-cyanamido-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**68**) as a white solid.

To a suspension of N-(5-cyanamido-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**68**) 3.52 g (12.1mmol) in 200 mL of EtOH was added 0.75 mL NH_2OH (50 wt% in water, 12.1 mmol). The resulting mixture was stirred at room temperature

overnight. The precipitate was filtered, washed with EtOH (10 mL) and air dried to give N-(5-(2-hydroxyguanidino)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**69**) as a white solid, which was used directly in the next step without further purification. ^{1}H NMR (400MHz, *d*6-DMSO) δ 9.44 (s, 1H), 9.46 (dd, *J* = 6.8, 0.8 Hz, 1 H), 8.54 (s, 1 H), 8.34 (s, 1 H), 7.76 (dd, *J* = 7.2, 2.2 Hz, 1 H), 7.59 (s, 1 H), 7.52 – 7.43 (m, 2 H), 7.18 – 7.06 (m, 2 H), 2.13 (s, 3 H). MS *m/z* 325.1 $(M+1)^+$.

Synthesis of 6-(3-(*tert*-butoxy)-3-oxopropyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**72**)



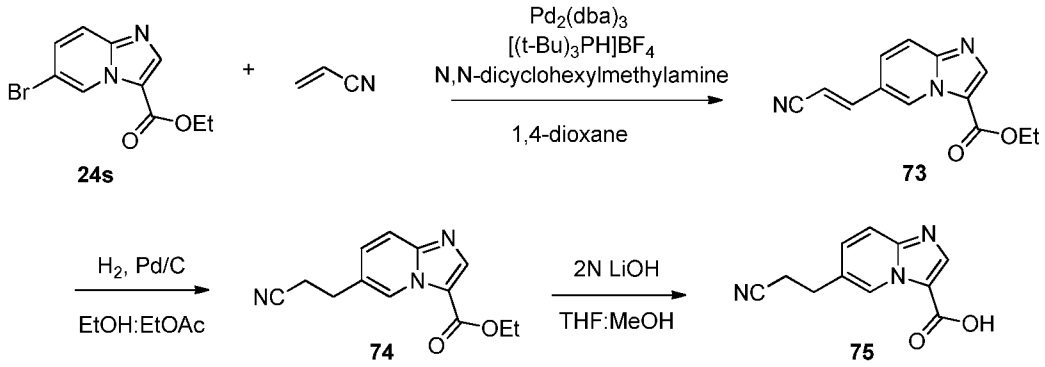
A stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (**24s**) (500 mg, 1.86 mmol), tert-butyl acrylate (408 uL, 2.79 mmol), tris(dibenzylideneacetone)diplalladium(0) (51 mg, 0.056 mmol), $[(t\text{-}Bu)_3PH]BF_4$ (27 mg, 0.093 mmol) and N,N-dicyclohexylmethylamine (738 uL, 3.48 mmol) in anhydrous 1,4-dioxane (5 mL) was heated at 95 °C overnight. The reaction was cooled to room temperature and filtered. The solvent was concentrated and the crude product was purified by silica chromatography to yield ethyl 6-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)imidazo[1,2-a]pyridine-3-carboxylate (**70**). MS *m/z* 317.14 $(M+1)^+$.

A stirring mixture of ethyl 6-(3-(tert-butoxy)-3-oxoprop-1-en-1-yl)imidazo[1,2-a]pyridine-3-carboxylate (**70**) (460 mg, 1.80 mmol) and 10 wt% Pd/C (wet) in ethanol:ethylacetate (1:1, 10 mL) was hydrogenated overnight. The reaction was filtered over celite and the solvent was concentrated. Crude ethyl 6-(3-tert-butoxy-3-oxopropyl)imidazo[1,2-a]pyridine-3-carboxylate (**71**) was used in the next step without further purification. MS *m/z* 319.16 $(M+1)^+$.

A stirring mixture of ethyl 6-(3-tert-butoxy-3-oxopropyl)imidazo[1,2-a]pyridine-3-carboxylate (**71**) (400 mg, 1.26 mmol) and 2N LiOH (1 mL) in THF:MeOH (4:1, 4 mL) was heated at 60 °C for 30 minutes. The reaction was cooled to room temperature and the pH was adjusted between 3-5 with 10% citric acid. The solvent was partially reduced. The resulting solid was collected by vacuum filtration and washed with excess water. Crude 6-(3-(*tert*-butoxy)-3-oxopropyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**72**) was dried and used in the next step without further purification. ^{1}H NMR (400MHz, d_6-DMSO)

δ 9.11 (s, 1 H), 8.20 (s, 1 H), 7.72 (dd, *J* = 0.8, 9.2 Hz, 1 H), 7.50 (dd, *J* = 1.6, 9.2 Hz, 1 H), 2.91 (t, *J* = 6.8 Hz, 2 H), 2.60 (t, *J* = 7.2, 2 H), 1.33 (s, 9 H). MS *m/z* 291.13 $(M+1)^+$.

Synthesis of 6-(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**75**)

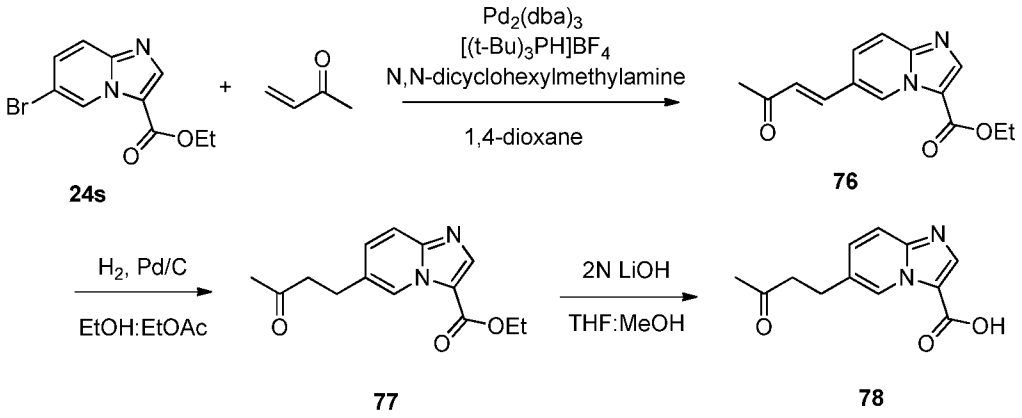


A stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (**24s**) (250 mg, 0.929 mmol), acrylonitrile (92 uL, 1.39 mmol), tris(dibenzylideneacetone)diplalladium(0) (26 mg, 0.0279 mmol), $[(t\text{-}Bu)_3PH]BF_4$ (13 mg, 0.0465 mmol) and N,N-dicyclohexylmethylamine (217 uL, 1.02 mmol) in anhydrous 1,4-dioxane (4 mL) was heated at 95 °C overnight. The reaction was cooled to room temperature and filtered. The solvent was concentrated and crude 6-(2-cyanovinyl)imidazo[1,2-a]pyridine-3-carboxylate (**73**) was purified by silica chromatography. MS *m/z* 242.09 $(M+1)^+$.

A stirring mixture of ethyl 6-(2-cyanovinyl)imidazo[1,2-a]pyridine-3-carboxylate (**73**) (115 mg, 0.451 mmol) and 10 wt% Pd/C (wet) in ethanol:ethylacetate (1:1, 5 mL) was hydrogenated overnight. The reaction was filtered over celite and the solvent was removed. Crude ethyl 6-(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxylate (**74**) was used in the next step without further purification. MS *m/z* 244.10 $(M+1)^+$.

A stirring mixture of ethyl 6-(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxylate (**74**) (100 mg, 0.411 mmol) and 2N LiOH (0.2 mL) in THF:MeOH (4:1, 3 mL) was heated at 50 °C for 45 minutes. The reaction was cooled to room temperature and the pH was adjusted between 3-5 with 10% citric acid. The solvent was partially reduced. The resulting solid was collected by vacuum filtration and washed with excess water. Crude 6-(2-cyanoethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**75**) was dried and used in the next step without further purification. MS *m/z* 416.07 $(M+1)^+$.

Synthesis of 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**78**)



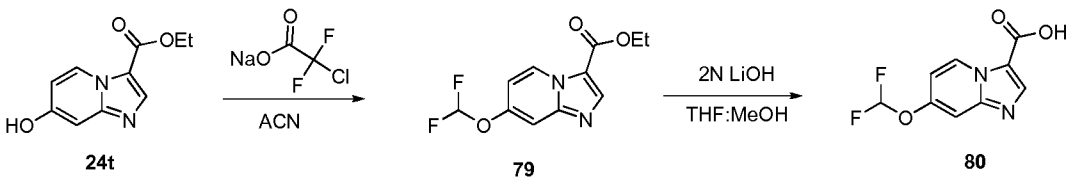
24s 76 77 78

A stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (**24s**) (250 mg, 0.929 mmol), methyl vinyl ketone (151 uL, 1.86 mmol), tris(dibenzylideneacetone)diplalladium(0) (26 mg, 0.0279 mmol), $[(t\text{-}Bu)_3PH]BF_4$ (13 mg, 0.0465 mmol) and N,N-dicyclohexylmethylamine (217 uL, 1.02 mmol) in anhydrous 1,4-dioxane (4 mL) was heated at 95°C overnight. The reaction was cooled to room temperature and filtered. The solvent was concentrated and crude 6-(3-oxobut-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate (**76**) was purified by silica chromatography. MS *m/z* 259.10 $(M+1)^+$.

A stirring mixture of ethyl 6-(3-oxobut-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate (**76**) (200 mg, 0.774 mmol) and 10 wt% Pd/C (wet) in ethanol:ethylacetate (1:1, 8 mL) was hydrogenated overnight. The reaction was filtered over celite and the solvent was concentrated. Crude 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylate (**77**) was used in the next step without further purification. MS *m/z* 261.12 $(M+1)^+$.

A stirring mixture of ethyl 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylate (**77**) (190 mg, 0.730 mmol) and 2N LiOH (0.2 mL) in THF:MeOH (4:1, 3 mL) was heated at 50°C for 45 minutes. The reaction was cooled to room temperature and the pH was adjusted between 3-5 with 10% citric acid. The solvent was partially reduced. The resulting solid was collected by vacuum filtration and washed with excess water. Crude 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**78**) was dried and used in the next step without further purification. MS *m/z* 233.08 $(M+1)^+$.

Synthesis of 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**80**)



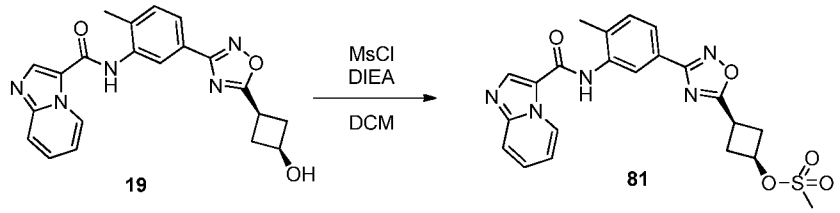
24t 79 80

A mixture of ethyl 7-hydroxyimidazo[1,2-a]pyridine-3-carboxylate (**24t**) (500 mg, 2.43 mmol) and sodium chlorodifluoroacetate (444 mg, 2.91 mmol) in anhydrous acetonitrile

(8 mL) was heated in the microwave at 125 °C for 12 minutes. The solvent was concentrated and the crude product ethyl 7-(difluoromethoxy)imidazo[1,2-a]pyridine-3-carboxylate (**79**) was purified by silica chromatography. MS *m/z* 257.07 $(M+1)^+$.

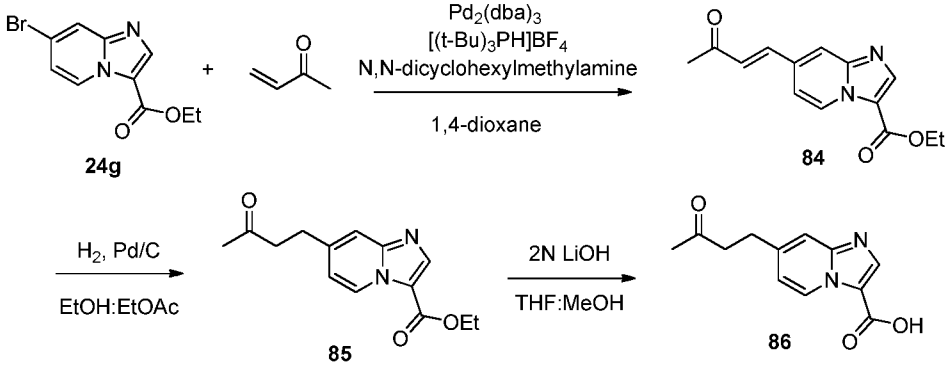
A stirring mixture of ethyl 7-(difluoromethoxy)imidazo[1,2-a]pyridine-3-carboxylate (**79**) (150 mg, 0.585 mmol) and 2N LiOH (1 mL) in THF:MeOH (4:1, 5 mL) was heated at 60 °C for 45 minutes. The reaction was cooled to room temperature and the pH was adjusted between 4-5 with 1N HCl. The solvent was partially reduced and the crude product was purified by reverse phase preparative HPLC to yield 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**80**). MS *m/z* 229.03 $(M+1)^+$.

Synthesis of 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)cyclobutyl methanesulfonate (**81**)



To a stirring suspension of N-(5-(5-(3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (220 mg, 0.565 mmol) (**19**) in anhydrous DCM (10 mL) at 0 °C was added DIEA (197 uL, 1.13 mmol) and methanesulfonyl chloride (542 uL, 0.678 mmol). The reaction was stirred to room for 30 minutes. The crude product was purified by silica chromatography to give 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)cyclobutyl methanesulfonate (**81**). MS *m/z* 468.13 $(M+1)^+$.

Synthesis of 7-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**86**)



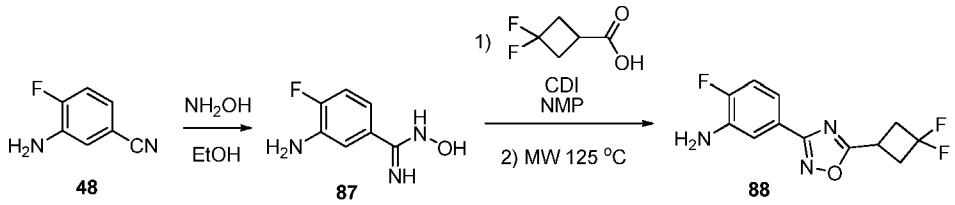
A stirring mixture of ethyl 7-bromoimidazo[1,2-a]pyridine-3-carboxylate (**24g**) (500 mg, 1.86 mmol), methyl vinyl ketone (301 uL, 3.72 mmol), tris(dibenzylideneacetone)diplalladium(0) (51 mg, 0.056 mmol), $[(t\text{-}Bu)_3PH]BF_4$ (27 mg, 0.093 mmol) and N,N-dicyclohexylmethylamine (433 uL, 2.04 mmol) in anhydrous 1,4-

dioxane (10 mL) was heated at 95 °C overnight. The reaction was cooled to room temperature and filtered. The solvent was concentrated and crude ethyl 7-(3-oxobut-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate (**84**) was purified by silica chromatography. MS *m/z* 259.10 $(M+1)^+$.

A stirring mixture of ethyl 7-(3-oxobut-1-enyl)imidazo[1,2-a]pyridine-3-carboxylate (**84**) (92 mg, 0.356 mmol) and 10 wt% Pd/C (wet) in ethanol:ethylacetate (1:1, 8 mL) was hydrogenated overnight. The reaction was filtered over celite and the solvent was concentrated. Crude ethyl 7-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylate (**85**) was used in the next step without further purification. MS *m/z* 261.12 $(M+1)^+$.

A stirring mixture of ethyl 7-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylate (**85**) (90 mg, 0.346 mmol) and 2N LiOH (0.5 mL) in THF:MeOH (4:1, 3 mL) was heated at 60 °C for 45 minutes. The reaction was cooled to room temperature and the pH was adjusted between 3-5 with 10% citric acid. The solvent was partially concentrated and the crude product was purified by reverse phase preparative HPLC to yield 7-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**86**). MS *m/z* 233.08 $(M+1)^+$.

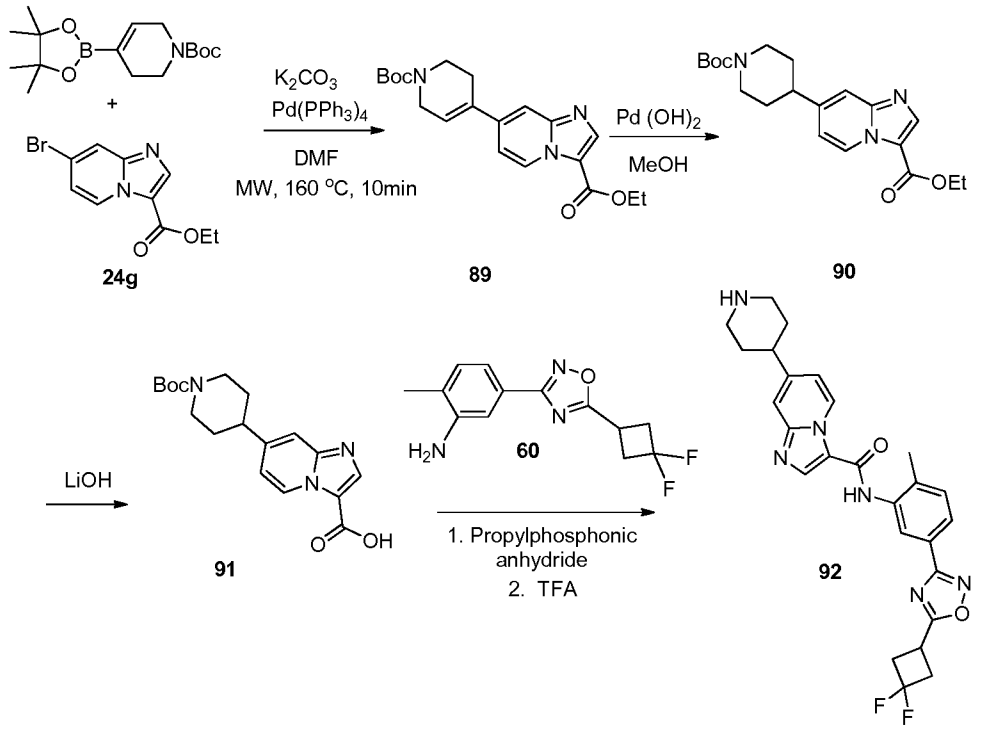
Synthesis of 5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-fluoroaniline (**88**)



NH_2OH (50% wt in water, 3.5 mL, 60.0 mmol) was added in one portion to a stirred suspension of 3-amino-4-fluorobenzonitrile (**48**) (1.36 g, 10.0 mmol) in EtOH (25 mL). The resulting suspension was heated at 70 °C for overnight and then the solvent was removed to yield 3-amino-4-fluoro-N-hydroxybenzimidamide (**87**), MS *m/z* 170.1 $(M+1)^+$.

To a solution of 3,3-difluorocyclobutanecarboxylic acid (0.90 g, 6.6 mmol) in NMP (5 mL) was slowly added CDI (1.07 g, 6.6 mmol). The resulting mixture was stirred at room temperature for 30 minutes. Then 3-amino-4-fluoro-N-hydroxybenzimidamide (**87**) (0.56 g, 3.3 mmol) was added and stirred for another 30 minutes until LCMS indicated complete reaction. The mixture was then heated at 125 °C for 15 minutes in a microwave reactor and poured into water (100 mL). The mixture was extracted with EtOAc (2 x 50 mL), dried over Na_2SO_4, filtered and concentrated to give a crude product which was purified by silica-gel chromatography (0-60 % EtOAc in hexanes) to afford 5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-fluoroaniline (**88**). ^1H NMR (400MHz, $CDCl_3$) δ 7.53 (dd, *J* = 2.0, 8.4 Hz, 1H), 7.43-7.48 (m, 1H), 7.10 (dd, *J* = 10.8, 8.4 Hz, 1H), 3.90 (br, 2H), 3.67 (m, 1H), 3.09-3.18 (m, 4H). MS *m/z* 270.1 $(M+1)^+$.

Synthesis N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-(piperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (**92**)



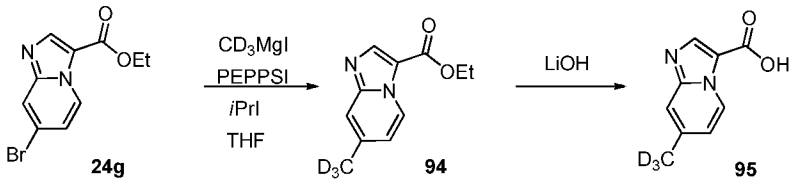
To a solution of 5-ethyl 7-bromoimidazo[1,2-a]pyridine-3-carboxylate (**24g**) (300 mg, 1.11 mmol) in DMF (9 mL) was added tert-butyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5,6-dihydropyridine-1(2H)-carboxylate (414 mg, 1.34 mmol), K_2CO_3 (1.8M, 1.85 mL, 3.33 mmol) and $Pd(PPh_3)_4$ (87 mg, 0.11 mmol). The reaction was evacuated and backfilled with nitrogen twice then heated at 160 ºC for 10 minutes via microwave. After the reaction mixture was filtered through a pad of Celite, the mixture was diluted with a saturated solution of NH_4Cl and extracted with ethyl acetate. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated to give crude ethyl 7-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridine-3-carboxylate (**89**) (MS (*m/z*) 372.1 $(M+1)^+$.

H_2 (balloon) was introduced to a stirred mixture of $Pd(OH)_2/C$ (0.055 g) and ethyl 7-(1-(tert-butoxycarbonyl)-1,2,3,6-tetrahydropyridin-4-yl)imidazo[1,2-a]pyridine-3-carboxylate (**89**) (0.55 g, 1.48 mmol) in MeOH (5 mL). After 6 hours, the mixture was filtered through a pad of Celite and the solvent was evaporated to give the crude product. The residue was purified over silica using EtOAc and hexanes to give ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxylate (**90**). ^1H NMR (400MHz, CD_2Cl_2) δ 9.27 (d, J = 7.2 Hz, 1H), 8.27 (s, 1H), 7.64 (s, 1H), 7.04 (dd, J =1.6, 7.2 Hz, 1H), 4.43 (q, J = 7.2 Hz, 2H), 4.31 (m, 2H), 2.87 (m, 1H), 2.83 (m, 2H), 1.95 (m, 2H), 1.67 (m, 2H), 1.49 (s, 9H), 1.43 (t, J = 7.2 Hz, 3H) . MS *m/z* 374.2 $(M+1)^+$.

To a stirring suspension of ethyl 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxylate (**90**) (84 mg, 0.23 mmol) in THF:MeOH:H_2O (3:2:1, 1 mL) was added 6N LiOH (0.13 mL). The reaction was stirred at room temperature for 2.5 hours then neutralized with NH_4Cl and concentrated to afford 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (**91**) which was immediately used without purification. MS (*m/z*) 346.1 $(M+1)^+$.

To a stirring solution of 7-(1-(tert-butoxycarbonyl)piperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (**91**) (124 mg, 0.36 mmol), and 5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**60**) (96 mg, 0.36 mmol) in ethyl acetate (0.3 mL) was added propylphosphonic anhydride (50 wt % in ethyl acetate 1.07 mL). The reaction was heated at 90 °C for 12 hours. The resulting mixture was diluted in ethyl acetate and washed with 1N Na_2CO_3. The product stayed in aqueous layer and was concentrated to afford tert-butyl 4-(3-((5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)carbamoyl)imidazo[1,2-a]pyridin-7-yl)piperidine-1-carboxylate. The solid was taken up in trifluoroacetic acid and stirred for 25 minutes. The solvent was concentrated and placed under high vacuum to yield N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-(piperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (**92**). MS (*m/z*) 493.1 $(M+1)^+$.

Synthesis of 7-methyl-d_3-imidazo[1,2-a]pyridine-3-carboxylic acid (**95**)

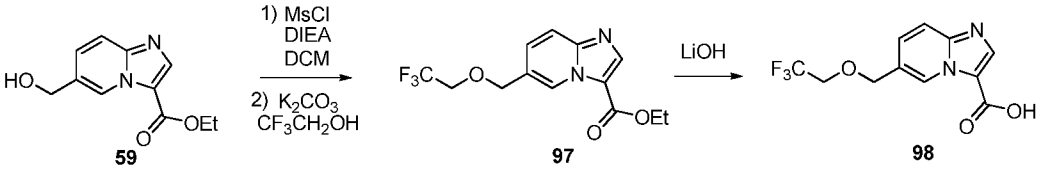


To a stirring solution of ethyl 7-bromoimidazo[1,2-a]pyridine-3-carboxylate (**24g**) (500 mg, 1.86 mmol), PEPPSI (63.2mg, 0.093 mmol) and 2-iodopropane (928 uL, 9.3 mmol) in anhydrous THF (3 mL) at 0°C under a stream of nitrogen was added methyl-d_3-magnesium iodide (5.6 mL, 5.57 mmol). The reaction was stirred to room temperature for 5 hours. Then, the reaction was quenched with NH_4Cl. The crude product was extracted with ether, washed with water and brine and dried over sodium sulfate. The product was purified on silica gel using 10% MeOH in dichloromthane to yield ethyl 7-methyl-d_3-imidazo[1,2-a]pyridine-3-carboxylate (**94**). ^1H NMR (400MHz, d_6-DMSO) δ 8.85 (dd, *J* = 0.4, 7.0 Hz, 1H), 7.98 (s, 1H), 7.36 (s, 1H), 6.86 (dd, *J* =1.6, 7.2 Hz, 1H), 4.10 (q, *J* = 7.2 Hz, 2H), 1.09 (t, *J* = 7.2 Hz, 3H). MS *m/z* 208.1 $(M+1)^+$.

To a stirring suspension of ethyl 7-methyl-d_3-imidazo[1,2-a]pyridine-3-carboxylate (**94**) (142 mg, 0.69 mmol) in THF: MeOH: H_2O (3:2:1, 3 mL) was added 6N LiOH (0.34 mL). The reaction was stirred at room temperature for 2 hours then neutralized with

sodium bisulfate monohydrate and concentrated to afford 7-methyl-d_3-imidazo[1,2-a]pyridine-3-carboxylic acid (**95**), which was immediately used without purification. MS (*m/z*) 180.1 $(M+1)^+$.

Synthesis of 6-((2,2,2-trifluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**98**)

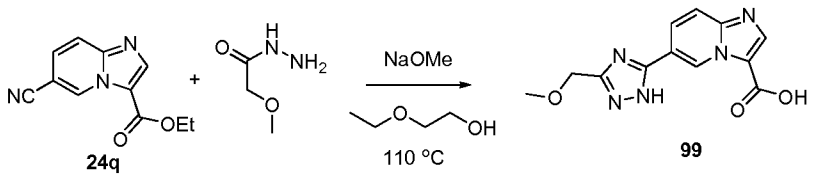


59 **97** **98**

To a soultion of ethyl 6-(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxylate (**59**) (460 mg, 2.2 mmol) and DIEA (0.78 mL, 4.4 mmol) in DCM (5 mL) was added MsCl (303 mg, 2.64 mmol). The mixture was stirred at room temperature for 10 minutes then subjected to standard aqueous work up to give a residue. The crude product was dissolved in 2,2,2-trifluoroethanol (2 mL) and and was added K_2CO_3 (608 mg, 4.4 mmol). The reaction mixture was heated at 80 °C for 2 hours. Once complete, the reaction mixture was diluted and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to afford a residue which was purified by silica chromatography to yield ethyl 6-((2,2,2-trifluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxylate (**97**). ^{1}H NMR (400MHz, $CDCl_3$) δ 9.33 (m, 1H), 8.32 (s, 1H), 7.76 (dd, *J* = 0.8, 9.2 Hz, 1H), 7.47 (dd, *J* = 2.0, 9.2 Hz, 1H), 4.76 (s, 2H), 4.44 (q, *J* = 7.2 Hz, 2H), 3.92 (q, *J* = 8.4 Hz, 2H), 1.45 (t, *J* = 7.2 Hz, 3H). MS *m/z* 303.1 $(M+1)^+$.

A solution of ethyl 6-((2,2,2-trifluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxylate (**97**) (280 mg, 0.92 mmol) in THF/MeOH/H_2O (3:2:1, 5 mL) was treated with 6N LiOH (0.92 mL, 5.52 mmol) and stirred at room temperature for 1 hour. All solvents were removed and 6N HCl was added to adjust pH 5-6. Then the mixture was purified by HPLC to give 6-((2,2,2-trifluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**98**). ^{1}H NMR (400MHz, d_6-DMSO) δ 9.34 (m, 1H), 8.40 (s, 1H), 7.88 (dd, *J* = 0.8, 9.2 Hz, 1H), 7.65 (dd, *J* = 1.6, 9.2 Hz, 1H), 4.83 (s, 2H), 4.18 (q, *J* = 9.6 Hz, 2H). MS *m/z* 275.1 $(M+1)^+$.

Synthesis of 6-(3-(methoxymethyl)-1H-1,2,4-triazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (**99**)

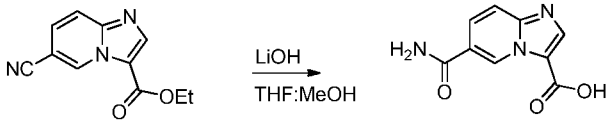


24q **99**

To a solution of ethyl 6-cyanoimidazo[1,2-a]pyridine-3-carboxylate (**24q**) (265 mg, 1.23 mmol) and 2-methoxyacetohydrazide (193 mg, 1.85 mmol) in 2-ethoxyethanol (5

mL) was added NaOMe (0.5 M in MeOH, 3.7 mL). The mixture was heated at 110 °C in a sealed vial overnight. The reaction mixture was purified by HPLC to give 6-(3-(methoxymethyl)-1H-1,2,4-triazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (**99**). MS *m/z* 274.1 $(M+1)^+$.

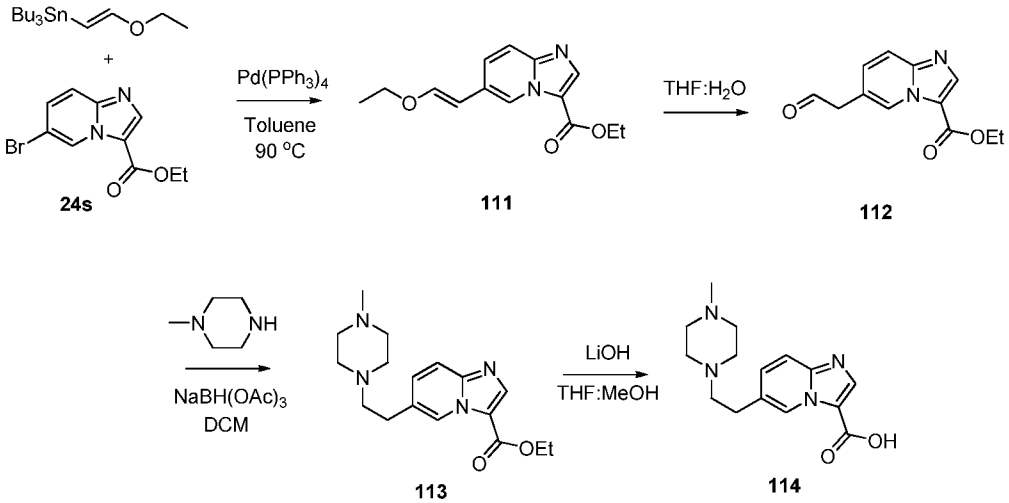
Synthesis of 6-carbamoylimidazo[1,2-a]pyridine-3-carboxylic acid (**110**)



24q **110**

To a stirring solution of ethyl 6-cyanoimidazo[1,2-a]pyridine-3-carboxylate (**24q**) (500 mg, 2.32 mmol) in THF:MeOH (4:1, 5 mL) was added 2N LiOH (4 mL). The reaction was heated at 60 °C for 2 h then acidified with 10% citric acid. The solvent was partially concentrated and the resulting solid was collected by vacuum filtration and was washed with excess water. The product was purified from the crude solid to afford 6-carbamoylimidazo[1,2-a]pyridine-3-carboxylic acid (**110**). ^{1}H NMR (400MHz, d_6-DMSO) δ 9.80 (s, 1H), 8.33 – 8.31 (m, 1H), 8.29 (s, 1H), 7.95 (dd, *J* = 2.0, 9.6 Hz, 1H), 7.83 (dd, *J* = 0.8, 9.2 Hz, 1H), 7.69 (s, 1H). MS *m/z* 205.05 $(M+1)^+$.

Synthesis of 6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**114**)



24s **111** **112**

113 **114**

To a stirring mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (**24s**) (1 g, 3.72 mmol) and tetrakis(triphenylphosphine)palladium(0) (215 mg, 0.19 mmol) in anhydrous toluene (10 mL) under argon was added tributyl[2-ethoxyethenyl]stannane (1.7 g, 4.65 mmol). The reaction mixture was heated in a microwave sealed tube overnight at 90 °C. The reaction was cooled to room temperature and was filtered

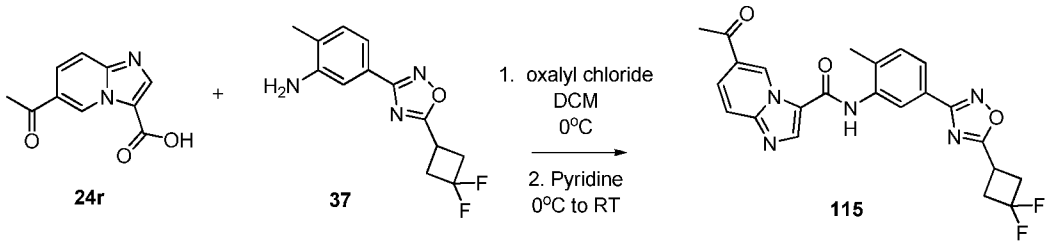
through celite. The solvent was concentrated and the crude product was purified by silica chromatography to afford (E)-ethyl 6-(2-ethoxyvinyl)imidazo[1,2-a]pyridine-3-carboxylate (**111**). MS *m/z* 261.3 $(M+1)^+$.

A stirring solution of ethyl 6-(2-ethoxyvinyl)imidazo[1,2-a]pyridine-3-carboxylate (**111**) (240 mg, 1.15 mmol) in THF:H_2O (1:1, 4 mL) was heated at 50 °C overnight. The reaction was cooled to room temperature and neutralized with saturated solution of sodium bicarbonate. The ccrude product was extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was concentrated and crude ethyl 6-(2-oxoethyl)imidazo[1,2-a]pyridine-3-carboxylate (**112**) was used in the next step without further purification. MS *m/z* 233.3 $(M+1)^+$.

To a stirring solution of crude ethyl 6-(2-oxoethyl)imidazo[1,2-a]pyridine-3-carboxylate (**112**) (214 mg ,0.92 mmol) in DCM (5 mL) and 1-methylpiperazine (231 μL, 2.30 mmol) at room temperature was added portion-wise sodium triacetoxyborohydride (586 mg, 2.77 mmol). The reaction was stirred at room temperature overnight. The solvent was concentrated. The crude was taken in 10% sodium bicarbonate and ethyl acetate. The organic was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was concentrated and the crude product was purified by silica chromatography to afford methyl 6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxylate (**113**). MS *m/z* 304.4 $(M+1)^+$.

To a stirring solution of methyl 6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxylate (**113**) (215 mg, 0.68 mmol) in THF:MeOH (4:1, 4 mL) was added 2N LiOH (3 mL). The reaction was heated at 60 °C for 45 minutes. The pH was adjusted between 4-5 with 1N HCl and concentrated. The crude product was purified by preparative HPLC to affod 6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**114**). ^{1}H NMR (400MHz, d_6-DMSO) δ 9.25 (s, 1H), 8.35 (s, 1H), 7.83 (d, *J* = 9.2 Hz, 1H), 7.61 (dd, *J* = 1.6, 9.2 Hz, 1H), 4.65 – 4.19 (m, 8H), 3.49 – 3.30 (m, 2H), 3.04 – 2.99 (m, 2H), 2.81 (s, 3H). MS *m/z* 316.1 $(M+1)^+$.

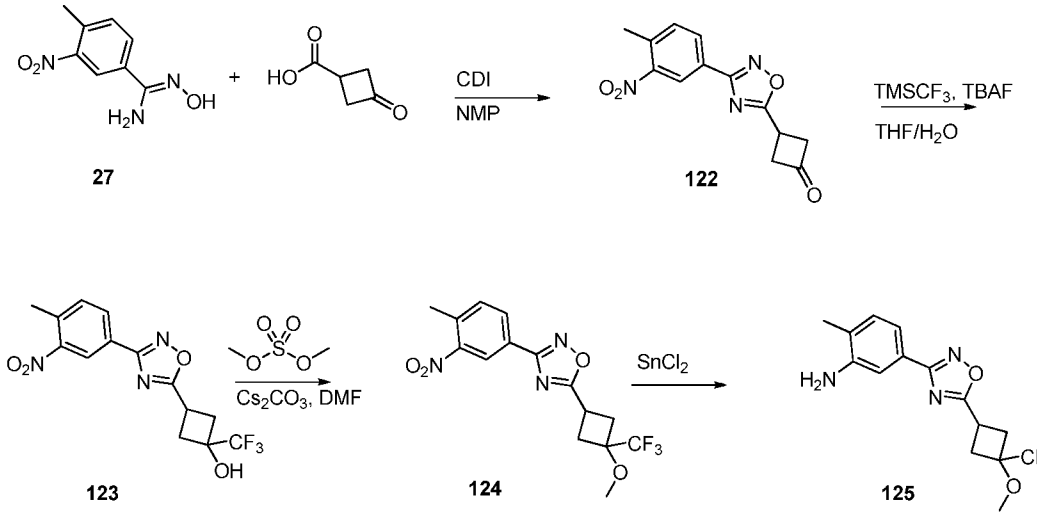
Synthesis of 6-acetyl-N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**115**)



24r **37** **115**

To a stirring suspension of 6-acetylimidazo[1,2-a]pyridine-3-carboxylic acid (**24r**) (71 mg, 0.39 mmol) in dichloromethane (2 mL) was added dropwise oxalyl chloride (173 uL, 1.98 mmol) and a drop of anhydrous N,N-dimethylformamide. The reaction mixture was stirred at room temperature for 30 minutes and concentrated. The residue was treated with 5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**37**) (85 mg, 0.29 mmol) in anhydrous pyridine (2 mL) with stirring at room temperature for 30 minutes. The crude product was purified on silica gel using 10% MeOH in dichloromethane to give 6-acetyl-N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**115**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.24 (s, 1H), 10.13 (s, 1H), 8.70 (s, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.95 (dd, J = 2.0, 9.6 Hz, 1H), 7.88 – 7.84 (m, 2H), 7.52 (d, J = 8.4 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.24 – 3.02 (m, 4H), 2.64 (s, 3H), 2.38 (s, 3H). MS m/z 433.16 $(M+1)^+$.

Synthesis of 5-(5-(3-methoxy-3-(trifluoromethyl)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**125**)



To a stirring solution of 3-oxocyclobutanecarboxylic acid (595 mg, 5.12 mmol) in 1-methyl-2-pyrrolidinone (6 mL) was added 1,1′-carbonyldiimidazole (831 mg, 5.12 mmol). The reaction was stirred for 5 minutes. Then, N'-hydroxy-4-methyl-3-nitrobenzimidamide (**27**) (500 mg, 2.56 mmol) was added and the reaction was stirred for 15 minutes. Next, the reaction was heated in the microwave at 130 °C for 10 minutes. The crude product was taken in ethyl acetate and water. The organic was washed with 2x water/brine mixture and dried over anhydrous sodium sulfate. The solvent was concentrated and the crude product was purified by silica chromatography to afford 3-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)cyclobutanone (**122**). MS m/z 274.07 $(M+1)^+$.

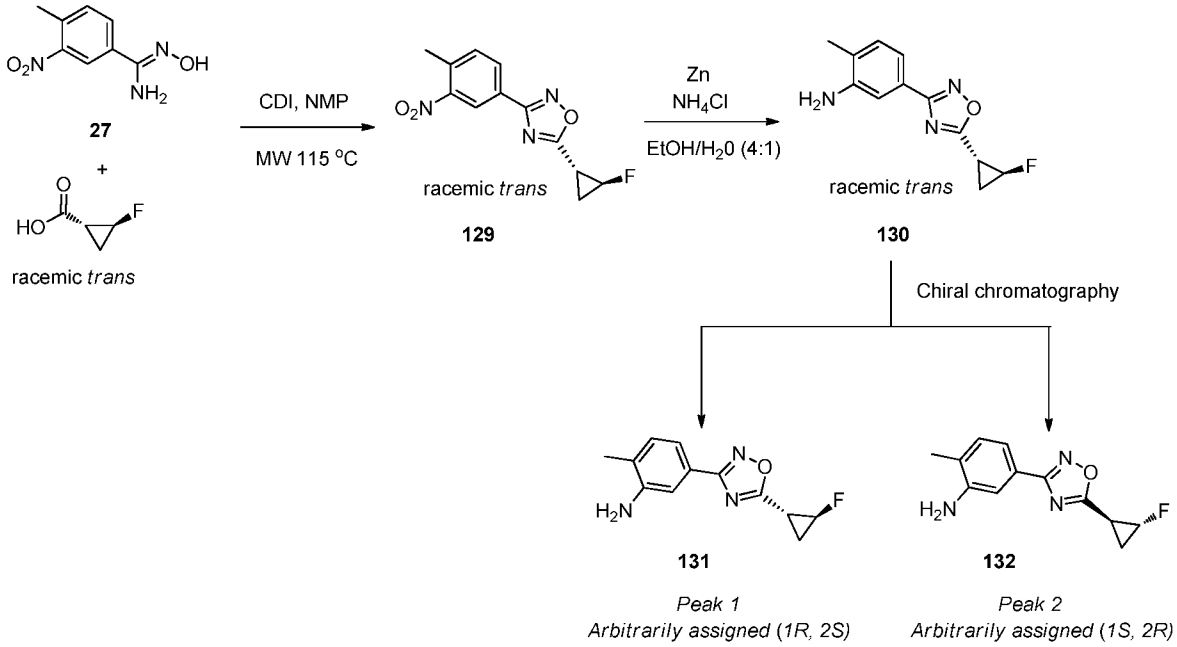
To a stirring solution of 3-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)cyclobutanone (**122**) (250 mg, 0.915 mmol) in anydrous THF (2 mL) at 0 °C was

added TMS-CF3 (429 uL, 2.75 mmol) and TBAF in THF and 5% water (50 uL). The reaction turned a light red color and further deepened with continuous stirring. The reaction was stirred to room temperature for 10 minutes. Then, the reaction was cooled back to 0 °C and TBAF in THF and 5% water (0.4 mL) was slowly added and the reaction was stirred for 25 minutes at room temperature. The reaction turned into a deep purple color. The solvent was concentrated and the crude product 3-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)-1-(trifluoromethyl)cyclobutanol (**123**) was purified by silica chromatography (tlc hexanes:ethylacetate (3:2)). 344.08 $(M+1)^+$.

To a stirring suspension of 3-(3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazol-5-yl)-1-(trifluoromethyl)cyclobutanol (**123**) (65 mg, 0.189 mmol) and cesium carbonate (93 mg, 0.284 mmol) in anhydrous DMF (1 mL) was added dimethyl sulfate (18 L, 0.189 mmol). The reaction was stirred at room temperature overnight. The reaction was poured into a separatory funnel containing water and ethyl acetate. The organic was washed with 2x water/brine mixture and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography. (**124**). MS *m/z* 358.09 $(M+1)^+$.

Step 4. A stirring mixture of 5-(3-methoxy-3-(trifluoromethyl)cyclobutyl)-3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazole (**124**) (40 mg, 0.112 mmol) and tin (II) chloride dihydrate (101 mg, 0.448 mmol) in ethanol (2 mL) was heated at 65 °C for 2 hours. The reaction was cooled to room temperature and the pH was adjusted between 8-10 with saturated sodium bicarbonate. The slurry was filtered and washed with aqueous ethanol. The solvent was partially reduced and the crude product was extracted with ethyl acetate. The organic was washed with 1x water and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography to yield 5-(5-(3-methoxy-3-(trifluoromethyl)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**125**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.24 (s, 1H), 10.13 (s, 1H), 8.70 (s, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.95 (dd, J = 2.0, 9.6 Hz, 1H), 7.88 – 7.84 (m, 2H), 7.52 (d, J = 8.4 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.24 – 3.02 (m, 4H), 2.64 (s, 3H), 2.38 (s, 3H). MS *m/z* 433.16 $(M+1)^+$.

Synthesis of 5-(5-((1R,2S)-2-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline and 5-(5-((1S,2R)-2-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**131** and **132**)



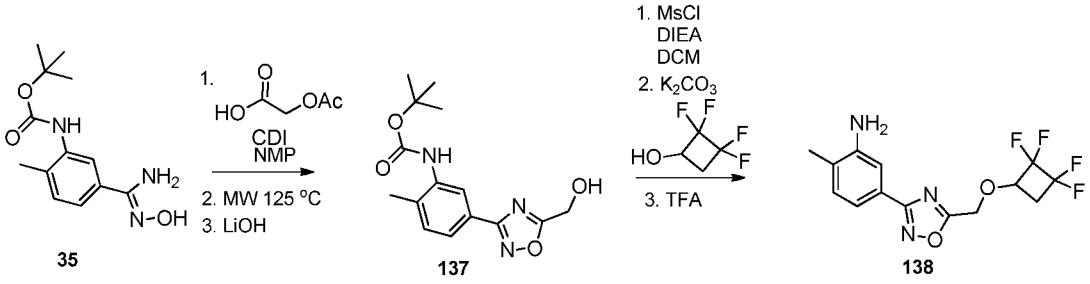
To a stirring solution of *trans*-2-Fluoro-cyclopropanecarboxylic acid (0.38 g, 3.68 mmol) in anhydrous NMP (12 mL) was added 1,1'-carbonyldiimidazole (CDI) (0.59 g, 3.68 mmol). The reaction was stirred for 3 minutes. N'-hydroxy-4-methyl-3-nitrobenzimidamide (**27**) (0.72 g, 3.68 mmol) was added and the reaction was stirred for 25 minutes then heated in the microwave at 120 °C for 15 minutes. The crude product was extracted with ethyl acetate. The organic layer was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was concentrated and the crude product was purified on silica gel using ethyl acetate and hexane to yield 5-(2-fluorocyclopropyl)-3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazole (**129**). MS *m/z* 264.1 $(M+1)^+$.

To a suspenion of 5-(2-fluorocyclopropyl)-3-(4-methyl-3-nitrophenyl)-1,2,4-oxadiazole (**129**) (162 mg, 0.62 mmol) in EtOH:H_20 (4:1) (3.3 mL) was added zinc dust (161 mg, 2.46 mmol) and ammonium chloride (132 mg, 2.46 mmol). The reaction mixture was heated at 85 °C for 24 hours, then filtered hot over celite and rinsed with ethyl acetate. The solvent was concentrated to give 5-(5-(2-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**130**).

The separation of enantiomers was performed using a 21.2 x 250 mm Lux-Cellulose-2 column at a flow rate of 80g/min, using CO_2/Methanol (85: 15) at 30 °C. Analytical methods using the same column and solvent mixture showed peak 1 eluting at 2.80 min, and peak 2 at 3.28 min. Peak 1 was arbitrarily assigned to be the isomer 5-(5-((*1R,2S*)-2-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**131**) and Peak 2 was assigned to be the isomer 5-(5-((*1S,2R*)-2-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2-

methylaniline (**132**). MS *m/z* 234.1 $(M+1)^+$.

Synthesis of 2-methyl-5-(5-((2,2,3,3-tetrafluorocyclobutoxy)methyl)-1,2,4-oxadiazol-3-yl)aniline (**138**)

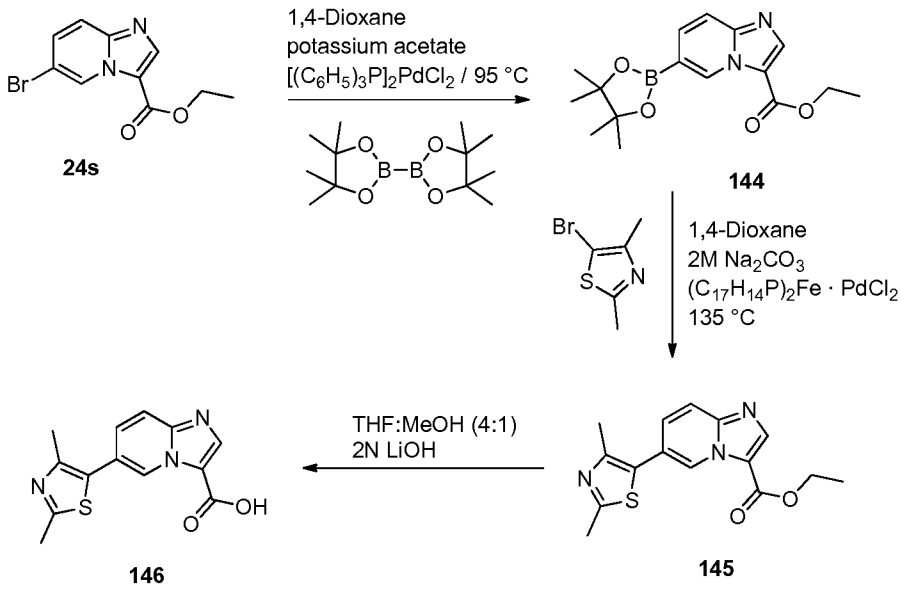


CDI (1.76 g, 10.78 mmol) was added portion-wise to a stirred solution of 2-acetoxyacetic acid (1.27 g, 10.78 mmol) in NMP (5 mL). After 10 minutes, (Z)-tert-butyl 5-(N'-hydroxycarbamimidoyl)-2-methylphenylcarbamate (**35**) (1.43 g, 5.39 mmol) was added in one portion and stirred for another hour at room temperature. The solution was then heated via microwave at 125 °C for 15 minutes. The solution was partitioned with EtOAc and water. The organic phase was separated, dried over Na_2SO_4 and concentrated to give a residue which was dissolved in THF/MeOH/H_2O (3:2:1, 5 mL) and followed by addition of 6N LiOH (5.4 mL). The resulting mixture was stirred for 10 minutes. Then aqueous 2M $NaHCO_3$ (30 mL) was added and the solution was extracted with EtOAc. The organic layers were dried over Na_2SO_4 and concentrated to give a residue which was purified over silica gel to afford tert-butyl (5-(5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)carbamate (**137**). MS *m/z* 306.0 $(M+1)^+$.

Tert-butyl (5-(5-(hydroxymethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)carbamate (**137**) (0.35 g, 1.15 mmol) was dissovled in dichloromethane (5 mL) and followed by addtion of DIEA (0.6 mL, 3.45 mmol) and MsCl (197 mg, 1.72 mmol). The reaction was stirred for 10 minutes. The mixture was diluted with dichloromethane (10 mL) and washed with water. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to give a residue which was dissolved in 2,2,3,3-tetrafluorocyclobutanol (2 mL) and followed by addition of K_2CO_3 (476 mg, 3.45 mmol). The reaction mixture was heated at 90 °C for 2-3 hours. The mixture was diluted with water (10 mL) and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. To this residue was added TFA (1 mL) and stirred for 15 minutes. Then aqueous Na_2CO_3 (2M, 20 mL) was added and extracted with EtOAc. The organic layers were dried over Na_2SO_4, filtered and concentrated. Purification by column chromatography on silica gel gave 2-methyl-5-(5-((2,2,3,3-tetrafluorocyclobutoxy)methyl)-1,2,4-oxadiazol-3-yl)aniline (**138**). ^1H NMR (400MHz, $CDCl_3$) δ 9.36 (bs, 2H), 8.12 (d, *J* = 1.2 Hz, 1H), 7.91 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.40 (d, *J*

= 8.4 Hz, 1H), 4.95 (dd, *J* = 14.4, 68.4 Hz, 2H), 4.51 (m, 1H), 2.95 (m, 1H), 2.51-2.68 (m, 4H). MS *m/z* 332.0 $(M+1)^+$.

Synthesis of 6-(2,4-dimethylthiazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylic acid (**146**)



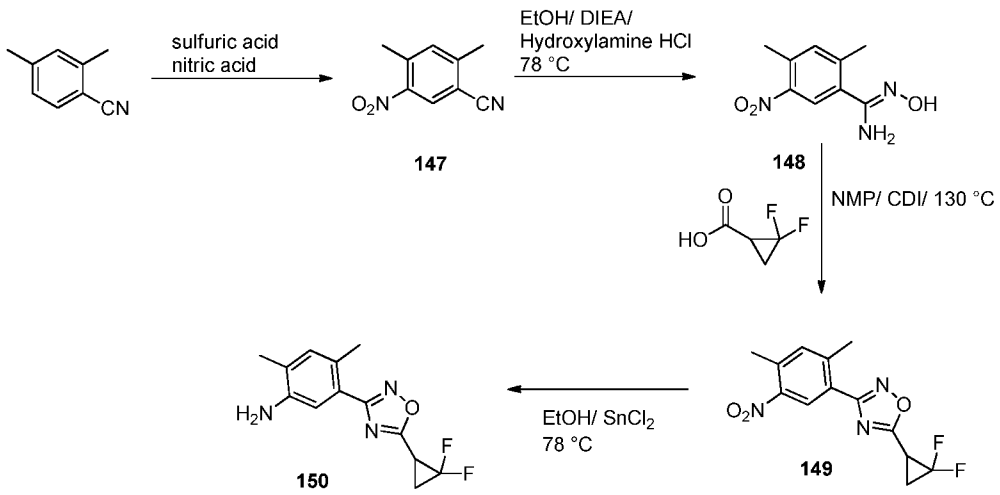
A mixture of ethyl 6-bromoimidazo[1,2-a]pyridine-3-carboxylate (**24s**) (500 mg, 1.86 mmol), bis(pinacolato)diboron (472 mg, 1.86 mmol), dichloro-bis(triphenylphosphine)palladium (65 mg, 0.093 mmol) and potassium acetate (456 mg, 4.65 mmol) in anhydrous dioxane (8 mL) was heated at 95 °C for 4 hours. The reaction turned black. The reaction was cooled and filtered through celite. The solvent was concentrated. The oil was taken in EtOAc. The organic was washed with water/brine mixture, brine and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography. MS *m/z* 317 $(M+1)^+$.

A mixture of 5-bromo-2,4-dimethylthiazole (171 mg, 0.89 mmol), ethyl 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)imidazo[1,2-a]pyridine-3-carboxylate (**144**) (250 mg, 1.07 mmol), [1,1′-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) (39 mg, 0.05 mmol) and a solution of 2M sodium carbonate (300 uL) in anhydrous dioxane (4 mL) was heated in the microwave at 135 °C for 25 minutes. The reaction was filtered through celite. The crude product was taken in water and ethylacetate. The organic was washed with water/brine mixture and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography. MS *m/z* 302.09 $(M+1)^+$.

A mixture of ethyl 6-(2,4-dimethylthiazol-5-yl)imidazo[1,2-a]pyridine-3-carboxylate (**145**) (190 mg, 0.630 mmol) and 2N LiOH (1 mL) in THF:MeOH (4:1, 4 mL) was heated at 60 °C for 30 minutes. The reaction was cooled to room temperature and the pH was adjusted between 4-5 with 10% citric acid. The solvent was partially reduced and the resulting solid was collected by vacuum filtration to give 6-(2,4-dimethylthiazol-5-

yl)imidazo[1,2-a]pyridine-3-carboxylic acid (**146**). ^{1}H NMR (400MHz, d_6-DMSO) δ 9.34 (s, 1H), 8.29 (s, 1H), 7.87 (dd, J = 0.8, 9.2 Hz, 1H), 7.62 (dd, J = 2.0, 9.2 Hz, 1H), 2.66 (s, 3H), 2.41 (s, 3H). MS *m/z* 274.06 $(M+1)^+$.

Synthesis of 5-(5-(2,2-difluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2,4-dimethylaniline (**150**)



To a stirring solution of 2,4-dimethylbenzonitrile (1 g, 7.62 mmol) in sulfuric acid (12 mL) at -10 °C was added dropwise nitric acid (325 uL, 7.62 mmol) over a period of 10 minutes. The reaction was stirred between -10 to 0 °C for 10-15 minutes. The reaction was monitored by tlc for completion. The reaction was poured into a flask containing ice. The resulting solid was collected by vacuum filtration and washed with excess water. MS *m/z* 177.06 $(M+1)^+$.

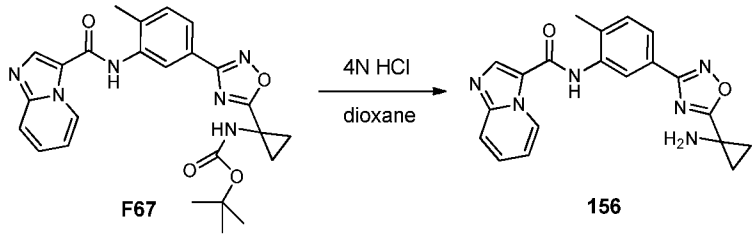
A stirrng mixture of 2,4-dimethyl-5-nitrobenzonitrile (**147**) (3.5 g, 19.58 mmol), hydroxylamine hydrogen chloride (2 g, 29.38 mmol) and N,N-diisopropylethylamine (6.8 mL, 39.17 mmol) in ethanol (40 mL) was heated at 78 °C for 2.5 hours. The reaction was cooled to room temperature and the solvent was concentrated. The crude product was purified by silica chromatography. MS *m/z* 210.08 $(M+1)^+$.

To a stirring solution of 2,2-difluorocyclopropanecarboxylic acid (100 mg, 0.819 mmol) in anhydrous 1-methyl-2-pyrrolidinone (2 mL) was added 1,1′-carbonyldiimidazole (133 mg, 0.819 mmol). The reaction was stirred for 5 minutes. Then, the reaction was added to a flask containing N'-hydroxy-2,4-dimethyl-5-nitrobenzimidamide (**148**) (171 mg, 0.819 mmol) and the reaction was stirred for 25 minutes. Next, the reaction was heated in the microwave at 130 °C for 12 minutes. The reaction was taken in ethyl acetate and water. The organic was washed with water/brine mixture and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography. MS *m/z* 296.08 $(M+1)^+$.

A stirring mixture of 5-(2,2-difluorocyclopropyl)-3-(2,4-dimethyl-5-nitrophenyl)-1,2,4-oxadiazole (**149**) (190 mg, 0.644 mmol) and tin (II) chloride dihydrate (581 mg, 2.57

mmol) in ethanol (10 mL) was heated at 78 °C for 2 hours. The reaction was cooled to room temperature and the pH was adjusted to basic with a saturated solution of sodium bicarbonate. The resulting solid was filtered through a plug of celite and washed with excess ethanol. The solvent was partially reduced and the crude product was extracted with ethyl acetate. The organic was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was concentrated and the crude product was purified by silica chromatography. ^{1}H NMR (400MHz, d_6-DMSO) δ 7.21 (s, 1H), 6.93 (s, 1H), 4.96 (s, 2H), 3.70 – 3.62 (m, 1H), 2.47 – 2.41 (m, 1H), 2.37 – 2.28 (m, 1H), 2.35 (s, 3H), 2.08 (s, 3H). MS *m/z* 266.10 $(M+1)^+$.

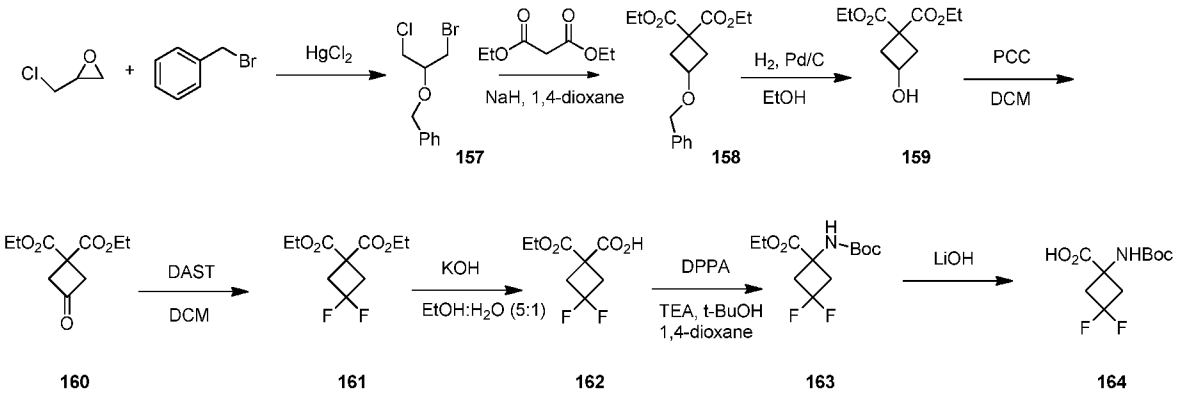
Synthesis of N-(5-(5-(1-aminocyclopropyl)-1,2,4-oxadiazol-3-yl)-2 methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**156**)



F67 156

To a vial was added tert-butyl (1-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)cyclopropyl)carbamate (**F67**) (275 mg, 0.6 mmol) and 4N HCl in 1,4-dioxane (3 mL). The reaction was stirred for 30 minutes. The solvent was concentrated and placed under high vacuum. The solid was taken in water/acetonitrile and the pH was adjusted to neutral with an aqueous solution of ammonium carbonate and lyophilized to afford N-(5-(5-(1-aminocyclopropyl)-1,2,4-oxadiazol-3-yl)-2 methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**156**). MS *m/z* 375.1 $(M+1)^+$.

Synthesis of 1-((tert-butoxycarbonyl)amino)-3,3-difluorocyclobutanecarboxylic acid (**164**)



157 158 159 160 161 162 163 164

To a stirred mixture of benzyl bromide (10g, 59 mmol) and (88 mg) of mercury chloride was added epichlorohydrin (5.4g, 59 mmol). The reaction mixture was heated for 12 hours at 100 °C. Product formation was confirmed by TLC. The crude product

was purified by column chromatography using 20% ethyl acetate/hexanes to give (((1-bromo-3-chloropropan-2-yl)oxy)methyl)benzene (**157**). ^{1}H NMR (400MHz, CD_2Cl_2) δ 7.4 – 7.36 (m, 5H), 4.69 (d, *J* = 2.4 Hz, 2H), 4, 3.90 – 3.85 (m, 1H), 3.77 (d, *J* = 5.2 Hz, 2H), 3.63 (q, *J* = 2.4 Hz, 2H). MS *m/z* 263.10 $(M+1)^+$.

To a stirred suspension of sodium hydride (920 mg, 23 mmol, 60% in mineral oil) in dry dioxane (33 mL), was added diethyl malonate (3.5 mL, 23 mmol) dropwise over 20 min. After the addition was complete, (((1-bromo-3-chloropropan-2-yl)oxy)methyl)benzene (**157**) (6.1g, 23 mmol) was added over 20 minutes. The mixture was then heated at reflux for 24 hours. After cooling to room temperature, sodium hydride (920 mg, 23 mmol) in dioxane (2 mL) was added to the mixture and heating at reflux for another 48 hours. The solvent was partially removed under reduced pressure and the mixture was treated with water (50mL). The mixture was extracted with ethyl acetate (3 x 30 mL), dried with magnesium sulfate and concentrated *in vacuo*. The crude product was purified by column chromatography using hexanes/ ethyl acetate as eluent (25%) to yield diethyl 3-(benzyloxy)cyclobutane-1,1-dicarboxylate (**158**). ^{1}H NMR (400MHz, CD_2Cl_2) δ 7.39 – 7.30 (m, 5H), 4.4 (s, 2H), 4.23 – 4.13 (m, 5H), 2.83 – 2.78 (m, 2H), 2.55 – 2.49 (m, 2H), 1.32 – 1.25 (m, 6H). MS *m/z* 307.2 $(M+1)^+$.

To a solution of diethyl 3-(benzyloxy)cyclobutane-1,1-dicarboxylate (**158)** (1.43g, 4.7 mmol) in EtOH (18 mL) was added 10% palladium on carbon (143 mg) and the mixture was hydrogenated with a H_2 balloon for 12 hours at room temperature. The catalyst was removed by filtration using celite, washed with ethyl acetate and EtOH and the solvent was removed under reduced pressure. The crude product was purified via column chromatography using hexanes/ethyl acetate as eluent to yield diethyl 3-hydroxycyclobutane-1,1-dicarboxylate (**159**). ^{1}H NMR (400MHz, CD_2Cl_2) δ 4.4 – 4.32 (m, 1H), 4.21 (qd, *J* = 7.2, 2.0 Hz, 4H), 2.89 – 2.84 (m, 2H), 2.46 – 2.41 (m, 2H), 2.20 (d, *J* = 6.4 Hz, 1H), 1.27(t, *J* = 7.2 Hz, 6H). MS *m/z* 217.1 $(M+1)^+$.

To a solution of diethyl 3-hydroxycyclobutane-1,1-dicarboxylate (**159)** (649 mg, 3 mmol) in DCM (7 mL) was added PCC (1.37g, 6.3 mmol) and the mixture was stirred for 4 hours at room temperature. The product was filtered through a silica gel plug and the residue was purified using column chromatography with hexanes/ethyl acetate as eluent to yield diethyl 3-oxocyclobutane-1,1-dicarboxylate (**160**). ^{1}H NMR (400MHz, CD_2Cl_2) δ 4.28 (q, *J* = 7.2 Hz, 4H), 3.63 (s, 4H), 1.31 (t, *J* = 7.2 Hz, 6H). MS *m/z* 215.1 $(M+1)^+$.

To a cooled solution of diethyl 3-oxocyclobutane-1,1-dicarboxylate (**160)** (4.8g, 22 mmol) in dry DCM (53 mL) was added dropwise a solution of DAST (6.6 mL, 50.2 mmol) and the mixture was stirred at room temperature overnight. The mixture was poured onto ice water and was extracted three times with DCM. The solution was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified

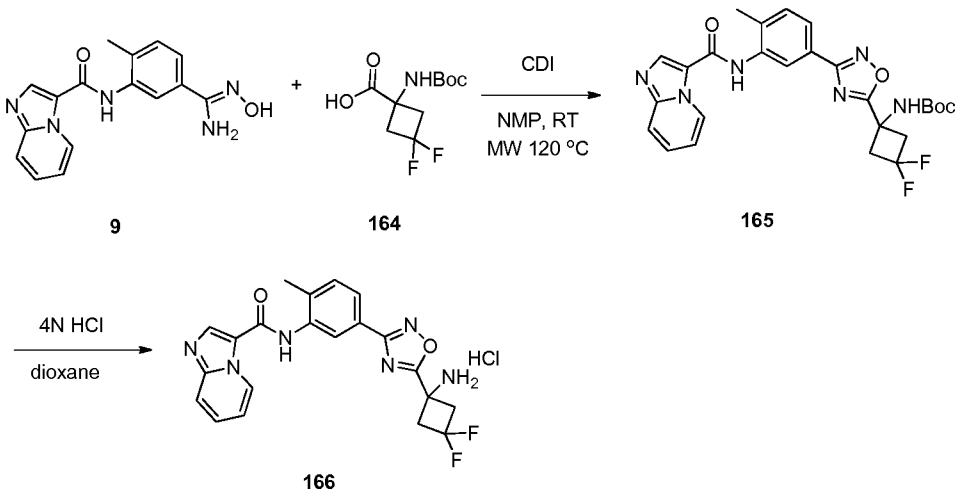
by silica gel chromatography using 25% ethyl acetate/hexanes as eluent to yield diethyl 3,3-difluorocyclobutane-1,1-dicarboxylate (**161**). ^{1}H NMR (400MHz, CD_2Cl_2) δ 4.14 (q, *J* = 7.2 Hz, 4H), 3.04 (t, *J* = 12.0 Hz, 4H), 1.18 (t, *J* = 6.8 Hz, 6H). MS *m/z* 237.1 $(M+1)^+$.

Diethyl 3,3-difluorocyclobutane-1,1-dicarboxylate (**161**) (2.8g, 12 mmol) was dissolved in ice cooled ethanolic potassium hydroxide solution (0.5 M, 11 mL) and water (2.2 mL). The mixture was stirred at room temperature overnight. An additional 0.5 eq was added to the solution at room temperature and the mixture was stirred at room temperature overnight. Water was added and most of the EtOH was removed under reduced pressure. The mixture was acidified with 2M HCl and extracted three times with ethyl acetate. The organic layer was dried with magnesium sulfate and concentrated to yield 1-(ethoxycarbonyl)-3,3-difluorocyclobutanecarboxylic acid (**162**). ^{1}H NMR (400MHz, CD_2Cl_2) δ 4.33 – 4.24 (m, 2H), 3.26 – 3.13 (m, 4H), 1.34 – 1.27 (m, 3H). MS *m/z* 209.2 $(M+1)^+$.

To a solution of 1-(ethoxycarbonyl)-3,3-difluorocyclobutanecarboxylic acid (**162**) (1g, 4.8 mmol) in dry dioxane (18 mL) was added tert-butanol (0.4 mL, 4.3 mmol), DPPA (1.03 mL, 4.8 mmol) and TEA (0.7mL, 4.9 mmol) and the mixture was refluxed overnight. Ethyl acetate was added and the organic layer was washed twice with 5% citric acid and saturated sodium hydrogen carbonate. The solution was dried and evaporated under reduced pressure. The product was purified using silica gel chromatography using hexanes/ethyl acetate to yield ethyl 1-((tert-butoxycarbonyl)amino)-3,3-difluorocyclobutanecarboxylate (**163**). ^{1}H NMR (400MHz, CD_2Cl_2) δ 4.12 (q, *J* = 6.8 Hz, 2H), 3.18 – 3.08 (m, 2H), 2.73 – 2.55 (m, 2H), 1.34 (s, 9H), 1.19 (t, *J* = 6.8 Hz, 4H). MS *m/z* 280.1 $(M+1)^+$.

To a stirring solution of ethyl 1-((tert-butoxycarbonyl)amino)-3,3-difluorocyclobutanecarboxylate(**163**) (282 mg, 1.01 mmol) in THF:MeOH:H_2O (3:2:1, 2 mL), was added 3N LiOH (1 mL) and stirred at room temperature. The pH was adjusted to between 4-5 with sodium bisulfate monohydrate and concentrated. The crude product (**164**) was used in the next step without further purification. MS *m/z* 252.1 $(M+1)^+$.

Synthesis of N-(5-(5-(1-amino-3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**166**)



9 164 165

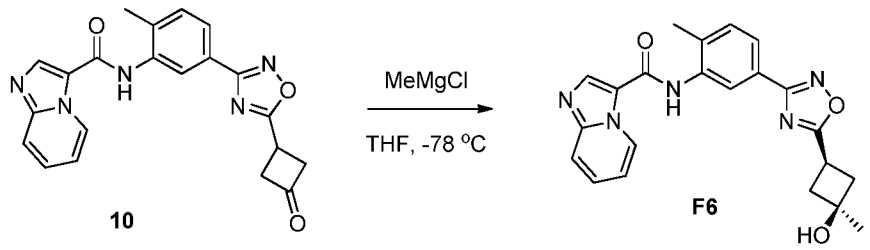
166

To a stirring solution of 1-((tert-butoxycarbonyl)amino)-3,3-difluorocyclobutanecarboxylic acid (**164**) (45 mg, 0.18 mmol) in anhydrous NMP (1.3 mL) was added 1,1′-carbonyldiimidazole (CDI) (29 mg, 0.18 mmol). The reaction was stirred for 3 minutes. N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**9**) (69 mg, 0.22 mmol) was added and the reaction was stirred for 25 minutes. Then, the reaction was heated at 120 °C for 15 minutes. The crude product was taken up in ethyl acetate and water. The organic was washed with 2x water/brine mixture and dried over magnesium sulfate. The solvent was concentrated and the crude product was purified using silica gel chromatography using 60% ethyl acetate/hexanes to afford tert-butyl (3,3-difluoro-1-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)cyclobutyl)carbamate (**165**). MS *m/z* 525.2 $(M+1)^+$

To a flask was added tert-butyl (3,3-difluoro-1-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)cyclobutyl)carbamate (**165**) (169 mg, 0.3 mmol) and 4N HCl in 1,4-dioxane (1 mL). The reaction was stirred for 30 minutes. The solvent was concentrated and placed under high vacuum to afford N-(5-(5-(1-amino-3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide hydrochloride (**166**). MS *m/z* 425.2 $(M+1)^+$.

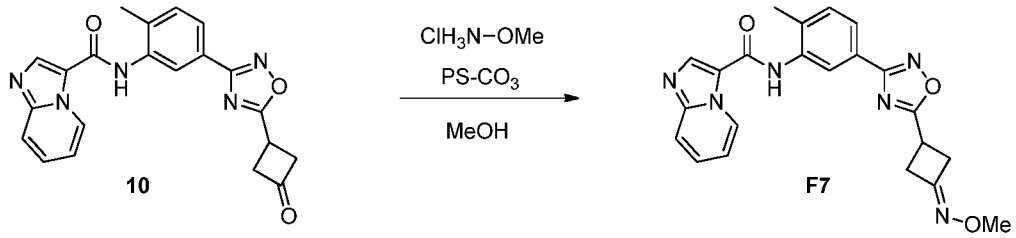
Synthesis of final compounds

Synthesis of N-(5-(5-((1s,3s)-3-hydroxy-3-methylcyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F6**)



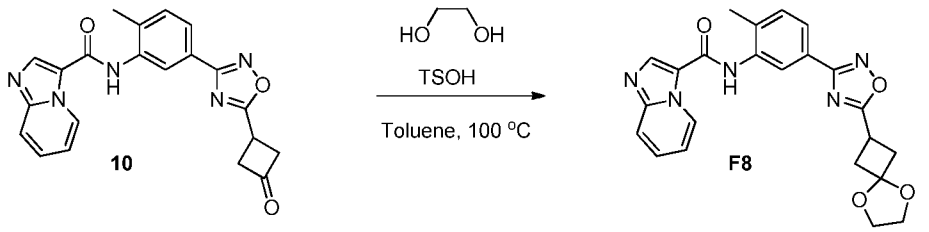
The ketone N-(2-methyl-5-(5-(3-oxocyclobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**10**) (0.3 g, 0.77 mmol) in THF (5 mL) was added to a stirred solution of MeMgCl (1.3 mL, 3.9 mmol, 3 M in THF) in THF (20 mL) at -78 °C. After addition, the resulting solution was warmed to 0 °C and quenched with saturated NH_4Cl. The mixture was partitioned with EtOAc and the organic phase was washed with brine and dried over $MgSO_4$. After evaporation the residue was purified over silica gel using 10% MeOH in dichloromethane to obtain N-(5-(5-((1s,3s)-3-hydroxy-3-methylcyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F6**). ^{1}H NMR (400MHz, d_4-MeOH) δ 9.53 (d, J = 7.2 Hz, 1H), 8.49 (s, 1H), 8.13 – 8.12 (m, 1H), 7.90 (dd, J = 8.2, 2.0 Hz, 1H), 7.75 (d, J = 9.6 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.18 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 3.48 – 3.40 (m, 1H), 2.58 – 2.54 (m, 4H), 2.42 (s, 3H), 1.46 (s, 3H). MS *m/z* 404.1 $(M+1)^+$.

Synthesis of N-(5-(5-(3-(methoxyimino)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F7**)



NH_3OMeCl (60 mg, 0.67 mmol) was added in one portion to a stirred suspension of N-(2-methyl-5-(5-(3-oxocyclobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**10**) (0.13 g, 0.33 mmol) and polymer supported carbonate (0.5 g) in MeOH (10 mL). After 3 hours at room temperature the mixture was filtered and concentrated. The residue was dissolved in isopropanol and N-(5-(5-(3-(methoxyimino)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F7**) was precipitated by adding Et_2O. ^{1}H NMR (400MHz, d_4-MeOH) δ 9.55 (d, J = 7.2 Hz, 1H), 8.50 (s, 1H), 8.13 – 8.12 (m, 1H), 7.90 (dd, J = 8.2, 2.0 Hz, 1H), 7.75 (d, J = 9.6 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.18 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.82 (s, 3H), 3.57 – 3.30 (m, 4H), 2.86 (s, 3H). MS *m/z* 417.1 $(M+1)^+$.

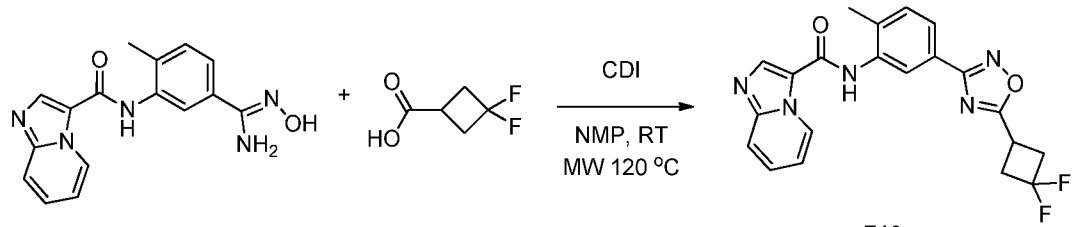
Synthesis of N-(5-(5-(5,8-dioxaspiro[3.4]octan-2-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F8**)



10 F8

Ethylene glycol (10 mg), TsOH (5 mg) and N-(2-methyl-5-(5-(3-oxocyclobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**10**) (50 mg) were combined in toluene (3 mL) and heated at 100 °C for 5 hours. The reaction was filtered and purified by preparative reverse phase HPLC to afford N-(5-(5-(5,8-dioxaspiro[3.4]octan-2-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F8**). ^{1}H NMR (400MHz, d_4-MeOH) δ 9.53 (d, J = 7.2 Hz, 1H), 8.50 (s, 1H), 8.13 – 8.12 (m, 1H), 7.90 (dd, J = 8.2, 2.0 Hz, 1H), 7.75 (d, J = 9.6 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.18 (ddd, J = 7.2, 7.2, 1.2 Hz, 1H), 4.45 – 4.43 (m, 1H), 3.98 – 3.81 (m, 4H), 3.32 – 3.31 (m, 4H), 2.43 (s, 3H). MS m/z 432.1 $(M+1)^+$.

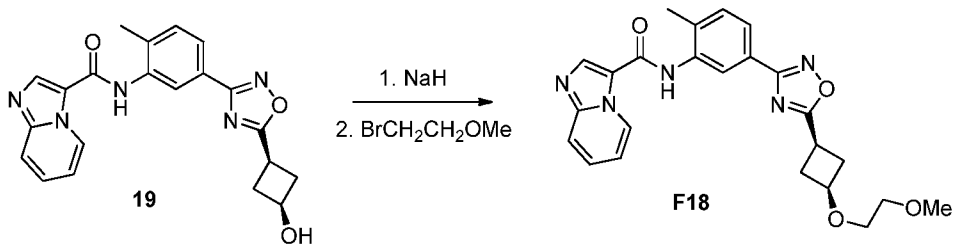
Synthesis of N-(5-(5-(3-fluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F13**)



9 F13

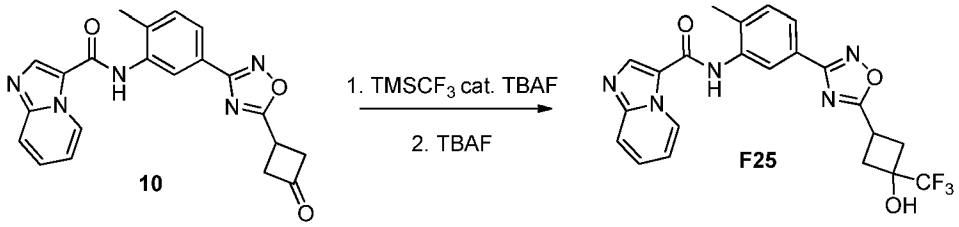
To a stirring solution of 3,3-difluorocyclobutanecarboxylic acid (264 mg, 1.94 mmol) in anhydrous NMP (6 mL) was added 1,1′-carbonyldiimidazole (315 mg, 1.94 mmol). The reaction was stirred for 5 minutes. 5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**9**) (500 mg, 1.62 mmol) was added and the reaction was stirred for 25 minutes, then heated in the microwave at 120 °C for 12 minutes. The crude product was purified by silica chromatography to give N-(5-(5-(3-fluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide **(F13)**. ^{1}H NMR (400MHz, d_6-DMSO) δ 10.19 (s, 1H), 9.53 – 9.50 (m, 1H), 8.70 (s, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.90 – 7.87 (m, 1H), 7.83 (d, J = 1.6, 8.0 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.33 – 7.29 (m, 1H), 3.93 –3.84 (m, 1H), 3.25 – 3.02 (m, 4H), 2.37 (s, 3H). MS m/z 410.3 $(M+1)^+$.

Synthesis of N-(5-(5-((1s,3s)-3-(2-methoxyethoxy)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F18**)



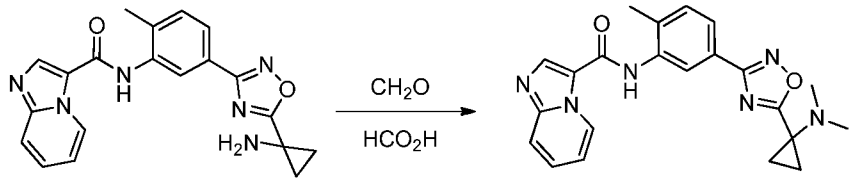
NaH (26 mg, 0.64 mmol) was added in one portion to a stirred solution of above alcohol (**19**) (0.1 g, 0.25 mmol). After 1 hour at room temperature, 1-bromo-2-methoxyethane (0.27 mmol) was added dropwise and the resulting solution was heated at 50 °C for 2 hours. The reaction was quenched with MeOH and purified with reverse phase HPLC to give N-(5-(5-((1s,3s)-3-(2-methoxyethoxy)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F18**). ^{1}H NMR (400MHz, d_4-MeOH) δ 9.78 (d, J = 7.2 Hz, 1H), 8.79 (s, 1H), 8.15 (d, J = 2.0 Hz, 1H), 8.02 (m, 2H), 7.93 (dd, J = 8.2, 1.6 Hz, 1H), 7.60 – 7.56 (m, 1H), 7.50 (d, J = 8.0 Hz, 1H), 4.17 – 4.09 (m, 1H), 3.59 – 3.52 (m, 4H), 3.45 – 3.38 (m, 1H), 3.37 (s, 3H), 2.85 – 2.78 (m, 2H), 2.72 – 2.54 (m, 2H), 2.44 (s, 3H). MS *m/z* 448.1 $(M+1)^+$.

Synthesis of N-(5-(5-(3-hydroxy-3-(trifluoromethyl)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F25**)



To a stirring solution of N-(2-methyl-5-(5-(3-oxocyclobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**10**) (150 mg, 0.387 mmol) in anydrous THF (2.5 mL) at 0 °C was added trifluoromethyltrimethylsilane (121 μL, 0.774 mmol) and TBAF (100 μL in THF and 5% water). The reaction was stirred to room temperature for 3 hours. Then TBAF (0.5 mL in THF and 5% water) was added and the reaction was stirred for 1 hour. The solvent was concentrated and the crude product was dissolved in ethyl acetate. The organic phase was washed with a water, brine and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography to yield N-(5-(5-(3-hydroxy-3-(trifluoromethyl)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F25**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.04 (s, 1H), 9.47 – 9.45 (m,1H), 8.60 (s, 1H), 8.09 (d, J = 1.6 Hz, 1H), 7.83 (dd, J = 2.0, 8.0 Hz, 1H), 7.80 – 7.78 (m, 1H), 7.55 – 7.50 (m, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.20 – 7.16 (m, 1H), 6.92 (s, 1H), 3.32 – 3.28 (m, 1H), 2.99 – 2.93 (m, 2H), 2.68 – 2.60 (m, 2H), 2.37 (s, 3H). MS *m/z* 458.41 $(M+1)^+$.

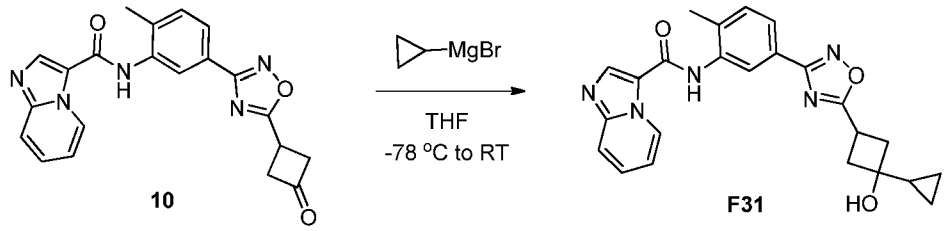
Synthesis of N-(5-(5-(1-(dimethylamino)cyclopropyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F29**)



156 **F29**

To a stirring solution of N-(5-(5-(1-aminocyclopropyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**156**) (0.02 mmol) and CH_2O (30 %wt. aqueous solution, 0.2 mL) was added HCO_2H (40 %wt. aqueous solution, 0.2 mL). The reaction mixture was heated at reflux for 1 hour. The solvent was removed and the crude was purified by preparative HPLC to afford N-(2-methyl-5-(5-((1-(methylsulfonyl)azetidin-3-yl)methyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F29**). MS *m/z* 403.2 $(M+1)^+$.

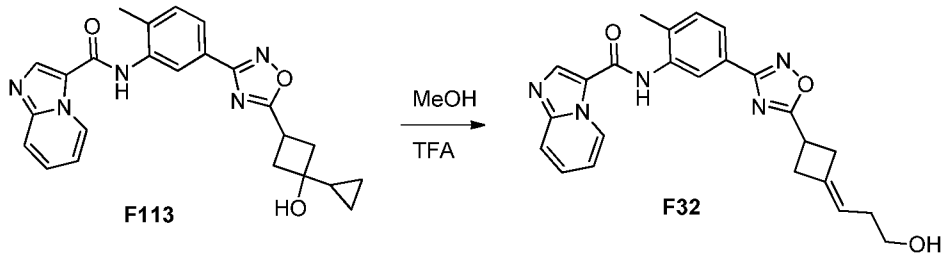
Synthesis of N-(5-(5-(3-cyclopropyl-3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F31**)



10 **F31**

To a stirring solution of N-(2-methyl-5-(5-(3-oxocyclobutyl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**10**) (250 mg, 0.645 mmol) in anhydrous THF (10 mL) at -78 °C under Argon was added cyclopropylmagnesium bromide (2.6 mL, 1.3 mmol). The reaction was stirred for 30 minutes at room temperature and quenched with 1N HCl at 0 °C. The crude product was extracted with ethylacetate. The organic layer was washed with saturated ammonium chloride, water and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography to give N-(5-(5-(3-cyclopropyl-3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F31**). ^1H NMR (400MHz, d_6-DMSO) δ 10.04 (s, 1H), 9.47 – 9.45 (m, 1H), 8.59 (s, 1H), 8.07 (d, J = 1.6 Hz, 1H), 7.83 – 7.76 (m, 2H), 7.55 – 7.52 (m, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.20 – 7.16 (m, 1H), 5.19 (s, 1H), 4.37 – 4.35 (m, 1H), 3.46 – 3.40 (m, 1H), 2.45 – 2.40 (m, 2H), 2.36 (s, 3H), 1.54 – 1.41 (m, 2H), 1.19 – 1.14 (m, 1H), 0.34 – 0.26 (m, 2H), 0.22 – 0.11 (m, 1H). MS *m/z* 430.47 $(M+1)^+$.

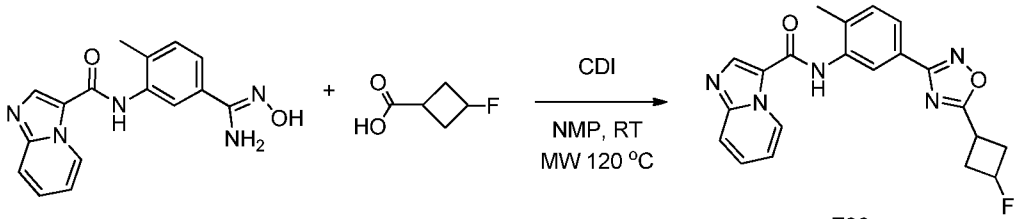
Synthesis of N-(5-(5-(3-(3-hydroxypropylidene)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F32**)



F113 F32

A stirring solution of N-(5-(5-(3-cyclopropyl-3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F113**) (130 mg, 0.303 mmol) in trifluoroacetic acid (1 mL) was stirred at room temperature for 1.5 hours. The solvent was concentrated and dried under high vacuum. The crude product was taken in MeOH (1 mL) and a saturated solution of sodium bicarbonate (0.2 mL). The reaction mixture was stirred for 15 minutes. The crude product was extracted with ethyl acetate. The organic phase was washed with water and dried over anhydrous sodium sulfate. The solvent was concentrated to obtain the desired product N-(5-(5-(3-(3-hydroxypropylidene)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F32**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.04 (s, 1H), 9.48 – 9.45 (m, 1H), 8.59 (s, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.82 (dd, J = 1.6 Hz, 7.6 Hz, 1H), 7.81 – 7.77 (m, 1H), 7.55 – 7.52 (m, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.20 – 7.16 (m, 1H), 5.28 – 5.23 (m, 1H), 4.50 (s, 1H), 3.98 – 3.89 (m, 1H), 3.40 – 3.37 (m, 2H), 3.23 – 3.14 (m, 2H), 3.09 – 3.03 (m, 2H), 2.36 (s, 3H), 2.08 – 2.02 (m, 2H). MS m/z 430.47 $(M+1)^+$.

Synthesis of N-(5-(5-(3-fluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F36**)

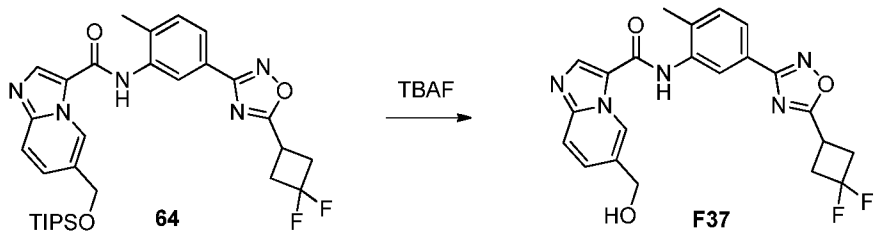


9 F36

To a stirring solution of 3-fluorocyclobutanecarboxylic acid (76 mg, 0.647 mmol) in anhydrous NMP (1.5 mL) was added 1,1′-carbonyldiimidazole (105 mg, 0.647 mmol). The reaction was stirred for 5 minutes. 5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**9**) (100 mg, 0.323 mmol) was added and the reaction was stirred for 25 minutes, then heated in the microwave at 120 °C for 10 minutes. The crude product was purified by reverse phase preparative HPLC to give N-(5-(5-(3-fluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F36**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.18 (s, 1H), 9.53 – 9.50 (m, 1H), 8.69 (s, 1H), 8.07 (d, J = 1.6 Hz, 1H), 7.89 – 7.86 (m, 1H), 7.84 (dd, J =

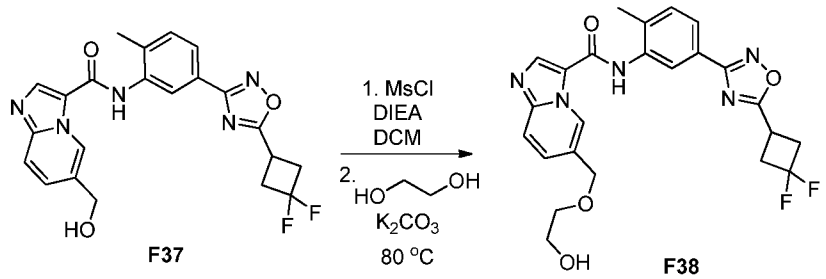
1.6, 8.0 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.29 (m, 1H), 5.48 – 5.28 (m, 1H), 3.99 – 3.91 (m, 1H), 2.81 – 2.73 (m, 4H), 2.37 (s, 3H). MS *m/z* 392.14 $(M+1)^+$.

Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxamide (**F37**)



To a solution of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(((triisopropylsilyl)oxy)methyl)imidazo[1,2-a]pyridine-3-carboxamide (**64**) (230 mg, 0.39 mmol) in THF (5 mL), was added TBAF (1M in THF, 0.43 mL) and the resulting mixture was stirred for 1 hour. THF was removed and the residue was added to a mixture of water (10 mL), MeOH (5 mL) and EtOAc (5 mL). Organic solvents were removed slowly to give a precipitate which was filtered and dried to afford N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxamide (**F37**). ^{1}H NMR (400MHz, $CDCl_3$) δ 9.39 (m, 1H), 8.42 (d, *J* = 1.6 Hz, 1H), 8.04 (s, 1H), 7.70 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.60 (d, *J* = 9.2 Hz, 1H), 7.42 (s, 1H), 7.36 (dd, *J* = 1.7, 9.2 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 4.63 (d, *J* = 5.7 Hz, 2H), 3.63–3.41 (m, 1H), 3.09–2.85 (m, 4H), 2.28 (s, 3H), 1.82 (t, *J* = 5.9 Hz, 1H). MS *m/z* 440.1 $(M+1)^+$.

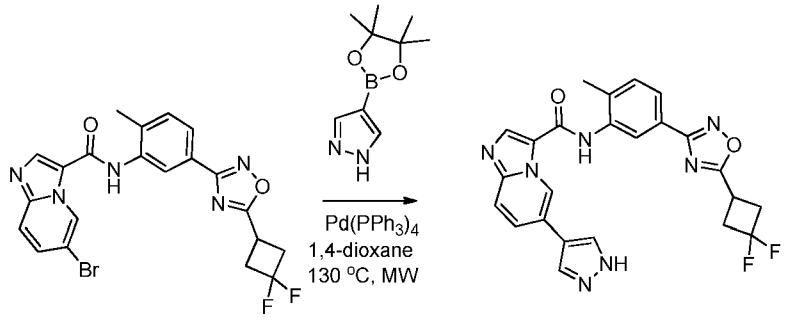
Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(2-hydroxyethoxy)imidazo[1,2-a]pyridine-3-carboxamide (**F38**)



N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxamide (**F37**) (0125 mg, 0.285 mmol) was dissolved in DCM (1 mL) and DIEA (0.854 mmol). MsCl (0.57 mmol) was added dropwise. After 15 minutes at roomtemperature the solvent was removed. MeOH (5 mL) and water (10 mL) were added to the residue. After sonication, most of the MeOH was removed from the mixture. Solid product was filtered and dried under vacuum to

give the crude mesylate, which was used in the next step without purification. MS *m/z* 518.0 $(M+1)^+$. A mixture of (3-((5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)carbamoyl)imidazo[1,2-a]pyridin-6-yl)methyl methanesulfonate (10.4 mg, 0.02 mmol) and K_2CO_3 (8.3 mg, 0.06 mmol) in ethane-1,2-diol (0.5 mL) was heated at 80 °C for 20 minutes. The reaction mixture was purified by preparative HPLC to afford N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(2-hydroxyethoxy)imidazo[1,2-a]pyridine-3-carboxamide (**F38**). ^{1}H NMR (400MHz, $CDCl_3$) δ 9.56 (m, 1H), 8.60 (d, *J* = 1.5 Hz, 1H), 8.21 (s, 1H), 7.89 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 7.60 (s, 1H), 7.50 (dd, *J* = 1.7, 9.2 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 4.65 (s, 2H), 3.82 (s, 2H), 3.73–3.61 (m, 3H), 3.15 (m, 4H), 2.46 (s, 3H), 2.04 (s, 1H). MS *m/z* 484.2 $(M+1)^+$.

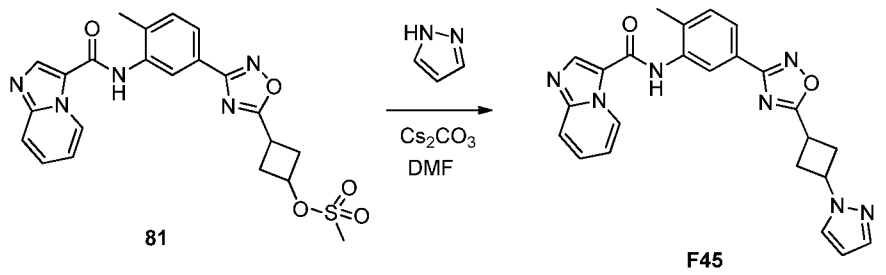
Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (**F40**)



42a **F40**

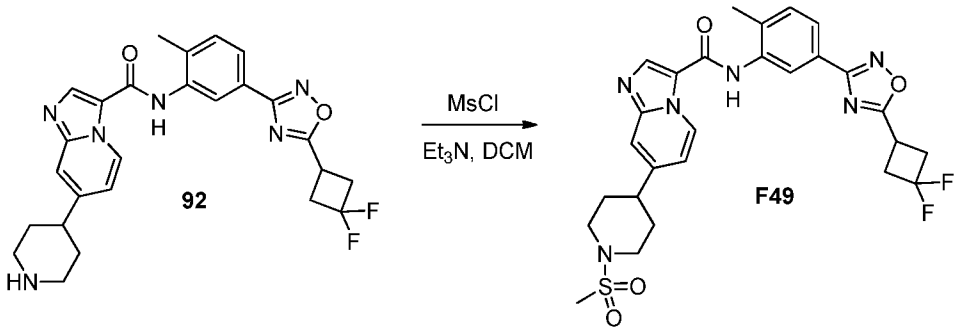
6-Bromo-N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**42a**) (98.0 mg, 0.2 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (60.0 mg, 0.3 mmol), K_3PO_4 (42.0 mg, 0.2 mmol) and $Pd(PPh_3)_4$ (46.2 mg, 0.04 mmol) were added to a flask equipped with a stir bar. The flask was evacuated and backfilled with nitrogen several times. 1,4-Dioxane (1 mL) and the reaction was heated at 130 ºC for 20 minutes in a microwave reactor. The reaction was filtered and purified by preparative HPLC to afford N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (**F40**). MS *m/z* 476.1 $(M+1)^+$.

Synthesis N-(5-(5-(3-(1H-pyrazol-1-yl)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F45**)



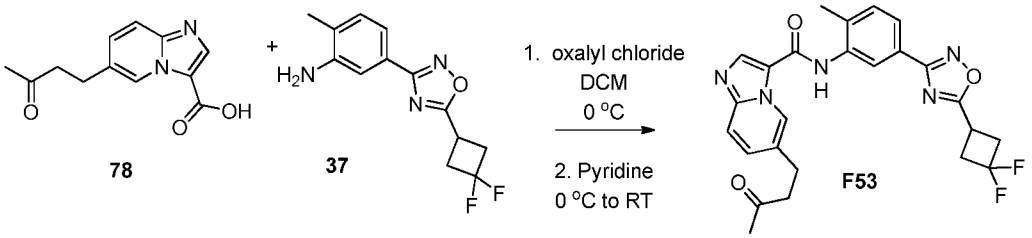
A stirring mixture of 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)cyclobutyl methanesulfonate (**81**) (25 mg, 0.0535 mmol), 1H-pyrazole (7 mg, 0.0802 mmol) and cesium carbonate (26 mg, 0.107 mmol) in anhydrous DMF (1 mL) was heated at 60 °C for 1 hour. Then, the reaction was cooled to room temperature and filtered. The crude product was purified by reverse phase preparative HPLC to give N-(5-(5-(3-(1H-pyrazol-1-yl)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F45**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.20 (s, 1H), 9.54 – 9.51 (m, 1H), 8.71 (s, 1H), 8.10 (dd, J = 1.6, 7.2 Hz, 1H), 7.89 – 7.85 (m, 3H), 7.70 – 7.66 (m, 1H), 7.54 – 7.50 (m, 2H), 7.33 – 7.29 (m, 1H), 6.28 – 6.25 (m, 1H), 5.04 – 4.96 (m, 1H), 3.82 – 3.73 (m, 1H), 3.10 – 2.85 (m, 4), 2.37 (s, 3H). MS *m/z* 440.18 $(M+1)^+$.

Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (**F49**)



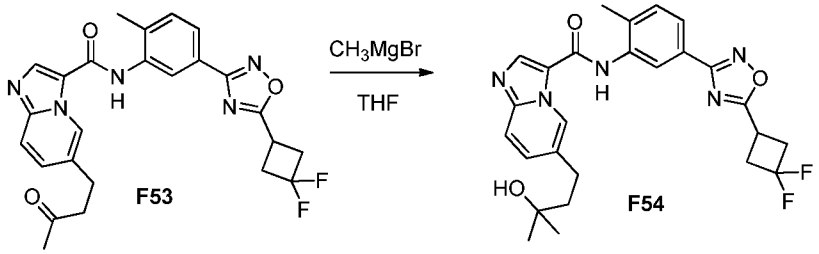
A solution of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-(piperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (**92**) (15.6 mg, 0.032 mmol) and Et_3N (0.013 mL, 0.095 mmol) in dichloromethane (1 mL) was added methanesulfonyl chloride (0.0074 mL, 0.095 mmol) and stirred at room temperature for 1 hour. The crude product was purified by preparative HPLC to yield N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-(1-(methylsulfonyl)piperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (**F49**). MS (*m/z*) 571.1 $(M+1)^+$.

Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxamide (**F53**)



To a stirring suspension of 6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxylic acid (**78**) (150 mg, 0.646 mmol) in anhydrous dichloromethane (5 mL) at 0 °C under Argon was added dropwise oxalyl chloride (60 µL, 0.710 mmol). Then, a drop of anhydrous N,N-dimethylformamide was added and the reaction mixture was stirred at room temperature for 45 minutes. The solvent was concentrated. A stirring mixture of the acid chloride and 5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**37**) (86 mg, 0.323 mmol) in anhydrous pyridine (3 mL) was stirred at room temperature for 3 hours. The crude product was purified by silica chromatography to give N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxamide (**F53**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.19 (s, 1H), 9.37 (s, 1H), 8.70 (s, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.86 – 7.83 (m, 2H), 7.66 (dd, J = 1.6, 9.2 Hz, 1H), 7.51 (d, J = 8.0 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.24 – 3.05 (m, 4H), 2.89 – 2.86 (m, 4H), 2.37 (s, 3H), 2.11 (s, 3H). MS m/z 480.18 $(M+1)^+$.

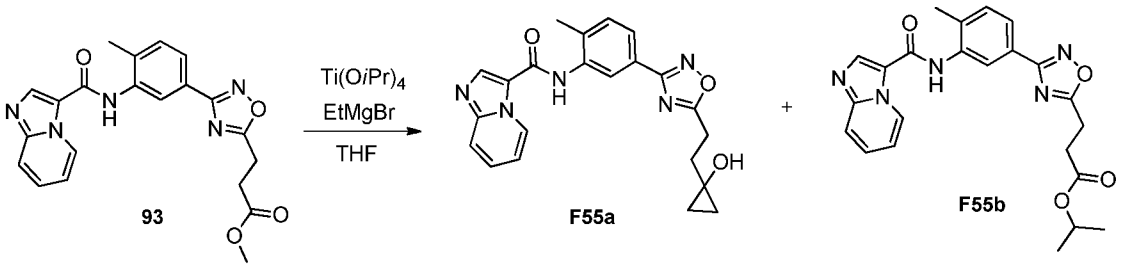
Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(3-hydroxy-3-methylbutyl)imidazo[1,2-a]pyridine-3-carboxamide (**F54**)



To a stirring solution of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxamide (**F53**) (40 mg, 0.083 mmol) in anhydrous THF (2 mL) at -78 °C under a stream of Argon was added methylmagnesium bromide (83 uL, 0.25 mmol). The reaction was stirred to room temperature for 30 minutes. The reaction was cooled to 0 °C and was quenched with saturated NH_4Cl (2 mL). The crude product was extracted with ethylacetate. The organic was washed with water, brine and dried over anhydrous sodium sulfate. The solvent was concentrated and the crude product was purified by reverse phase preparative HPLC to give N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(3-hydroxy-3-methylbutyl)imidazo[1,2-a]pyridine-3-carboxamide (**F54**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.18 (s, 1H), 9.36 (s, 1H), 8.68 (s, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.86 – 7.82 (m, 2H),

7.65 – 7.62 (m, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.25 – 3.04 (m, 4H), 2.78 – 2.73 (m, 2H), 2.37 (s, 3H), 1.71 – 1.67 (m, 2H), 1.16 (s, 6H). MS *m/z* 496.21 $(M+1)^+$.

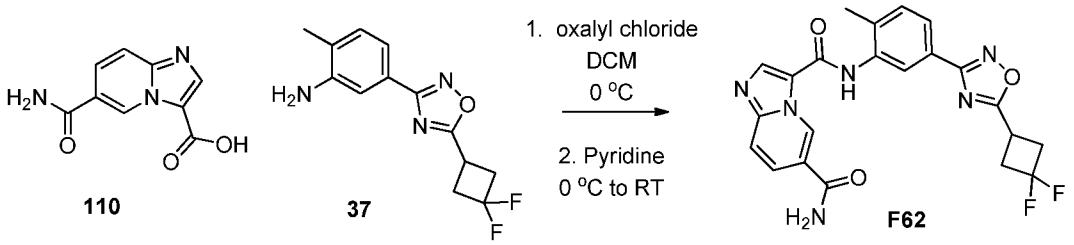
Synthesis of N-(5-(5-(2-(1-hydroxycyclopropyl)ethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F55a**)



To a stirring solution of methyl 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)propanoate (**93**) (100 mg, 0.25 mmol) in anhydrous THF at -15 °C under argon was added dropwise a solution of ethylmagnesium bromide (247 L, 0.74 mmol). The reaction was stirred at room temperature for 16 hours. The reaction was quenched with saturated NH_4Cl. The crude product was extracted with ethyl acetate, washed with water and brine and dried over sodium sulfate. The crude product was purified by preparative HPLC to to yield both N-(5-(5-(2-(1-hydroxycyclopropyl)ethyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F55a**) and isopropyl 3-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)propanoate (**F55b**). ^{1}H NMR for (**F55a**) (400MHz, CD_2Cl_2) δ 9.89 (d, *J* = 6.8 Hz, 1H), 9.81 (s, 1H), 9.56 (s, 1H), 8.21 (s, 1H), 8.19 (d, *J* = 8.0 Hz, 1H), 8.0 (t, *J* = 8.0 Hz, 1H), 7.88 (dd, *J* = 1.6, 7.6 Hz 1H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 3.23 (t, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 2.12 (t, *J* = 7.2 Hz, 2H), 0.79 (t, *J* = 6.8 Hz , 2H), 0.53 (t, *J* = 6.8 Hz 2H). MS *m/z* 404.2 $(M+1)^+$.

^{1}H NMR for (**F55b**) (400MHz, CD_2Cl_2) δ 9.85 (d, *J* = 6.8 Hz, 1H), 9.47 (s, 1H), 9.21 (s, 1H), 8.28 (d, *J* = 1.6 Hz, 1H), 8.13 (d, *J* = 9.2 Hz, 1H), 7.94 – 7.87 (m, 2H), 7.47 (t, *J* = 6.8 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 5.04 (m, 1H), 3.26 (t, *J* = 7.2 Hz, 2H), 2.91 (t, *J* = 7.2 Hz, 2H), 2.44 (s, 3H), 1.25 (d, *J* = 6.4 Hz, 6H). MS *m/z* 434.2 $(M+1)^+$.

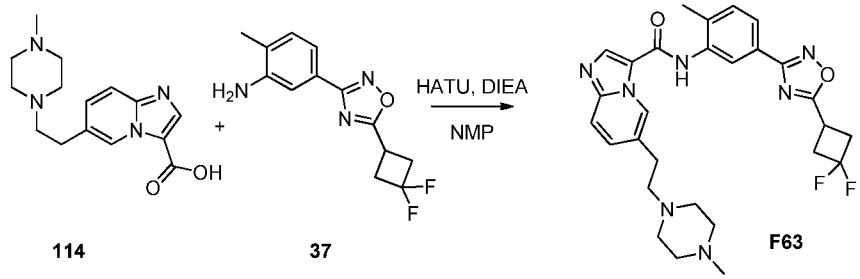
Synthesis ofN3-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3,6-dicarboxamide (**F62**)



110 37 F62

To a stirring suspension of 6-carbamoylimidazo[1,2-a]pyridine-3-carboxylic acid (**110**) (50 mg, 0.172 mmol) in anhydrous dichloromethane (2 mL) at 0 °C under Argon was added dropwise oxalyl chloride (16 uL, 0.189 mmol). Then, a drop of anhydrous N,N-dimethylformamide was added and the reaction mixture was stirred at 0 °C for 1 hour. The solvent was concentrated. A stirring mixture of the acid chloride and methyl 5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**37**) (23 mg, 0.0861 mmol) in anhydrous pyridine (2 mL) was stirred at room temperature for 20 minutes. The crude product was purified by reverse phase preparative HPLC to give N3-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3,6-dicarboxamide (**F62**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.18 (s, 1H), 9.99 – 9.98 (m, 1H), 8.68 (s, 1H), 8.28 (s, 1H), 8.10 (d, J = 1.6 Hz, 1H), 7.98 (dd, J = 1.6, 9.2 Hz, 1H), 7.88 – 7.83 (m, 2H), 7.66 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.22 – 3.06 (m, 4H), 2.38 (s, 3H). MS *m/z* 452.14 $(M+1)^+$.

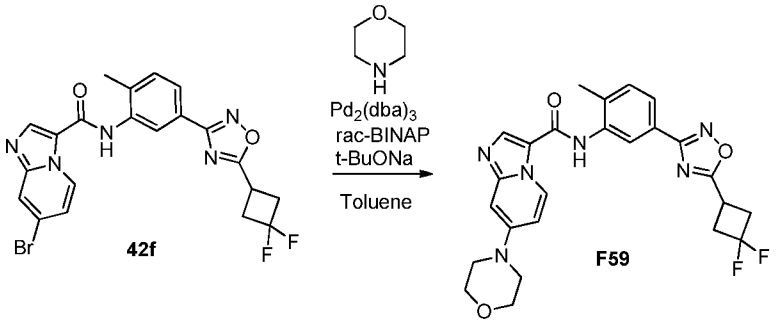
Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxamide (**F63**)



114 37 F63

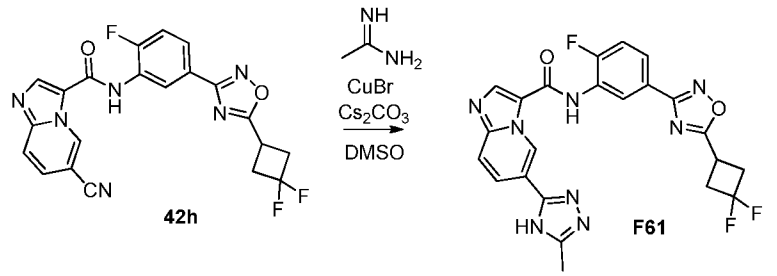
To a stirring solution of ethyl 6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxylate (**114**) (25 mg, 0.087 mmol) in anhydrous NMP (1 mL) was added HATU (26 mg, 0.104 mmol) and DIEA (23 uL, 0.130 mmol). The reaction mixture was stirred at room temperature for 10 minutes. Then, 5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**37**) (23 mg, 0.087 mmol) was added and the reaction was stirred for two days. The crude product was purified by reverse phase preparative HPLC to afford N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxamide (**F63**). MS *m/z* 453.14 $(M+1)^+$.

Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-morpholinoimidazo[1,2-a]pyridine-3-carboxamide (**F59**)



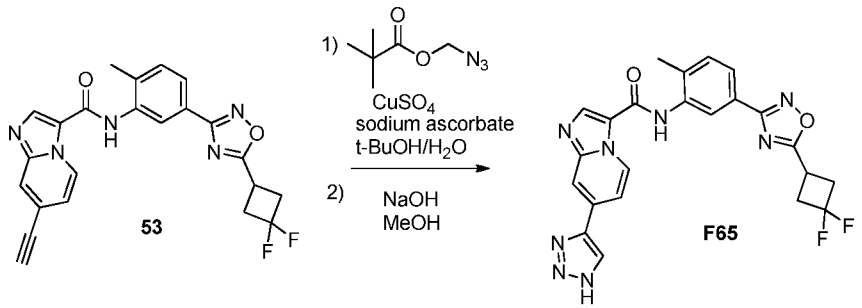
A mixture of 7-bromo-N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**42f**) (50.0 mg, 0.10 mmol), $Pd_2(dba)_3$ (9.2 mg, 0.01 mmol), rac-BINAP (18.7 mg, 0.03mmol), NaOt-Bu (14.4 mg, 0.15 mmol) and morphline (17.4 mg, 0.2 mmol) in toluene (3 mL) was heated at 110 °C overnight. Once complete, the reaction mixture was diluted and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to afford a residue which was purified by HPLC to give N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-morpholinoimidazo[1,2-a]pyridine-3-carboxamide (**F59**). MS *m/z* 495.1 $(M+1)^+$.

Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-fluorophenyl)-6-(5-methyl-4H-1,2,4-triazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide (**F61**)



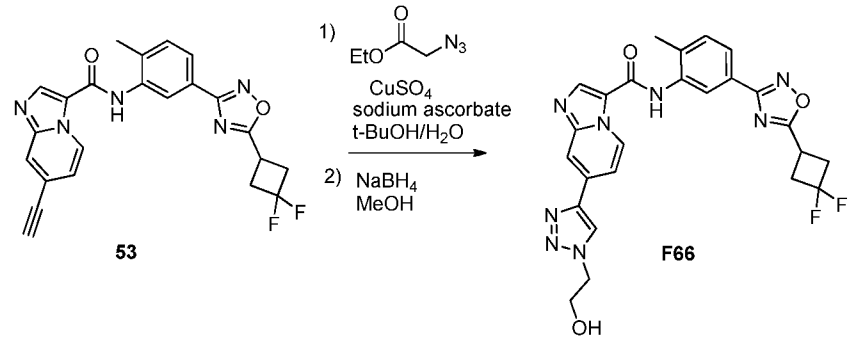
A mixture of 6-cyano-N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide (**42h**) (15.0 mg, 0.034 mmol), CuBr (9.2 mg, 0.007 mmol), Cs_2CO_3 (39 mg, 0.12 mmol), and acetimidamide hydrochloride (6.6 mg, 0.07 mmol) in DMSO (1 mL) was heated at 120 °C overnight. The reaction mixture was purified by HPLC to give N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-fluorophenyl)-6-(5-methyl-4H-1,2,4-triazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide (**F61**). MS *m/z* 495.1 $(M+1)^+$.

Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-(1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (**F65**)



A mixture of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-ethynylimidazo[1,2-a]pyridine-3-carboxamide (**53**) (10 mg, 0.023mmol), azidomethyl pivalate (3.64 mg, 0.023 mmol), $CuSO_4$ (2 μL of 0.5M aqueous solution, 0.001 mmol) and sodium ascorbate (1.4 mg, 0.007 mmol) in *t*BuOH/H_2O (1 mL, 2:1) was stirred at room temperature overnight. Then the reaction mixture was diluted and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to afford a residue which was dissolved in MeOH (1 mL). Aqueous NaOH (0.6 mL, 1N) was added and the reaction mixture was stirred for 30 minutes. The above mixture was purified by HPLC to give N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-(1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (**F65**). MS *m/z* 477.1 $(M+1)^+$.

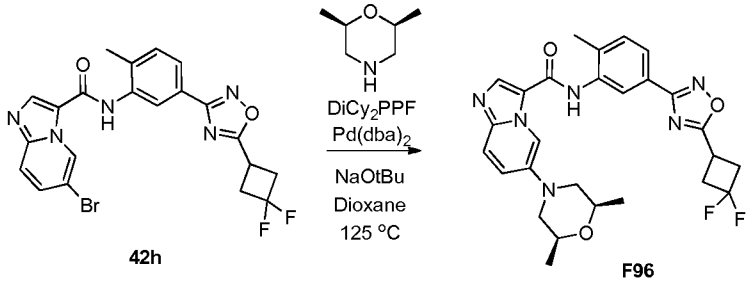
Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-(1-(2-hydroxyethyl)-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (**F66**)



A mixture of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-7-ethynylimidazo[1,2-a]pyridine-3-carboxamide (**53**) (20 mg, 0.046mmol), ethyl 2-azidoacetate (5.9 mg, 0.046 mmol), $CuSO_4$ (4 μL of 0.5M aqueous solution, 0.002 mmol) and sodium ascorbate (2.8 mg, 0.014 mmol) in *t*BuOH/H_2O (1 mL, 2:1) was stirred at room temperature overnight. Then the reaction mixture was diluted and extracted with EtOAc. The organic layers were combined, dried over Na_2SO_4, filtered and concentrated to afford a residue which was dissolved in MeOH (2 mL). $NaBH_4$ (17 mg, 0.46 mmol) was added and the reaction mixture was stirred for 30 minutes. The above mixture was purified by HPLC to give N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-

methylphenyl)-7-(1-(2-hydroxyethyl)-1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide (**F66**). ^{1}H NMR (400MHz, d_4-MeOH) δ 9.70 (m, 1H), 8.60-8.80 (m, 2H), 8.33 (s, 1H), 8.16 (d, J = 1.6 Hz, 1H), 7.96 (m, 1H), 7.85 (d, J = 7.2 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 4.62 (t, J = 4.8 Hz, 2H), 4.02 (t, J = 4.8 Hz, 2H), 3.79 (m, 1H), 3.13 (m, 4H), 2.44 (s, 3H). MS m/z 521.1 $(M+1)^+$.

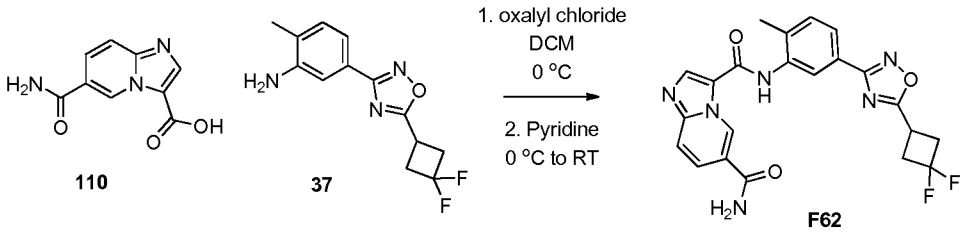
Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-((2S,6R)-2,6-dimethylmorpholino)imidazo[1,2-a]pyridine-3-carboxamide (**F96**)



42h **F96**

A mixture of 6-bromo-N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**42h**) (25 mg, 0.051 mmol), cis-2,6-dimethylmorpholine (9mg, 0.077 mmol), 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl (4 mg, 0.01 mmol), tris(dibenzylideneacetone)dipalladium(0) (2 mg, 0.003 mmol), and sodium t-butoxide (10 mg, 0.102 mmol) in anhydrous dioxane (1 mL) was heated in the microwave at 125 °C for 25 minutes. The reaction was cooled to room temperature and filtered through a plug of celite. The solvent was concentrated and the crude product was purified by reverse phase preparative HPLC to afford N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-((2S,6R)-2,6-dimethylmorpholino)imidazo[1,2-a]pyridine-3-carboxamide (**F96**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.17 (s, 1H), 8.95 (d, J = 1.6 Hz, 1H), 8.64 (s, 1H), 8.03 (d, J = 1.6 Hz, 1H), 7.84 (dd, J = 1.6, 8.0 Hz, 1H), 7.79 –7.71 (m, 2H), 7.50 (d, J = 8.0 Hz, 1H), 3.91 –3.86 (m, 1H), 3.76 –3.71 (m, 2H), 3.54 –3.51 (m, 2H), 3.23 –3.03 (m, 4H), 2.36 (s, 3H), 2.31 – 2.25 (m, 2H), 1.17 (s, 3H), 1.15 (s, 3H). MS m/z 522.22 (M+1)+.

Synthesis of N3-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3,6-dicarboxamide (**F62**)

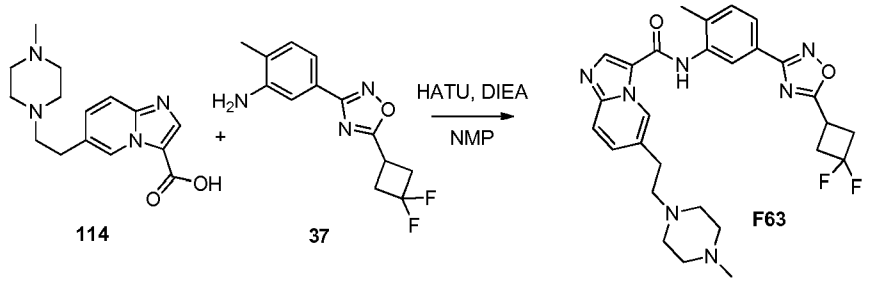


110 **37** **F62**

To a stirring suspension of 6-carbamoylimidazo[1,2-a]pyridine-3-carboxylic acid (**110**)

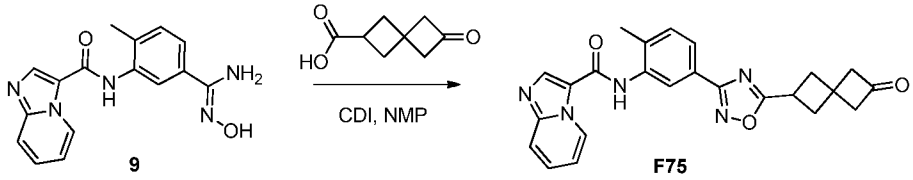
(50 mg, 0.172 mmol) in anhydrous dichloromethane (2 mL) at 0 °C under Argon was added dropwise oxalyl chloride (16 uL, 0.189 mmol). Then, a drop of anhydrous N,N-dimethylformamide was added and the reaction mixture was stirred at 0 °C for 1 hour. The solvent was concentrated. A stirring mixture of the acid chloride and methyl 5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**37**) (23 mg, 0.0861 mmol) in anhydrous pyridine (2 mL) was stirred at room temperature for 20 minutes. The crude product was purified by reverse phase preparative HPLC to give N3-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3,6-dicarboxamide (**F62**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.18 (s, 1H), 9.99 – 9.98 (m, 1H), 8.68 (s, 1H), 8.28 (s, 1H), 8.10 (d, J = 1.6 Hz, 1H), 7.98 (dd, J = 1.6, 9.2 Hz, 1H), 7.88 – 7.83 (m, 2H), 7.66 (s, 1H), 7.52 (d, J = 8.0 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.22 – 3.06 (m, 4H), 2.38 (s, 3H). MS *m/z* 452.14 $(M+1)^+$.

Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxamide (**F63**)



To a stirring solution of ethyl 6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxylate (**114**) (25 mg, 0.087 mmol) in anhydrous NMP (1 mL) was added HATU (26 mg, 0.104 mmol) and DIEA (23 uL, 0.130 mmol). The reaction mixture was stirred at room temperature for 10 minutes. Then, 5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**37**) (23 mg, 0.087 mmol) was added and the reaction was stirred for two days. The crude product was purified by reverse phase preparative HPLC to afford N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(2-(4-methylpiperazin-1-yl)ethyl)imidazo[1,2-a]pyridine-3-carboxamide (**F63**). MS *m/z* 536.3 $(M+1)^+$.

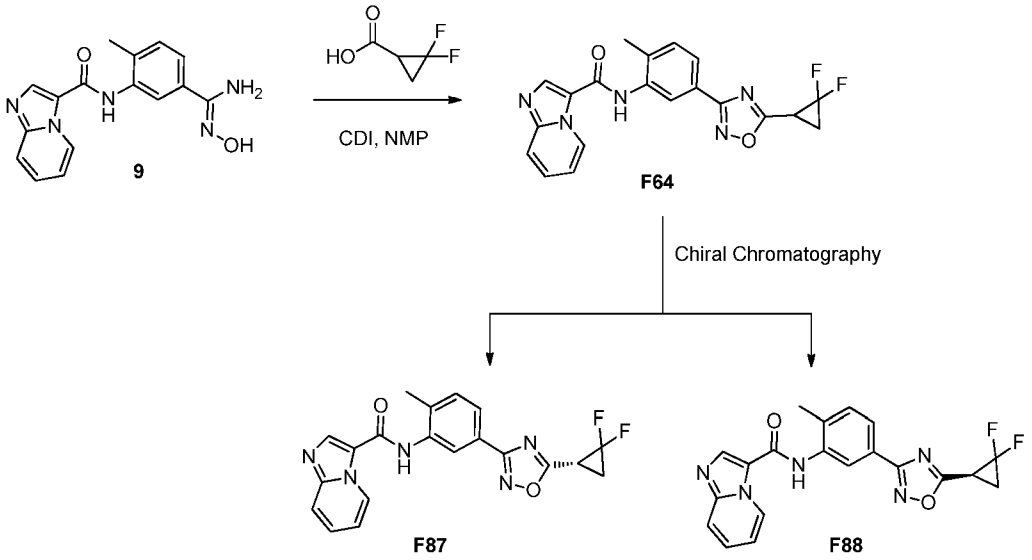
Synthesis of N-(2-methyl-5-(5-(6-oxospiro[3.3]heptan-2-yl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F75**)



To a stirring solution of 6-oxospiro[3.3]heptane-2-carboxylic acid (50 mg, 0.32 mmol)

in anhydrous NMP (1 mL) was added 1,1′-carbonyldiimidazole (CDI) (52.3 mg, 0.32 mmol). The reaction was stirred for 3 minutes. N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**9**) (100 mg, 0.32 mmol) was added and the reaction was stirred for 25 minutes. Then, the reaction was heated at 120 °C for 15 minutes. The crude reaction was purified by reverse phase preparative HPLC to give N-(2-methyl-5-(5-(6-oxospiro[3.3]heptan-2-yl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F75**). MS *m/z* 428.2 $(M+1)^+$.

Synthesis of N-(5-(5-(2,2-difluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F87** and **F88**)



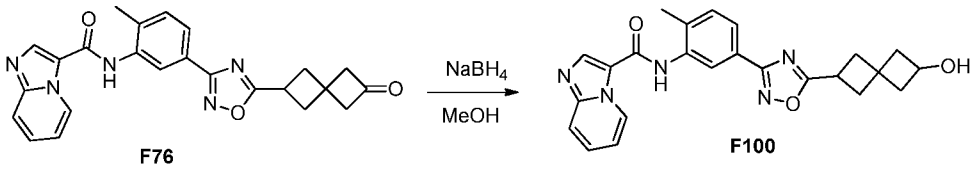
To a stirring solution of 2,2-difluorocyclopropanecarboxylic acid (325 mg, 2.66 mmol) in anhydrous NMP (7 mL) was added 1,1′-carbonyldiimidazole (CDI) (432 mg, 2.66 mmol). The reaction was stirred for 3 minutes. N-(5-(N'-hydroxycarbamimidoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**9**) (825 mg, 2.66 mmol) was added and the reaction was stirred for 25 minutes. Then, the reaction was heated at 120 °C for 15 minutes. The crude product was purified on silica gel using 10% MeOH in dichloromethane to give N-(5-(5-(2,2-difluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F64**). ^{1}H NMR (400MHz, d_6-DMSO) δ 9.60 (d, *J* = 7.2 Hz, 1H), 8.56 (d, *J* = 1.6 Hz, 1H), 8.51 (s, 1H), 8.12 (bs, 1H), 7.87 (dd, *J* = 2.0, 7.8 Hz, 1H), 7.82 (d, *J* = 9.2 Hz, 1H), 7.58 – 7.53 (m, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.16 (td, *J* = 0.8, 6.8 Hz, 1H), 3.19 – 3.12 (m, 1H), 2.48 (s, 3H), 2.45 – 2.36 (m, 1H), 2.27 – 2.18 (m, 1H). MS *m/z* 396.1 $(M+1)^+$.

The separation of enantiomers was performed using a 20x250mm ChiralPak IA column at a flow rate of 20mL/min, using Hexanes: EtOH: MeOH (60: 20: 20). Analytical methods using the same column and solvent mixture showed peak 1 eluting at 9.19 min,

and peak 2 at 13.34 min. Peak 1 was arbitrarily assigned to be the *R* isomer (**F87**) and Peak 2 was assigned to be the *S* isomer (**F88**). ^{1}H NMR for **F87** (400MHz, CD_2Cl_2) δ 9.48 (d, *J* = 6.8 Hz, 1H), 8.45 (d, *J* = 1.6 Hz, 1H), 8.35 (bs, 1H), 7.94 (bs, 1H), 7.75 (dd, *J* = 1.6, 11.6 Hz, 1H), 7.69 (d, *J* = 9.2 Hz, 1H), 7.42 (td, *J* = 1.2, 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 6.8 Hz, 1H), 3.08 – 3.01 (m, 1H), 2.36 (s, 3H), 2.33 – 2.24 (m, 1H), 2.15 – 2.06 (m, 1H). MS *m/z* 396.1 $(M+1)^+$.

^{1}H NMR for **F88** (400MHz, CD_2Cl_2) δ 9.69 (d, *J* = 7.2 Hz, 1H), 8.91 (s, 1H), 8.78 (s, 1H), 8.46 (d, *J* = 1.6 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 7.88 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.66 (td, *J* = 1.2, 7.2 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 3.19 – 3.12 (m, 1H), 2.44 – 2.36 (m, 1H), 2.27 – 2.18 (m, 1H). MS *m/z* 396.1 $(M+1)^+$.

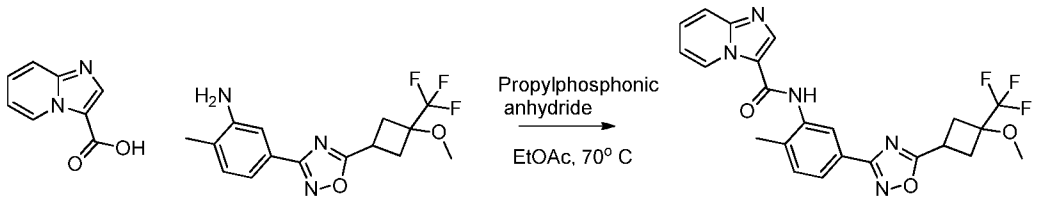
Synthesis of N-(5-(5-(6-hydroxyspiro[3.3]heptan-2-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F100**)



F76 F100

To a stirring solution of N-(2-methyl-5-(5-(6-oxospiro[3.3]heptan-2-yl)-1,2,4-oxadiazol-3-yl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F76**) (100mg, 0.23 mmol) in anhydrous methanol (1 mL) was added sodium borohydride (10.6 mg, 0.28 mmol). The reaction mixture was stirred at room temperature for 12 hours. The reaction was quenched with water and the solvent was concentrated. Purification by silica gel using 10% MeOH in dichloromethane afforded N-(5-(5-(6-hydroxyspiro[3.3]heptan-2-yl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F100**). MS *m/z* 430.1 $(M+1)^+$.

Synthesis of N-(5-(5-(3-methoxy-3-(trifluoromethyl)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F97**)

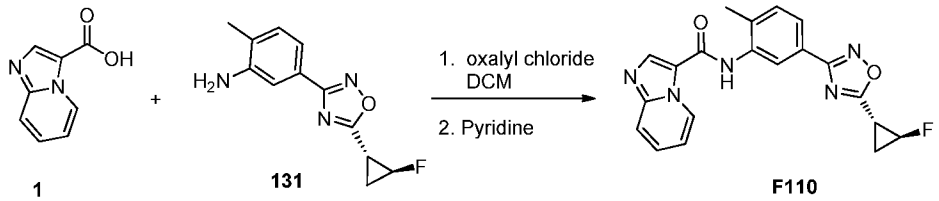


1 125 F97

A stirring mixture of imidazo[1,2-a]pyridine-3-carboxylic acid (**1**) (10 mg, 0.064 mmol) and 5-(5-(3-methoxy-3-(trifluoromethyl)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**125**) (21 mg, 0.064 mmol) in ethylacetate (1 mL) was added propylphosphonic anhydride solution 50 wt. % in ethyl acetate (76 uL, 0.128 mmol). The reaction was

heated at 70° C for 3 hours. The reaction was cooled to room temperature and diluted with a solution of saturated sodium bicarbonate. The organic was separated and washed with 2x water/brine mixture and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography using DCM:EtOAc:MeOH (1:1:0.1). N-(5-(5-(3-methoxy-3-(trifluoromethyl)cyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide **(F97)**. ^{1}H NMR (400MHz, d_6-DMSO) δ 10.06 (s, 1H), 9.47 – 9.44 (m 1H), 8.59 (s, 1H), 8.08 (d, J = 1.6 Hz, 1H), 7.83 (dd, J = 1.6, 7.6 Hz, 1H), 7.80 – 7.78 (m, 1H), 7.55 – 7.50 (m, 1H), 7.50 (d, J = 8.4 Hz, 1H), 7.20 – 7.16 (m, 1H), 3.76 – 3.68 (m, 1H), 3.38 (s, 3H), 2.88 – 2.85 (m, 4H), 2.36 (s, 3H) MS *m/z* 471.15 $(M+1)^+$.

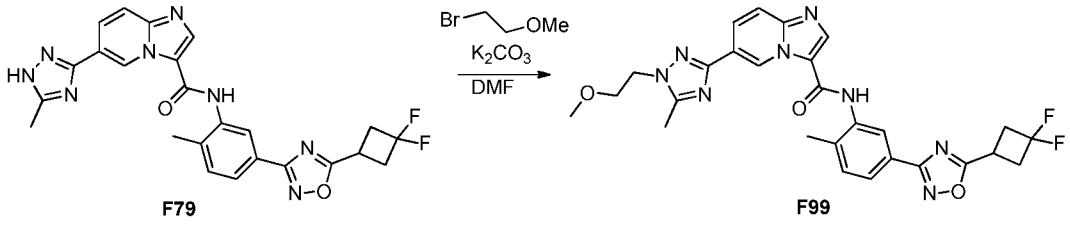
Synthesis of N-(5-(5-((1R,2S)-2-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F110**)



1 131 F110

To a stirring suspension of imidazo[1,2-a]pyridine-3-carboxylic acid (**1**) (52 mg, 0.32 mmol) in anhydrous dichloromethane (2 mL) at 0 °C under Argon was added dropwise oxalyl chloride (56 μL, 0.64 mmol). Then, a drop of anhydrous DMF was added and the reaction mixture was stirred at room temperature for 1.5 hours. The solvent was concentrated and the crude solid was added portion-wise to a stirring solution of 5-(5-((1R,2S)-2-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**131**) (62 mg, 0.27 mmol) in anhydrous pyridine (1 mL) at 0 °C. The reaction was stirred at room temperature under Argon for 30 minutes and quenched with water. The crude product was purified by preparative HPLC to yield N-(5-(5-((1R,2S)-2-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F110**). MS *m/z* 378.1 $(M+1)^+$.

Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(1-(2-methoxyethyl)-5-methyl-1H-1,2,4-triazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide (**F99**)

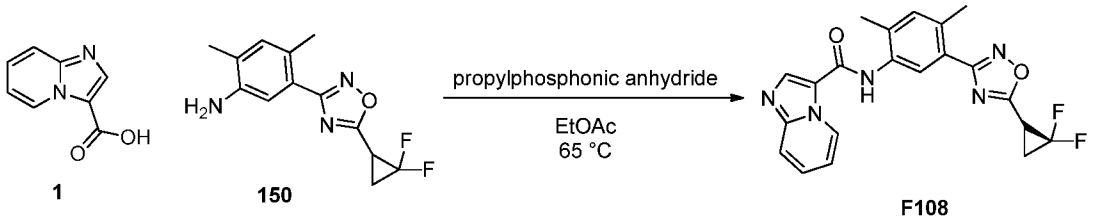


F79 F99

N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(5-methyl-1H-1,2,4-triazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide (**F79**) (6.0 mg, 0.012 mmol), 1-

bromo-2-methoxyethane (1.7 mg, 0.012 mmol) and K_2CO_3 (5.0 mg, 0.036 mmol) in DMF (0.5 mL) was heated at 120 °C for 30 minutes. The reaction mixture was purified by preparative HPLC to afford N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-(1-(2-methoxyethyl)-5-methyl-1H-1,2,4-triazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide (**F99**). ^{1}H NMR (400MHz, d_6-DMSO) δ 10.15 (s, 1H), 10.11 (m, 1H), 8.65 (s, 1H), 8.12 (d, J = 1.6 Hz, 1H), 8.06 (dd, J = 2.0, 9.2 Hz, 1H), 7.88 (dd, J = 0.8, 9.2 Hz, 1H), 7.85 (dd, J = 2.0, 8.0 Hz, 1H), 7.52 (d, J = 8.0 Hz, 1H), 4.34 (t, J = 5.2 Hz, 2H), 3.89 (m, 1H), 3.72 (t, J = 5.2 Hz, 2H), 3.24 (s, 3H), 3.02-3.20 (m, 4H), 2.47 (s, 3H), 2.39 (s, 3H). MS *m/z* 549.1 $(M+1)^+$.

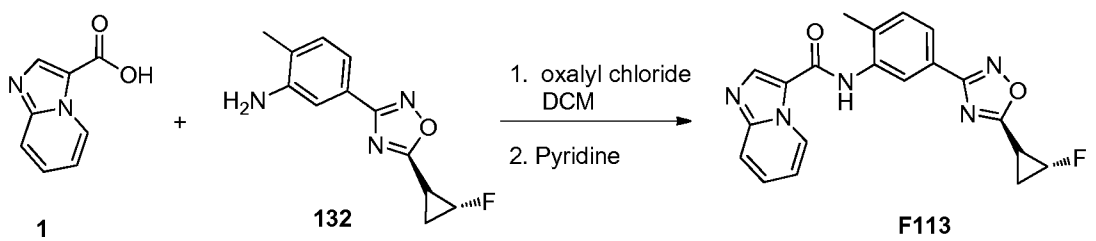
Synthesis of (R)-N-(5-(5-(2,2-difluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2,4-dimethylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F108**)



1 150 F108

To a stirring suspension of imidazo[1,2-a]pyridine-3-carboxylic acid (**1**) (25 mg, 0.154 mmol) and 5-(5-(2,2-difluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2,4-dimethylaniline (**150**) (41 mg, 0.154 mmol) in ethylacetate (1 mL) was added propylphosphonic anhydride solution 50 wt% in ethyl acetate (184 uL, 0.308 mmol). The reaction was heated at 65 °C overnight. The reaction was cooled to room temperature and diluted with a solution of saturated sodium bicarbonate. The organic was separated and washed with water/brine mixture and dried over anhydrous sodium sulfate. The crude product was purified by silica chromatography and then by a 20x250mm ChiralPak AD-H column to give (R)-N-(5-(5-(2,2-difluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2,4-dimethylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F108**). ^{1}H NMR (400MHz, *d4*-MeOD) δ 10.04 (s, 1H), 9.46 – 9.44 (m, 1H), 8.57 (s, 1H), 7.95 (s, 1H), 7.79 – 7.76 (m, 1H), 7.53 – 7.49 (m, 1H), 7.36 (s, 1H), 7.18 – 7.15 (m, 1H), 3.74 (m, 1H), 2.55 (s, 3H), 2.47 – 2.35 (m, 2H), 2.31 (s, 3H). MS *m/z* 409.14 $(M+1)^+$.

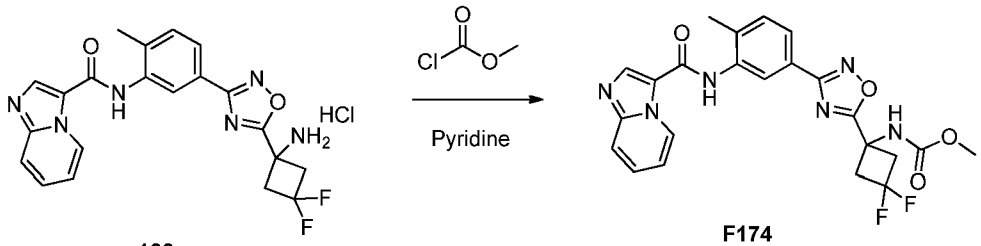
Synthesis of N-(5-(5-((1S,2R)-2-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F113**)



1 132 F113

To a stirring suspension of imidazo[1,2-a]pyridine-3-carboxylic acid (**1**) (52 mg, 0.32 mmol) in anhydrous dichloromethane (2 mL) at 0 °C under Argon was added dropwise oxalyl chloride (56 μL, 0.64 mmol). Then, a drop of anhydrous DMF was added and the reaction mixture was stirred at room temperature for 1.5 hours. The solvent was concentrated and the crude solid was added portion-wise to a stirring solution of 5-(5-((1S,2R)-2-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2-methylaniline (**132**) (62 mg, 0.27 mmol) in anhydrous pyridine (1 mL) at 0 °C. The reaction was stirred at room temperature under Argon for 30 minutes and quenched with water. The crude product was purified by preparative HPLC to yield N-(5-(5-((1R,2S)-2-fluorocyclopropyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (**F113**). MS *m/z* 378.1 $(M+1)^+$.

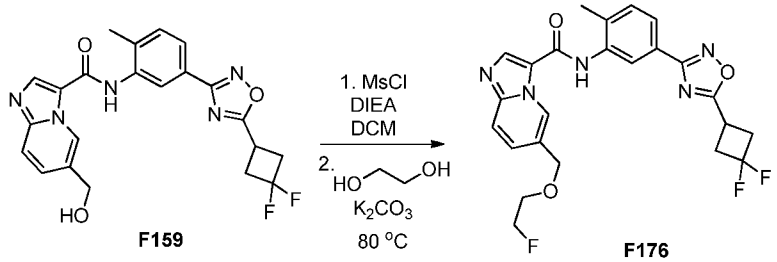
Synthesis of methyl (3,3-difluoro-1-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)cyclobutyl)carbamate (**F175**)



166 **F174**

To a stirring solution of N-(5-(5-(1-amino-3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide hydrochloride (**166**) in anhydrous pyridine (1 mL) at 0 °C was added drop-wise methyl chloroformate (19 uL, 0.26 mmol). The reaction was stirred to room temperature for 20 minutes. The crude was concentrated and purified by preparative HPLC to yield methyl (3,3-difluoro-1-(3-(3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylphenyl)-1,2,4-oxadiazol-5-yl)cyclobutyl)carbamate (**F174**). MS *m/z* 483.1 $(M+1)^+$.

Synthesis of N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-((2-fluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxamide (**F176**)



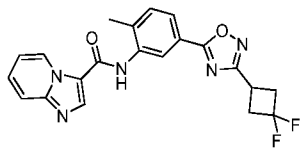
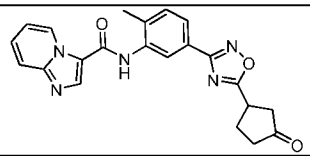
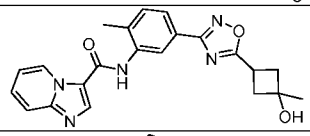
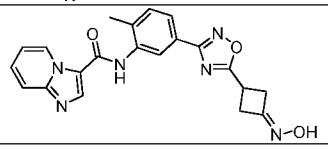
F159 **F176**

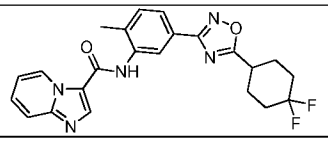
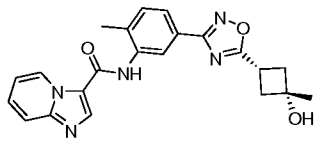
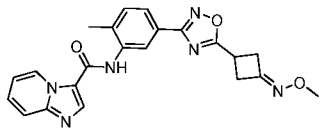
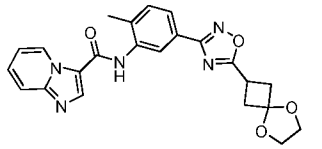
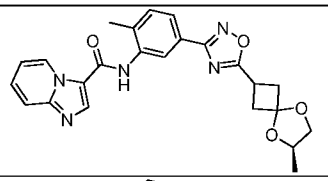
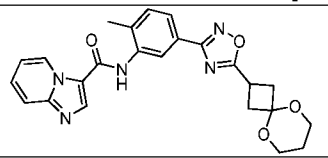
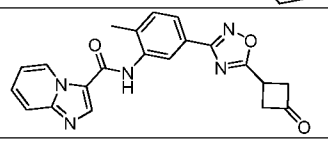
N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-

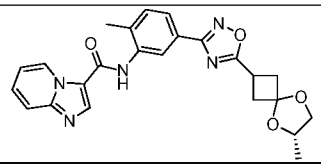
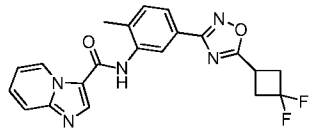
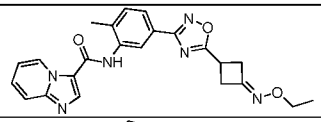
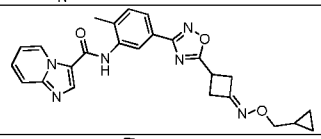
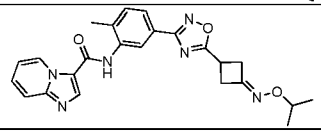
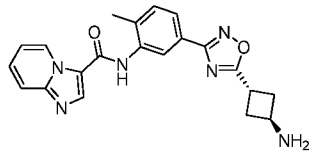
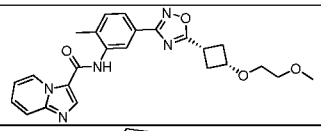
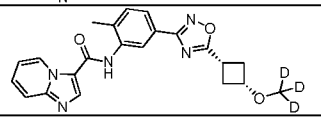
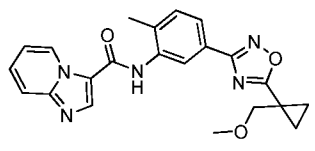
(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxamide (**F159**) (95 mg, 0.216 mmol) was dissolved in DCM (1 mL) and DIEA (0.65 mmol). MsCl (0.65 mmol) was added dropwise and the resulting mixture was stirred for 15 minutes at room temperature. The reaction mixture was subjected to aqueous workup, extracted with DCM (2 mL), dried over Na_2SO_4 and concentrated to give a crude which was dissolved in 0.8 mL of 2-fluoroethanol followed by addition of K_2CO_3 (90 mg, 0.65 mmol). The resulting mixture was heated at 120 °C for 20 minutes. The reaction mixture was subjected to standard aqueous workup and purified by silica chromatography to yield N-(5-(5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl)-2-methylphenyl)-6-((2-fluoroethoxy)methyl)imidazo[1,2-a]pyridine-3-carboxamide (**F176**). ^{1}H NMR (400 MHz, CDCl3) δ 9.56 (s, 1H), 8.60 (d, *J* = 1.6, 1H), 8.21 (s, 1H), 7.89 (dd, *J* = 1.7, 7.9, 1H), 7.77 (d, *J* = 9.2, 1H), 7.62 (s, 1H), 7.53 (dd, *J* = 1.7, 9.2, 1H), 7.42 (d, *J* = 8.1, 1H), 4.72 – 4.64 (m, 3H), 4.59 – 4.52 (m, 1H), 3.86 – 3.79 (m, 1H), 3.79 – 3.73 (m, 1H), 3.68 (m, 1H), 3.16 (m, 4H), 2.47 (s, 3H). MS *m/z* 486.1 $(M+1)^+$.

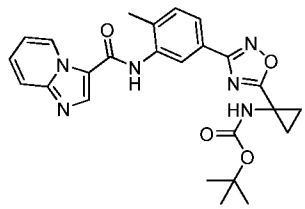
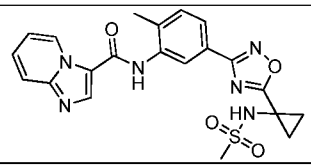
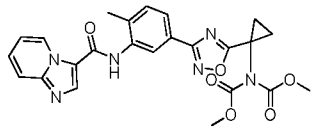
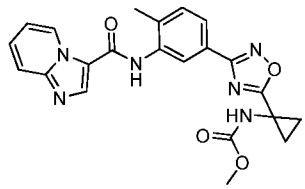
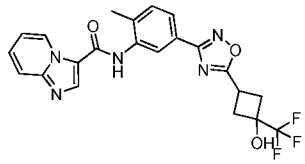
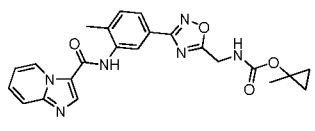
Representative compounds of Formula (I) and Formula (II) with c-kit inhibition IC_{50} values in the range of 1 nM to 100 nM, and prepared following the procedures described above, are set forth in Table 1.

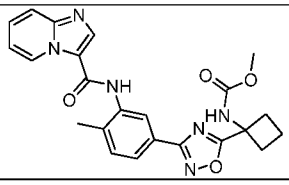
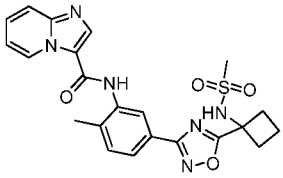
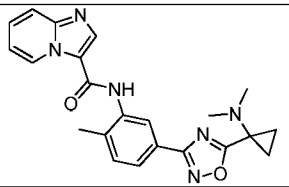
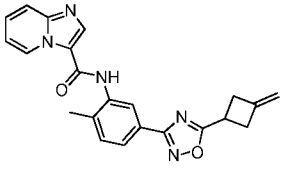
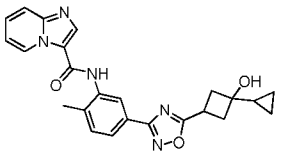
Table 1

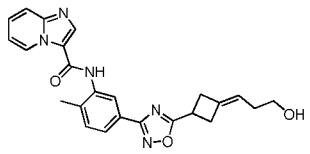
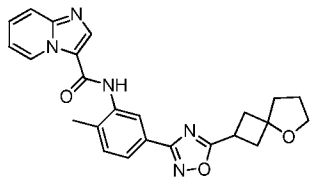
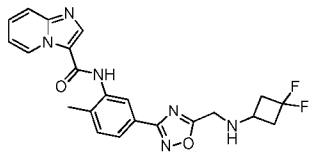
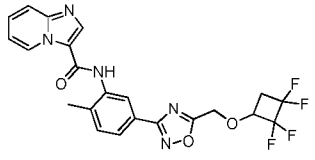
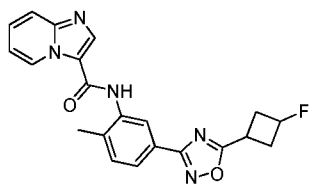
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F1		^{1}H NMR (400MHz, d_6-DMSO) δ 10.08 (s, 1H), 9.46 (d, *J* = 7.2 Hz, 1H), 8.61 (s, 1H), 8.21 (d, *J* = 2.0 Hz, 1H), 7.95 – 7.91 (m, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.19 (dt, *J* = 8.0, 1.2 Hz, 1H), 3.71 – 3.62 (m, 1H), 3.18 – 3.09 (m, 2H), 3.03 – 2.92 (m, 2H), 2.41 (s, 3H). MS *m/z* 410.1 $(M+1)^+$.	0.024
F2		MS *m/z* 402.1 $(M+1)^+$.	0.058*
F3		MS *m/z* 404.2 $(M+1)^+$.	0.164*
F4		MS *m/z* 403.1 $(M+1)^+$.	0.022

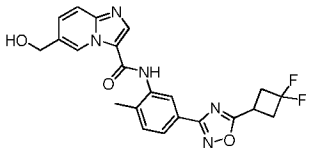
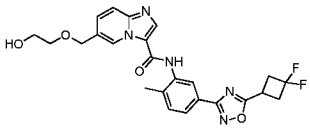
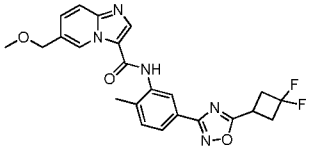
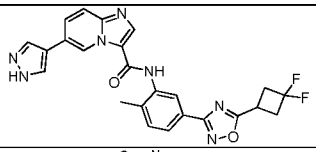
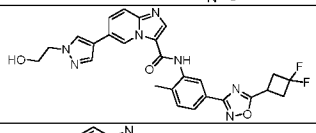
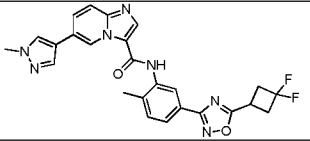
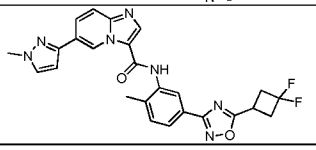
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F5		MS *m/z* 438.1 $(M+1)^+$.	0.024
F6		^{1}H NMR (400MHz, d_4-MeOH) δ 9.53 (d, *J* = 7.2 Hz, 1H), 8.49 (s, 1H), 8.13 – 8.12 (m, 1H), 7.90 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.75 (d, *J* = 9.6 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.18 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H), 3.48 – 3.40 (m, 1H), 2.58 – 2.54 (m, 4H), 2.42 (s, 3H), 1.46 (s, 3H). MS *m/z* 404.1 $(M+1)^+$.	0.119
F7		^{1}H NMR (400MHz, d_4-MeOH) δ 9.55 (d, *J* = 7.2 Hz, 1H), 8.50 (s, 1H), 8.13 – 8.12 (m, 1H), 7.90 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.75 (d, *J* = 9.6 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.18 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H), 4.02 – 3.94 (m, 1H), 3.82 (s, 3H), 3.57 – 3.30 (m, 4H), 2.86 (s, 3H). MS *m/z* 417.1 $(M+1)^+$.	0.015
F8		^{1}H NMR (400MHz, d_4-MeOH) δ 9.53 (d, *J* = 7.2 Hz, 1H), 8.50 (s, 1H), 8.13 – 8.12 (m, 1H), 7.90 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.75 (d, *J* = 9.6 Hz, 1H), 7.60 – 7.55 (m, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.18 (ddd, *J* = 7.2, 7.2, 1.2 Hz, 1H), 4.45 – 4.43 (m, 1H), 3.98 – 3.81 (m, 4H), 3.32 – 3.31 (m, 4H), 2.43 (s, 3H). MS *m/z* 432.1 $(M+1)^+$.	0.055
F9		MS *m/z* 446.1 $(M+1)^+$.	0.052
F10		MS *m/z* 446.1 $(M+1)^+$.	0.052
F11		MS *m/z* 388.1 $(M+1)^+$.	0.041*

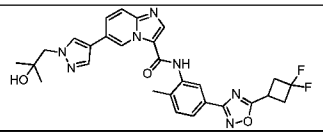
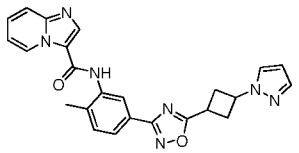
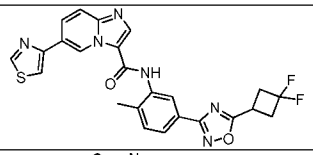
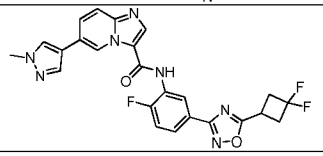
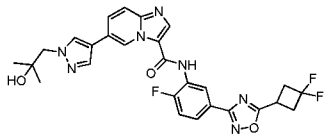
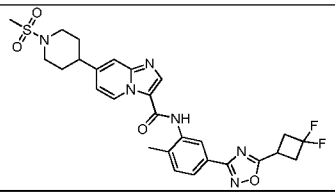
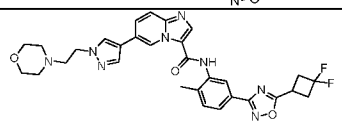
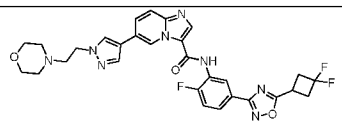
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F12		MS *m/z* 446.1 $(M+1)^+$.	0.012
F13		^{1}H NMR (400MHz, d_6-DMSO) δ 10.19 (s, 1H), 9.53 – 9.50 (m, 1H), 8.70 (s, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.90 – 7.87 (m, 1H), 7.83 (d, *J* = 1.6, 8.0 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.29 (m, 1H), 3.93 – 3.84 (m, 1H), 3.25 – 3.02 (m, 4H), 2.37 (s, 3H). MS *m/z* 410.3 $(M+1)^+$.	0.007
F14		MS *m/z* 431.2 $(M+1)^+$.	0.012
F15		MS *m/z* 457.5 $(M+1)^+$.	0.035
F16		MS *m/z* 445.2 $(M+1)^+$.	0.066
F17		^{1}H NMR (400MHz, d_6-DMSO) δ 10.16 (s, 1H), 9.50 – 9.47 (m, 1H), 8.69 (s, 1H), 8.24 (d, *J* = 4.8 Hz, 2H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.86 – 8.72 (m, 2H), 7.63 – 7.58 (m, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.27 – 7.23 (m, 1H), 4.07 – 3.95 (m, 2H), 2.76 – 2.63 (m, 4H), 2.37 (s, 3H). MS *m/z* 389.5 $(M+1)^+$.	0.109
F18		MS *m/z* 448.2 $(M+1)^+$.	0.025
F19		MS *m/z* 407.2 $(M+1)^+$.	0.009
F20		^{1}H NMR (400MHz, d_6-DMSO) δ 10.25 (s, 1H), 9.52 (d, *J*= 6.1 Hz, 1H), 8.75 (s, 1H), 8 (s, 1H), 7.9 (d, *J* = 7.7 Hz, 1H), 7.8 (d, *J* = 7 Hz, 1H), 7.71 (m, 1H), 7.49 (m, 1H), 7.32 (m, 1H), 3.73 (s, 2H), 3.31 (s, 3H), 2.36 (s, 3H), 1.42 (m, 2H), 1.29 (m, 2H).	0.049

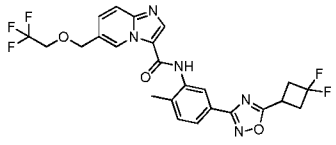
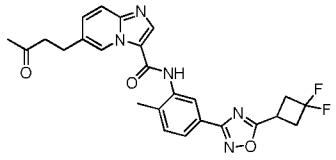
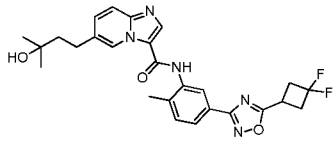
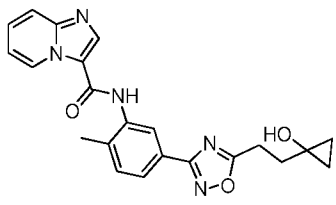
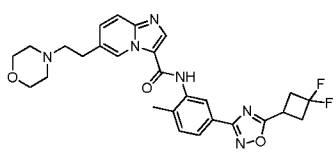
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
		MS *m/z* 404.2 $(M+1)^+$.	
F21		^{1}H NMR (400MHz, $CDCl_3$) δ 9.55 (d, *J* = 6.9 Hz, 1H), 8.46 (s, 1H), 8.23 (s, 1H), 7.82 (d, *J* = 7.4 Hz, 1H), 7.76 (d, *J* = 9 Hz, 1H), 7.72 (s, 1H), 7.45 (t, *J* = 7.3 Hz, 1H), 7.36 (d, *J* = 7.9 Hz 1H), 7.06 (t, *J* = 6.9 Hz 1H), 2.43 (s, 3H), 1.79 (m, 2H), 1.7 (m, 2H), 1.5 (s, 9H). MS *m/z* 475.2 $(M+1)^+$.	0.089
F22		MS *m/z* 453.1 $(M+1)^+$.	0.056
F23		^{1}H NMR (400MHz, DMSO) δ 10.15 (s, 1H), 9.48 (d, *J* = 6.7 Hz, 1H), 8.73 (s, 1H), 8.66 (s, 1H), 8.02 (s, 1H), 7.8 (m, 2H), 7.6 (m, 1H), 7.5 (m, 1H), 7.24 (m, 1H), 3.06 (s, 3H), 2.36 (s, 3H), 1.67 (m, 4H). MS *m/z* 453.1 $(M+1)^+$.	0.077
F24		^{1}H NMR (400MHz, $CDCl_3$) δ 9.54 (d, *J* = 7 Hz, 1H), 8.43 (s, 1H), 8.24 (s, 1H), 7.83 (dd, *J* = 7.9, 1.4 Hz, 1H), 7.77 (d, *J* = 9 Hz, 1H), 7.73 (s, 1H), 7.45 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.36 (d, *J* = 8 Hz, 1H), 7.06 (t, *J* = 6.9 Hz, 1H), 3.75 (s, 3H), 2.43 (s, 3H), 1.82 (m, 2H), 1.56 (m, 2H). MS *m/z* 433.2 $(M+1)^+$.	0.058
F25		^{1}H NMR (400MHz, d_6-DMSO) δ 10.04 (s, 1H), 9.47 – 9.45 (m,1H), 8.60 (s, 1H), 8.09 (d, *J* = 1.6 Hz, 1H), 7.83 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.80 – 7.78 (m, 1H), 7.55 – 7.50 (m, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.20 – 7.16 (m, 1H), 6.92 (s, 1H), 3.32 – 3.28 (m, 1H), 2.99 – 2.93 (m, 2H), 2.68 – 2.60 (m, 2H), 2.37 (s, 3H). MS *m/z* 458.4 $(M+1)^+$.	0.013
F26		^{1}H NMR (400MHz, d_6-DMSO) δ 10.19 (s, 1H), 9.54 – 9.51 (m, 1H), 8.72 (s, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.95 – 7.92 (m, 1H), 7.91 – 7.89 (m, 1H), 7.82 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.73 – 7.69 (m, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.35	0.058

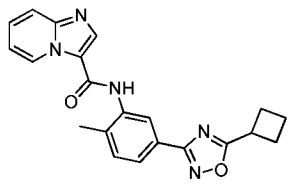
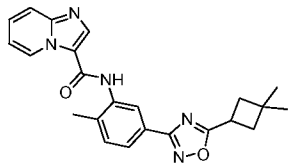
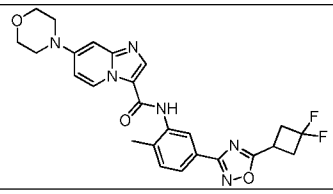
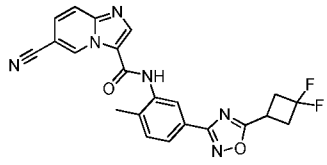
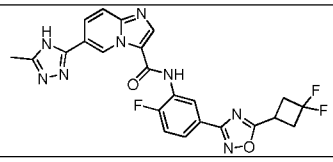
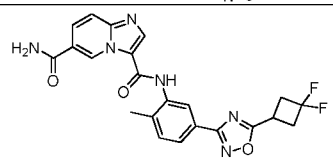
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
		– 7.32 (m, 1H), 4.54 (d, *J* = 6.0 Hz, 2H), 2.37 (s, 3H), 1.46 (s, 3H), 0.795 – 0.765 (m, 2H), 0.620 –0.587 (m, 2H). MS *m/z* 447.5 $(M+1)^+$.	
F27		MS *m/z* 447.46 $(M+1)^+$.	0.069
F28		^{1}H NMR (400MHz, d_6-DMSO) δ 10.16 (s, 1H), 9.50 (d, *J* = 6.9 Hz, 1H), 8.67 (s, 1H), 8.50 (s, 1H), 8.08 (s, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.63 (s, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.27 (s, 1H), 2.98 (s, 3H), 2.51-2.71 (m, 5H), 2.37 (s, 3H), 1.94-2.05 (m, 2H). MS *m/z* 467.51 $(M+1)^+$.	0.095
F29		MS *m/z* 403.2 $(M+1)^+$.	0.058
F30		^{1}H NMR (400MHz, $CDCl_3$) δ 9.47 (d, *J*= 7.2 Hz, 1H), 8.47 (d, *J*= 1.6 Hz, 1H), 8.14 (s, 1H), 7.80 (sd, *J*=1.6, 7.6 Hz, 1H), 7.68 (d, *J*= 8.8 Hz, 1H), 7.58 (s, 1H), 7.37 (m, 1H), 7.31 (d, *J*= 8.0 Hz, 1H), 6.97 (dt, *J*= 0.8, 7.2 Hz, 1H), 4.85 (m, 2H), 3.75 (m, 1H), 3.17 (m, 4H), 2.36 (s, 3H). MS *m/z* 386.2 $(M+1)^+$.	0.016
F31		^{1}H NMR (400MHz, d_6-DMSO) δ 10.03 (s, 1H), 9.46 (d, *J* = 6.9 Hz, 1H), 8.59 (s, 1H), 8.07 (d, *J* = 1.6 Hz, 1H), 7.84 – 7.76 (m, 2H), 7.55 – 7.46 (m, 2H), 7.11-7.15 (m, 1H), 5.19 (s, 1H), 4.31-4.45 (m, 1H), 3.31-3.45 (m, 1H), 2.43 (t, *J* = 9.0 Hz, 2H), 2.37 (s, 3H) 2.11-2.45 (m, 3H), 1.56 – 1.38 (m, 2H), 1.17 (t, *J* = 5.7 Hz, 1H), 0.36 – 0.25 (m, 2H), 0.24 – 0.09 (m, 1H). MS *m/z* 430.47 $(M+1)^+$.	0.05

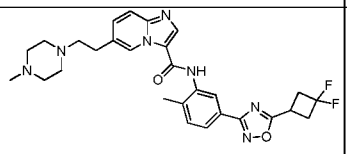
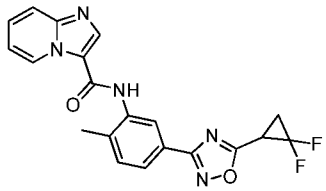
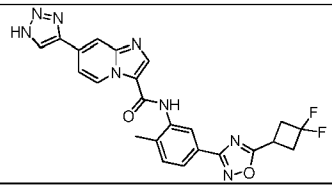
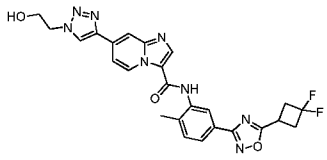
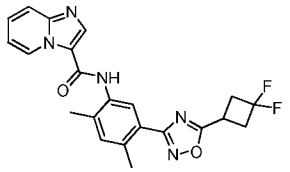
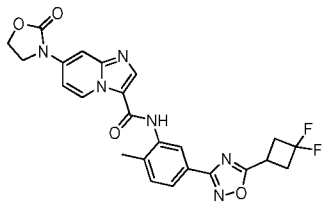
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F32		^{1}H NMR (400MHz, d_6-DMSO) δ 10.20 (s, 1H), 9.51 (d, J = 6.9 Hz, 1H), 8.70 (s, 1H), 8.05 (s, 1H), 7.91 – 7.83 (m, 2H), 7.69 (s, 1H), 7.51 (d, J = 8.1 Hz, 1H), 7.31 (s, 1H), 5.68-5.78 (m, 1H), 4.18 (q, J = 7.9 Hz, 2H), 3.81 (q, J = 7.9 Hz, 2H), 3.23-3.34 (m, 2H), 2.63-2.74 (m, 3H), 2.38 (s, 3H), 1.14-1.24 (m,7H). MS m/z 430.47 $(M+1)^+$.	0.025
F33		^{1}H NMR (400MHz, d_6-DMSO) δ 10.11 (d, J = 8.0 Hz, 1H), 9.48 (d, J = 6.9 Hz, 1H), 8.64 (s, 1H), 8.06 (d, J = 5.8 Hz, 1H), 7.82 (d, J = 9.2 Hz, 2H), 7.62 – 7.55 (m, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 6.5 Hz, 1H), 3.85 –3.77 (m, 2H), 3.63-3.72 (m, 3H), 3.51 (s, 1H), 2.66 (d, J = 9.8 Hz, 1H), 2.53 (s, 2H), 2.36 (s, 3H), 2.00 (t, J = 7.3 Hz, 1H), 1.93 – 1.77 (m, 2H). MS m/z 430.47 $(M+1)^+$.	0.088
F34		^{1}H NMR (400MHz, $CDCl_3$) δ 9.56 (d, J = 7.2 Hz, 1H), 8.62 (d, J = 1.6 Hz, 1H), 8.22 (s, 1H), 7.88 (dd, J = 1.6, 8.0 Hz, 1H), 7.78 (d, J = 9.2 Hz, 1H), 7.60 (s, 1H), 7.47 (m, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.08 (m, 1H), 4.10 (s, 2H), 3.41 (m, 1H), 2.85 (m, 2H), 2.46 (s, 3H), 2.38 (m, 2H), 2.01 (br, 1H). MS m/z 439.1 $(M+1)^+$.	0.016
F35		^{1}H NMR (400MHz, $CDCl_3$) δ = 9.56 (d, J = 6.9 Hz, 1H), 8.64 (d, J = 1.6 Hz, 1H), 8.22 (s, 1H), 7.90 (dd, J = 1.7, 7.9 Hz, 1H), 7.79 (d, J = 9.0 Hz, 1H), 7.60 (s, 1H), 7.51 – 7.44 (m, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.08 (t, J = 6.9 Hz, 1H), 5.05 (d, J = 14.2 Hz, 1H), 4.87 (d, J = 14.2 Hz, 1H), 4.53 (m, 1H), 2.94 (m, 1H), 2.74 – 2.50 (m, 1H), 2.47 (s, 3H). MS m/z 476.1 $(M+1)^+$.	0.003
F36		1H NMR (400MHz, d6-DMSO) δ 10.18 (s, 1H), 9.53 – 9.50 (m, 1H), 8.69 (s, 1H), 8.07 (d, J = 1.6 Hz, 1H), 7.89 – 7.86 (m, 1H), 7.84 (dd, J = 1.6, 8.0 Hz, 1H), 7.70 – 7.65 (m, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.32 – 7.29 (m, 1H), 5.48 – 5.28 (m, 1H), 3.99 – 3.91 (m, 1H), 2.81 – 2.73 (m, 4H), 2.37 (s, 3H).	0.028

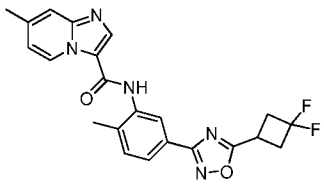
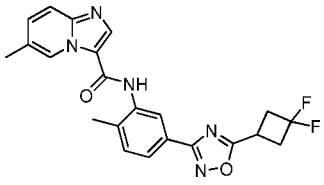
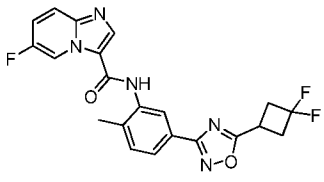
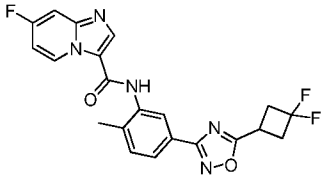
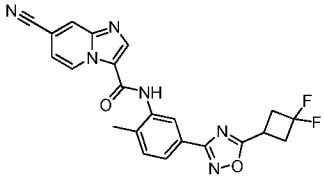
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
		MS m/z 392.14 (M+1)+.	
F37		^{1}H NMR (400MHz, $CDCl_3$) δ 9.39 (m, 1H), 8.42 (d, *J* = 1.6 Hz, 1H), 8.04 (s, 1H), 7.70 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.60 (d, *J* = 9.2 Hz, 1H), 7.42 (s, 1H), 7.36 (dd, *J* = 1.7, 9.2 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 1H), 4.63 (d, *J* = 5.7 Hz, 2H), 3.63–3.41 (m, 1H), 3.09–2.85 (m, 4H), 2.28 (s, 3H), 1.82 (t, *J* = 5.9 Hz, 1H). MS *m/z* 440.1 $(M+1)^+$.	0.06
F38		^{1}H NMR (400MHz, $CDCl_3$) δ 9.56 (m, 1H), 8.60 (d, *J* = 1.5 Hz, 1H), 8.21 (s, 1H), 7.89 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.77 (d, *J* = 9.2 Hz, 1H), 7.60 (s, 1H), 7.50 (dd, *J* = 1.7, 9.2 Hz, 1H), 7.42 (d, *J* = 7.9 Hz, 1H), 4.65 (s, 2H), 3.82 (s, 2H), 3.73–3.61 (m, 3H), 3.15 (m, 4H), 2.46 (s, 3H), 2.04 (s, 1H). MS *m/z* 484.2 $(M+1)^+$.	0.025
F39		^{1}H NMR (400MHz, $CDCl_3$) δ 9.55 (m, 1H), 8.62 (d, *J* = 1.6 Hz, 1H), 8.21 (s, 1H), 7.89 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.76 (d, *J* = 9.2 Hz, 1H), 7.59 (s, 1H), 7.50 (dd, *J* = 1.7, 9.2 Hz, 1H), 7.41 (d, *J* = 8.1 Hz, 1H), 4.54 (s, 2H), 3.78–3.62 (m, 1H), 3.44 (s, 3H), 3.23–3.08 (m, 4H), 2.44 (s, 3H). MS *m/z* 454.1 $(M+1)^+$.	0.037
F40		MS *m/z* 476.1 $(M+1)^+$.	0.009
F41		MS *m/z* 520.2 $(M+1)^+$.	0.011
F42		MS *m/z* 490.1 $(M+1)^+$.	0.007
F43		MS *m/z* 490.1 $(M+1)^+$.	0.012

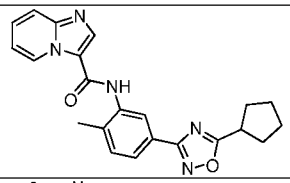
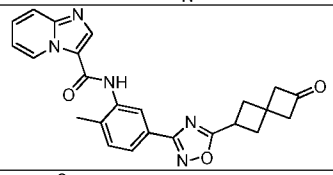
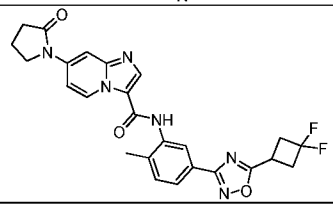
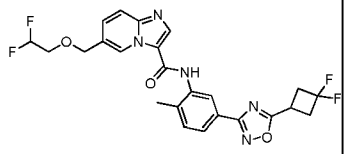
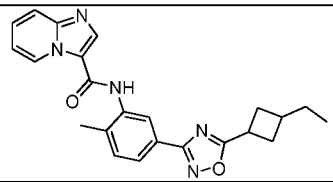
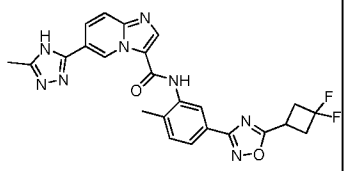
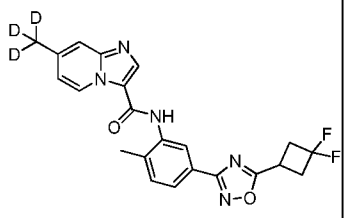
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F44		MS *m/z* 548.2 $(M+1)^+$.	0.006
F45		^{1}H NMR (400MHz, d_6-DMSO) δ 10.20 (s, 1H), 9.54 – 9.51 (m, 1H), 8.71 (s, 1H),8.10 (dd, *J* = 1.6, 7.2 Hz, 1H), 7.89 – 7.85 (m, 3H), 7.70 – 7.66 (m, 1H), 7.54 – 7.50 (m, 2H), 7.33 – 7.29 (m, 1H), 6.28 – 6.25 (m, 1H), 5.04 – 4.96 (m, 1H), 3.82 – 3.73 (m, 1H), 3.10 – 2.85 (m, 4H), 2.37 (s, 3H). MS *m/z* 440.18 $(M+1)^+$.	0.071
F46		MS *m/z* 493.1 $(M+1)^+$.	0.013
F47		MS *m/z* 494.1 $(M+1)^+$.	0.033
F48		^{1}H NMR (400MHz, d_6-DMSO) δ 10.35 (s, 1H), 9.63 (s, 1H), 8.61 (s, 1H), 8.38 (dd, *J* = 2.0, 7.2 Hz, 1H), 8.21 (s, 1H), 7.90-7.96 (m, 2H), 7.56 (dd, *J* = 8.4, 10.0 Hz,1H), 4.77 (s, 1H), 4.06 (s, 2H), 3.91 (m, 1H), 3.08-3.25 (m, 4H), 1.10 (s, 6H). MS *m/z* 552.2 $(M+1)^+$.	0.016
F49		MS *m/z* 571.2 $(M+1)^+$.	0.033
F50		MS *m/z* 588.9 $(M+1)^+$.	0.026
F51		MS *m/z* 592.8 $(M+1)^+$.	0.085

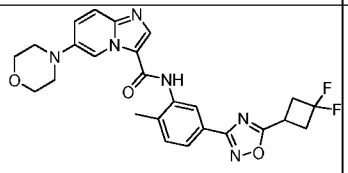
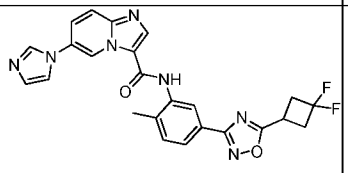
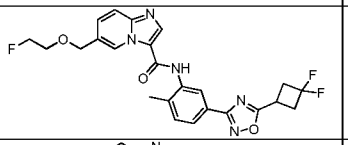
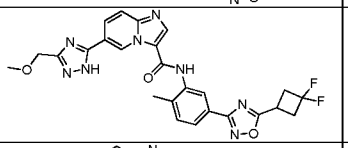
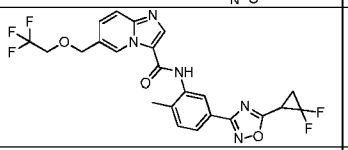
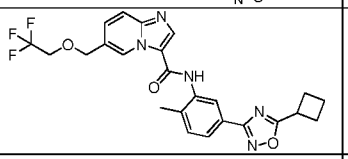
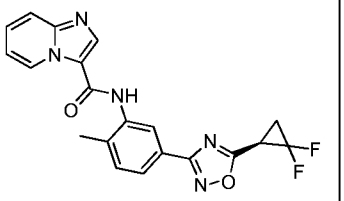
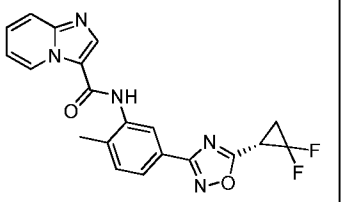
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F52		^{1}H NMR (400MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.59 (d, *J* = 1.6 Hz, 1H), 8.23 (s, 1H), 7.90 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.80 (d, *J* = 9.2 Hz, 1H), 7.63 (s, 1H), 7.51 (dd, *J* = 2.0, 9.2 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 4.75 (s, 2H), 3.91 (q, *J* = 8.4 Hz, 2H), 3.69 (m, 1H), 3.15 (m, 4H), 2.46 (s, 3H). MS *m/z* 522.1 $(M+1)^+$.	0.079
F53		^{1}H NMR (400MHz, d_6-DMSO) δ 10.19 (s, 1H), 9.37 (s, 1H), 8.70 (s, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.86 – 7.83 (m, 2H), 7.66 (dd, *J* = 1.6, 9.2 Hz, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.24 – 3.05 (m, 4H), 2.89 – 2.86 (m, 4H), 2.37 (s, 3H), 2.11 (s, 3H). MS *m/z* 480.18 $(M+1)^+$.	0.045
F54		^{1}H NMR (400MHz, d_6-DMSO) δ 10.18 (s, 1H), 9.36 (s, 1H), 8.68 (s, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.86 – 7.82 (m, 2H), 7.65 – 7.62 (m, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.25 – 3.04 (m, 4H), 2.78 – 2.73 (m, 2 H), 2.37 (s, 3H), 1.71 – 1.67 (m, 2H), 1.16 (s, 6H). MS *m/z* 496.21 $(M+1)^+$.	0.031
F55a		^{1}H NMR (400MHz, CD_2Cl_2) δ 9.89 (d, *J* = 6.8 Hz, 1H), 9.81 (s, 1H), 9.56 (s, 1H), 8.21 (s, 1H), 8.19 (d, *J* =8.0 Hz, 1H), 8.0 (t, *J* = 8.0 Hz, 1H), 7.88 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 3.23 (t, *J* = 7.2 Hz, 2H), 2.47 (s, 3H), 2.12 (t, *J* = 7.2 Hz, 2H), 0.79 (t, *J* = 6.8 Hz , 2H), 0.53 (t, *J* = 6.8 Hz 2H). MS *m/z* 404.2 $(M+1)^+$.	0.092
F56		^{1}H NMR (400MHz, d_6-DMSO) δ 10.10 (s, 1H), 9.46 (s, 1H), 8.63 (s, 1H), 8.10 (d, *J* = 1.6 Hz, 1H), 7.86 – 7.83 (m, 2H), 7.54 – 7.50 (m, 2H), 4.03 – 4.00 (m, 2H), 3.92 – 3.84 (m, 1H), 3.69 – 3.63 (m, 2H), 3.54 – 3.43 (m, 4H), 3.23 – 3.04 (m, 8H), 2.38 (s, 3H).	0.054

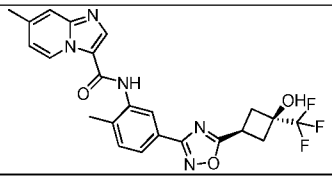
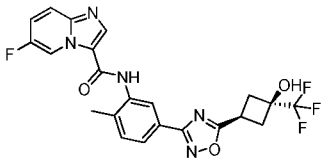
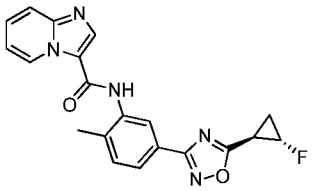
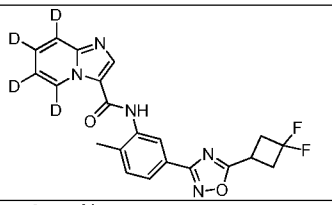
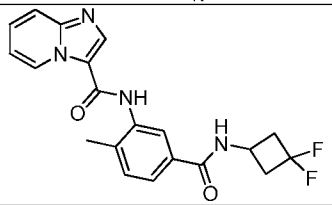
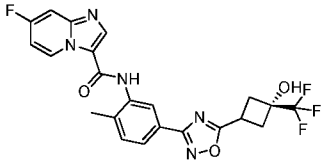
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
		MS *m/z* 522.22 $(M+1)^+$.	
F57		^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.56 (d, *J*=6.8, 1H), 8.62 (s, 1H), 8.39 (d, *J* = 1.6 Hz, 1H), 8.35 (s, 1H), 7.78 (dd, *J* = 1.7, 7.9 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.10 (t, *J* = 6.9 Hz, 1H), 3.75 (qd, *J* = 1.2, 8.8 Hz, 1H), 2.52 – 2.38 (m, 4H), 2.37 (d, *J* = 4.3 Hz, 3H), 2.18 – 1.89 (m, 2H). MS *m/z* 374.3 $(M+1)^+$.	0.023
F58		NMR (400 MHz, d_6-DMSO) δ 10.20 (s, 1H), 9.53 (d, *J* = 6.9 Hz, 1H), 8.71 (s, 1H), 8.06 (d, *J* = 1.6 Hz, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.84 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.69 (t, *J* = 7.9 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.32 (t, *J* = 6.9 Hz, 1H), 3.95 – 3.84 (m, 1H), 2.36 (s, 3H), 2.29 – 2.17 (m, 4H), 1.25 (s, 3H), 1.12 (d, *J* = 22.6 Hz, 3H). MS *m/z* 402.1 $(M+1)^+$.	0.02
F59		MS *m/z* 495.1 $(M+1)^+$.	0.007
F60		^{1}H NMR (400MHz, d_6-DMSO) δ 10.27 (s, 1H), 9.94 – 9.93 (m, 1H), 8.71 (s, 1H), 8.08 (d, *J* = 2.0 Hz, 1H), 7.96 (dd, *J* = 0.8, 9.2 Hz, 1H), 7.85 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.80 (dd, *J* = 1.6, 9.2 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 3.92 – 3.84 (m, 1H), 3.24 – 3.04 (m, 4H), 2.37 (s, 3H). MS *m/z* 434.13 $(M+1)^+$.	0.092
F61		MS *m/z* 495.1 $(M+1)^+$.	0.154
F62		^{1}H NMR (400MHz, d_6-DMSO) δ 10.18 (s, 1H), 9.99 – 9.98 (m, 1H), 8.68 (s, 1H), 8.28 (s, 1H), 8.10 (d, *J* = 1.6 Hz, 1H), 7.98 (dd, *J* = 1.6, 9.2 Hz, 1H), 7.88 – 7.83 (m, 2H), 7.66 (s, 1H), 7.52 (d, *J*	0.094

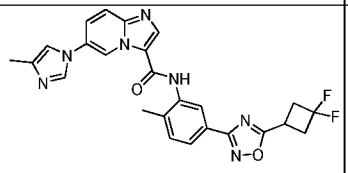
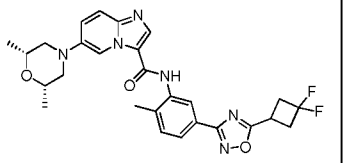
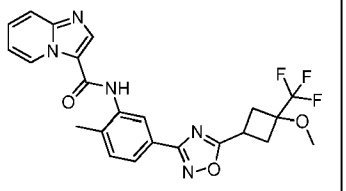
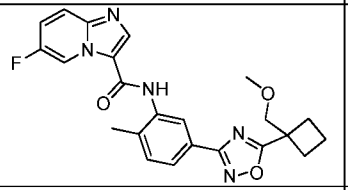
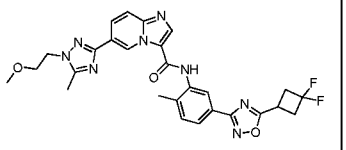
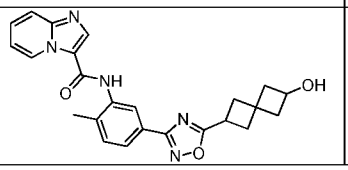
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
		= 8.0 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.22 – 3.06 (m, 4H), 2.38 (s, 3H). MS *m/z* 452.14 $(M+1)^+$.	
F63		MS *m/z* 536.3 $(M+1)^+$.	0.082
F64		^{1}H NMR (400 MHz, CD_2Cl_2) δ 9.60 (t, *J* = 11.7 Hz, 1H), 8.57 (t, *J* = 4.6 Hz, 1H), 8.51 (s, 1H), 8.12 (s, 1H), 7.87 (dd, *J* = 1.7, 7.9 Hz, 1H), 7.82 (d, *J* = 9.0 Hz, 1H), 7.62 – 7.48 (m, 1H), 7.48 – 7.37 (m, 1H), 7.16 (td, *J* = 0.8, 6.9 Hz, 1H), 3.16 (ddd, *J* = 7.9, 10.5, 11.3 Hz, 1H), 2.48 (s, 3H), 2.40 (dtd, *J* = 5.8, 8.1, 12.4 Hz, 1H), 2.22 (tdd, *J* = 5.6, 8.3, 11.5 Hz, 2H). MS *m/z* 396.1 $(M+1)^+$.	0.052
F65		MS *m/z* 477.1 $(M+1)^+$.	0.013
F66		^{1}H NMR (400MHz, d_4-MeOH) δ 9.70 (m, 1H), 8.60-8.80 (m, 2H), 8.33 (s, 1H), 8.16 (d, *J* = 1.6 Hz, 1H), 7.96 (m, 1H), 7.85 (d, *J* = 7.2 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 4.62 (t, *J* = 4.8 Hz, 2H), 4.02 (t, *J* = 4.8 Hz, 2H), 3.79 (m, 1H), 3.13 (m, 4H), 2.44 (s, 3H). MS *m/z* 521.1 $(M+1)^+$.	0.016
F67		^{1}H NMR (400MHz, d_4-MeOH) δ 9.75 (d, *J* = 6.8 Hz, 1H), 8.75 (s, 1H), 8.08 (s, 1H), 8.02 (m, 2H), 7.55 (m, 1H), 7.36 (s, 1H), 3.79 (m, 1H), 3.11 (m, 4H), 2.63 (s, 3H), 2.39 (s, 3H). MS *m/z* 424.1 $(M+1)^+$.	0.049
F68		^{1}H NMR (400MHz, d_6-DMSO) δ 10.12 (s, 1H), 9.45 (d, *J* = 7.6 Hz, 1H), 8.64 (s, 1 H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.84 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.76 (m, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 4.54 (t, *J* = 8.4 Hz, 2H), 4.19 (t, *J* = 8.4 Hz, 2H), 3.89 (m, 1H), 3.15 (m, 4H), 2.38 (s, 3H).	0.039

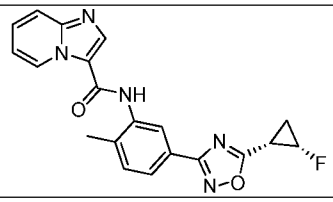
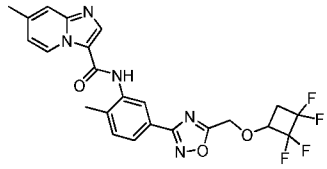
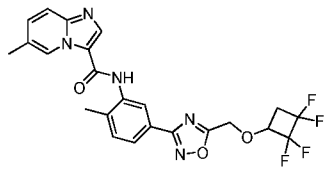
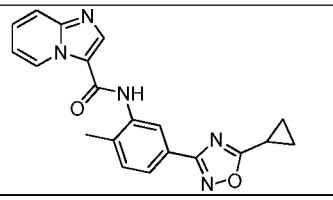
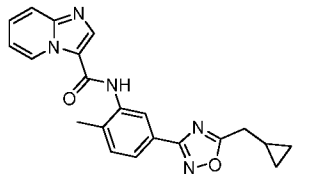
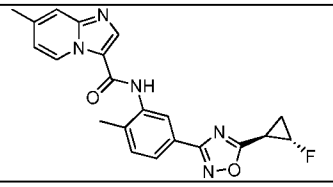
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
		MS *m/z* 495.1 $(M+1)^+$.	
F69		^{1}H NMR (400MHz, d_6-DMSO) δ 9.97 (s, 1H), 9.33 – 9.31 (m, 1H), 8.52 (s, 1H), 8.07 (d, *J* = 1.6 Hz, 1H), 7.82 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.57 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.03 (dd, *J* = 1.6, 7.2 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.23 – 3.06 (m, 4H), 2.43 (s, 3H), 2.36 (s, 3H). MS *m/z* 423.15 $(M+1)^+$.	0.020
F70		^{1}H NMR (400MHz, d_6-DMSO) δ 9.99 (s, 1H), 9.29 (s, 1H), 8.53 (s, 1H), 8.09 (d, *J* = 2.0 Hz, 1H), 7.82 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.71 – 7.69 (m, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.39 (dd, *J* = 1.6, 9.2 Hz, 1H), 3.91 – 3.84 (m, 1H), 3.23 – 3.05 (m, 4H), 2.36 (s, 6H). MS *m/z* 423.15 $(M+1)^+$.	0.026
F71		^{1}H NMR (400MHz, d_6-DMSO) δ 10.13 (s, 1H), 9.48 – 9.46 (m, 1H), 8.63 (s, 1H), 8.06 (d, *J* = 2.0 Hz, 1H), 7.90 – 7.86 (m, 1H), 7.84 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.67 – 7.62 (m, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 3.90 – 3.85 (m, 1H), 3.23 – 3.05 (m, 4H), 2.36 (s, 3H). MS *m/z* 427.13 $(M+1)^+$.	0.046
F72		^{1}H NMR (400MHz, d_6-DMSO) δ 10.08 (s, 1H), 9.50 – 9.46 (m, 1H), 8.58 (s, 1H), 8.06 (d, *J* = 1.6 Hz, 1H), 7.83 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.71 – 7.68 (m, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.26 – 7.22 (m, 1H), 3.90 – 3.85 (m, 1H), 3.23 – 3.04 (m, 4H), 2.36 (s, 3H). MS *m/z* 427.13 $(M+1)^+$.	0.032
F73		^{1}H NMR (400MHz, d_6-DMSO) δ 10.29 (s, 1H), 9.55 – 9.52 (m, 1H), 8.77 (s, 1H), 8.59 – 8.57 (m, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.85 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.51 (d, *J*= 8.4 Hz, 1H), 7.48 (dd, *J* = 2.0, 7.6 Hz, 1H), 3.90 – 3.85 (m, 1H), 3.23 – 3.03 (m, 4H), 2.36 (s, 3H). MS *m/z* 434.13 $(M+1)^+$.	0.104

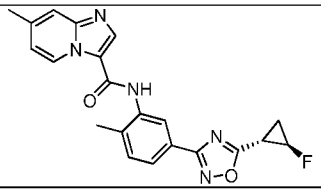
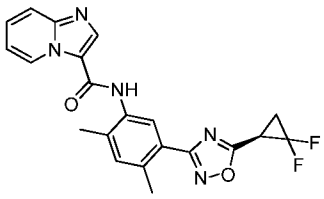
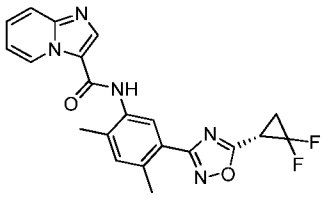
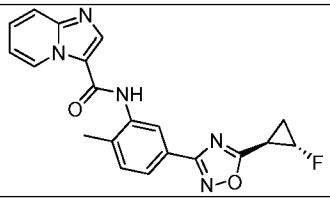
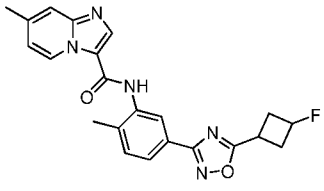
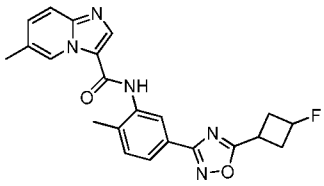
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F74		MS *m/z* 388.0 $(M+1)^+$.	0.033
F75		MS *m/z* 428.0 $(M+1)^+$.	0.017
F76		MS *m/z* 493.2 $(M+1)^+$.	0.037
F77		^{1}H NMR (400MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.58 (d, *J* = 1.6 Hz, 1H), 8.25 (s, 1H), 7.89 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.78 (d, *J* = 9.2 Hz, 1H), 7.68 (s, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 5.94 (tt, *J* = 55.2, 4.0 Hz, 1H), 4.70 (s, 2H), 3.75 (dt, *J* = 4.0, 13.6 Hz, 2H), 3.68 (m, 1H), 3.17 (m, 4H), 2.46 (s, 3 H). MS *m/z* 504.0 $(M+1)^+$.	0.032
F78		MS *m/z* 392.1 $(M+1)^+$.	0.01
F79		^{1}H NMR (400MHz, *d4*-MeOH) δ 10.21 (m, 1H), 8.52 (s, 1H), 8.19 (d, *J* = 1.6 Hz, 1H), 8.15 (dd, *J* = 1.6, 9.2 Hz, 1H), 7.93 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.82 (dd, *J* = 0.8, 9.2 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 3.79 (m, 1H), 3.15 (m, 4H), 2.51 (s, 3H), 2.45 (s, 3H). MS *m/z* 490.7 $(M+1)^+$.	0.055
F80		^{1}H NMR (400MHz, CD_2Cl_2) δ 9.56 (d, *J* = 7.2 Hz, 1H), 8.91 (s, 1H), 8.87 (s, 1H), 8.46 (d, *J* = 1.2 Hz, 1H), 7.89 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.69 (s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.09 (dd, *J* = 1.2, 7.2 Hz, 1H), 3.77 – 3.68 (m, 1H), 3.21 – 3.13 (m, 4H), 2.49 (s, 3H). MS *m/z* 427.2 $(M+1)^+$.	0.019

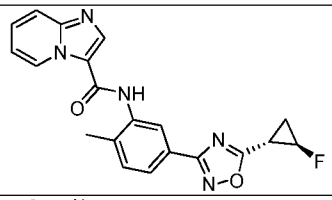
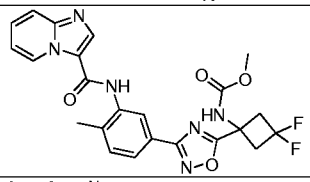
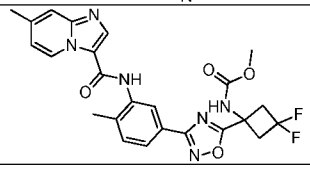
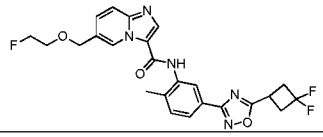
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F81		MS *m/z* 495.1 $(M+1)^+$.	0.026
F82		MS *m/z* 475.7 $(M+1)^+$.	0.078
F83		MS *m/z* 485.7 $(M+1)^+$.	0.029
F84		MS *m/z* 520.7 $(M+1)^+$.	0.022
F85		MS *m/z* 508.1 $(M+1)^+$.	0.069
F86		MS *m/z* 486.1 $(M+1)^+$.	0.049
F87		^{1}H NMR (400MHz, CD_2Cl_2) δ 9.49 (d, *J* = 6.8 Hz, 1H), 8.45 (d, *J* = 1.6 Hz, 1H), 8.35 (s, 1H), 7.94 (s, 1H), 7.75 (dd, *J* = 2.0, 7.8 Hz, 1H), 7.69 (d, *J* = 9.2 Hz, 1H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.03 (t, *J* = 6.8 Hz, 1H), 3.08–3.01 (m, 1H), 2.36 (s, 3H), 2.33–2.24 (m, 1H), 2.15-2.06 (m, 1H). MS *m/z* 396.1 $(M+1)^+$.	0.046
F88		^{1}H NMR (400MHz, CD_2Cl_2) δ 9.70 (d, *J* = 7.2 Hz, 1H), 8.91 (s, 1H), 8.78 (s, 1H), 8.46 (d, *J* = 1.6 Hz, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 8.38 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.66 (t, *J* = 8.4 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.25 (t, *J* = 6.8 Hz, 1H), 3.19–3.12 (m, 1H), 2.49 (s, 3H), 2.44–2.36 (m, 1H), 2.27-2.18 (m, 1H). MS *m/z* 396.1 $(M+1)^+$.	0.066

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F89		MS *m/z* 472.1 $(M+1)^+$.	0.025
F90		^{1}H NMR (400MHz, CD_2Cl_2) δ 9.69 (s, 1H), 8.71 (s, 1H), 8.33 (s, 1H), 8.11-8.05 (m, 2H), 7.84 (d, *J* = 9.6 Hz, 1H), 7.69 (t, *J* = 4.0 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 3.61 –3.53 (m, 1H), 3.04 –2.98 (m, 2H), 2.67 –2.61 (m, 2H), 2.35 (s, 3H). MS *m/z* 476.1 $(M+1)^+$.	0.04
F91		^{1}H NMR (400MHz, CD_2Cl_2) δ 9.75 (d, *J* = 7.2 Hz, 1H), 9.53 (s, 1H), 9.3 (s, 1H), 8.09 (d, *J* = 1.6 Hz, 1H), 8.04 (d, *J* = 8.8 Hz, 1H), 7.85 (t, *J* = 8.8 Hz, 1H), 7.75 (dd, 1.6, 7.8, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 5.07 – 4.89 (m, 1H), 2.69 –2.60 (m, 1H), 2.34 (s, 3H), 1.82 –1.71 (m, 1H), 1.56-1.48 (m, 1H). MS *m/z* 378.1 $(M+1)^+$.	0.02
F92		MS *m/z* 414.1 $(M+1)^+$.	0.035
F93		MS *m/z* 385.1 $(M+1)^+$.	0.024
F94		^{1}H NMR (400MHz, CD_2Cl_2) δ 9.51 (t, *J* = 6.4 Hz, 1H), 8.59 (s, 1H), 8.34 (s, 1H), 7.85 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.75 (s, 1H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 6.97 (td, *J* = 2.0, 7.4, 1H), 3.70 – 3.62 (m, 1H), 3.18 – 3.12 (m, 2H), 2.86-2.81 (m, 2H), 2.26 (s, 3H). MS *m/z* 476.1 $(M+1)^+$.	0.056

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F95		MS *m/z* 490.1 $(M+1)^+$.	0.077
F96		^{1}H NMR (400MHz, d_6-DMSO) δ 10.17 (s, 1H), 8.95 (d, *J* = 1.6 Hz, 1H), 8.64 (s, 1H), 8.03 (d, *J* = 1.6 Hz, 1H), 7.84 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.79 –7.71 (m, 2H), 7.50 (d, *J* = 8.0 Hz, 1H), 3.91 – 3.86 (m, 1H), 3.76 –3.71 (m, 2H), 3.54 –3.51 (m, 2H), 3.23 –3.03 (m, 4H), 2.36 (s, 3H), 2.31 –2.25 (m, 2H), 1.17 (s, 3H), 1.15 (s, 3H). MS *m/z* 522.22 $(M+1)^+$.	0.046
F97		^{1}H NMR (400MHz, d_6-DMSO) δ 10.06 (s, 1H), 9.47 – 9.44 (m 1H), 8.59 (s, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.83 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.80 – 7.78 (m, 1H), 7.55 – 7.50 (m, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.20 – 7.16 (m, 1H), 3.76 – 3.68 (m, 1H), 3.38 (s, 3H), 2.88 – 2.85 (m, 4H), 2.36 (s, 3H). MS *m/z* 471.15 $(M+1)^+$.	0.046
F98		MS *m/z* 436.2 $(M+1)^+$.	0.086
F99		^{1}H NMR (400MHz, d_6-DMSO) δ 10.15 (s, 1H), 10.11 (m, 1H), 8.65 (s, 1H), 8.12 (d, *J* = 1.6 Hz, 1H), 8.06 (dd, *J* = 2.0, 9.2 Hz, 1H), 7.88 (dd, *J* = 0.8, 9.2 Hz, 1H), 7.85 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 4.34 (t, *J* = 5.2 Hz, 2H), 3.89 (m, 1H), 3.72 (t, *J* = 5.2 Hz, 2H), 3.24 (s, 3H), 3.02-3.20 (m, 4H), 2.47 (s, 3H), 2.39 (s, 3H). MS *m/z* 549.1 $(M+1)^+$.	0.044
F100		MS *m/z* 430.1 $(M+1)^+$.	0.066

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F101		MS *m/z* 378.1 $(M+1)^+$.	0.067
F102		^{1}H NMR (400MHz, d_4-MeOD) δ 9.38 (d, *J* = 7.2 Hz, 1H), 8.42 (s, 1H), 8.14 (d, *J* = 1.6 Hz, 1H), 7.93 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.52 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.04 (dd, *J* = 1.6, 7.2 Hz, 1H), 5.01 (d, *J* = 3.6 Hz, 2H), 4.68 (m, 1H), 3.02 (m, 1H), 2.61 (m, 1H), 2.50 (s, 3H), 2.42 (s, 3H). MS *m/z* 490.1 $(M+1)^+$.	0.009
F103		^{1}H NMR (400MHz, d_4-MeOD) δ 9.36 (m, 1H), 8.45 (s, 1H), 8.16 (d, *J* = 1.6 Hz, 1H), 7.94 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.66 (d, *J* = 9.2 Hz, 1H), 7.47-7.52 (m, 2H), 5.02 (d, *J* = 3.2 Hz, 2H), 4.69 (m, 1H), 3.02 (m, 1H), 2.60 (m, 1H), 2.43 (m, 6H). MS *m/z* 490.1 $(M+1)^+$.	0.016
F104		MS *m/z* 360.1 $(M+1)^+$.	0.057
F105		^{1}H NMR (400MHz, CD_2Cl_2) δ 9.57 (d, *J* = 8.0 Hz, 1H), 8.64 (d, *J* = 1.6 Hz, 1H), 8.24 (s, 1H), 7.87 (dd, *J* = 1.6, 7.6 Hz,1H), 7.76 (d, *J* = 8.8 Hz, 1H), 7.65 (bs, 1H), 7.51-7.46 (m, 1H), 7.44 (d, *J* = 7.6, 1H), 7.10 (td, *J* = 1.2, 6.8 Hz, 1H), 2.91 (d, *J* = 6.8 Hz, 2H), 2.47 (s, 3H), 1.32-1.23 (m, 3H), 0.71-0.66 (m, 2H), 0.41-0.37 (m, 2H). MS *m/z* 374.1 $(M+1)^+$.	0.04
F106		MS *m/z* 392.1 $(M+1)^+$.	0.052

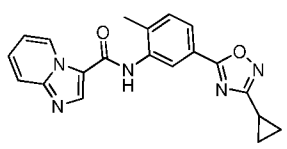
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F107		MS *m/z* 392.1 $(M+1)^+$.	0.085
F108		^{1}H NMR (400MHz, d_6-DMSO) δ 10.04 (s, 1H), 9.46 – 9.44 (m, 1H), 8.57 (s, 1H), 7.95 (s, 1H), 7.79 – 7.76 (m, 1H), 7.53 – 7.49 (m, 1H), 7.36 (s, 1H), 7.18 – 7.15 (m, 1H), 3.74 (m, 1H), 2.55 (s, 3H), 2.47 – 2.35 (m, 2H), 2.31 (s, 3H). MS *m/z* 409.14 $(M+1)^+$.	0.043
F109		^{1}H NMR (400MHz, d_6-DMSO) δ 10.04 (s, 1H), 9.46 – 9.44 (m, 1H), 8.57 (s, 1H), 7.95 (s, 1H), 7.79 – 7.76 (m, 1H), 7.53 – 7.49 (m, 1H), 7.36 (s, 1H), 7.18 – 7.15 (m, 1H), 3.74 (m, 1H), 2.55 (s, 3H), 2.47 – 2.35 (m, 2H), 2.31 (s, 3H). MS *m/z* 409.14 $(M+1)^+$.	0.089
F110		MS *m/z* 378.1 $(M+1)^+$.	0.058
F111		^{1}H NMR (400MHz, d_6-DMSO) δ 9.98 (s, 1H), 9.33 (d, *J* = 7.2 Hz, 1H), 8.53 (s, 1H), 8.07 (d, *J* = 1.6 Hz, 1H), 7.82 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.58 (s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.04 (dd, *J* = 1.6, 7.2 Hz, 1H), 5.48 – 5.30 (m, 1H), 3.98 – 3.93 (m, 1H), 2.82 – 2.73 (m, 4H), 2.43 (s, 3H), 2.36 (s, 3H). MS *m/z* 406.16 $(M+1)^+$.	0.046
F112		^{1}H NMR (400MHz, d_6-DMSO) δ 9.99 (s, 1H), 9.28 (s, 1H), 8.53 (s, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.82 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.70 (d, *J* = 9.2 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.39 (dd, *J* = 1.6, 9.2 Hz, 1H), 5.47 – 5.30 (m, 1H), 3.98 – 3.94 (m, 1H), 2.81 – 2.73 (m, 4H), 2.36 (s, 6H). MS *m/z* 406.16 $(M+1)^+$.	0.056

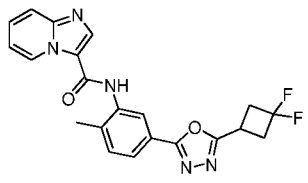
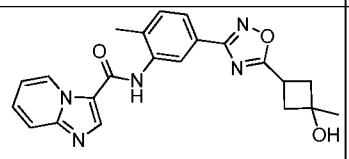
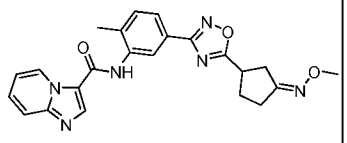
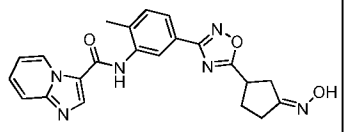
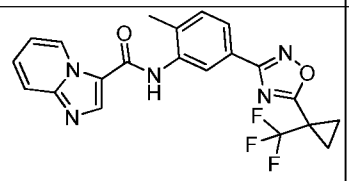
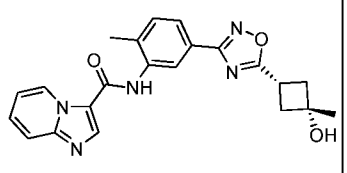
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F113		MS *m/z* 378.1 $(M+1)^+$.	0.056
F175		MS *m/z* 483.1 $(M+1)^+$.	0.073
F176		MS *m/z* 497.1 $(M+1)^+$.	0.067
F177		NMR (400 MHz, CDCl3) δ 9.56 (s, 1H), 8.60 (d, *J* = 1.6, 1H), 8.21 (s, 1H), 7.89 (dd, *J* = 1.7, 7.9, 1H), 7.77 (d, *J* = 9.2, 1H), 7.62 (s, 1H), 7.53 (dd, *J* = 1.7, 9.2, 1H), 7.42 (d, *J* = 8.1, 1H), 4.72 – 4.64 (m, 3H), 4.59 – 4.52 (m, 1H), 3.86 – 3.79 (m, 1H), 3.79 – 3.73 (m, 1H), 3.68 (m, 1H), 3.16 (m, 4H), 2.47 (s, 3H). MS *m/z* 486.1 $(M+1)^+$.	0.029

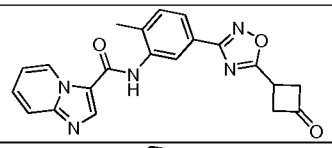
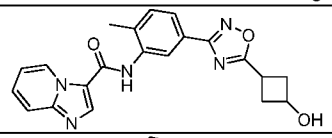
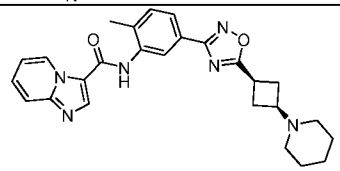
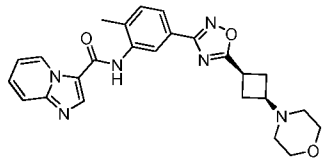
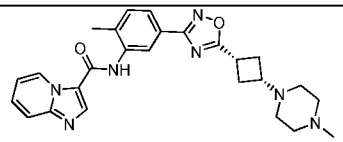
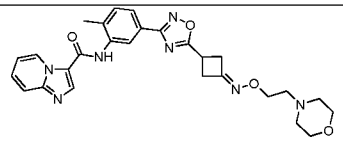
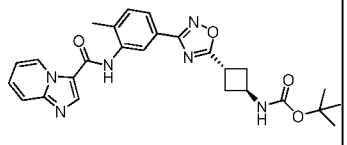
***20% FBS, otherwise 1% FBS**

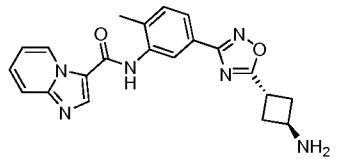
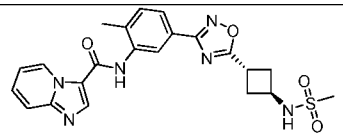
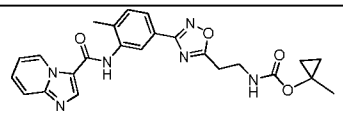
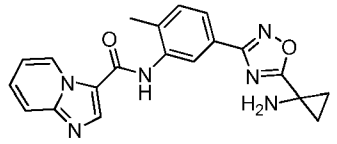
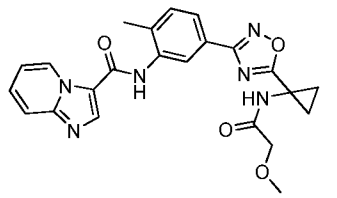
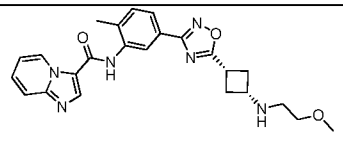
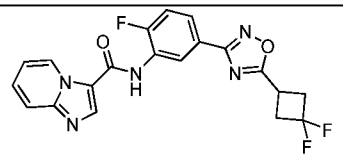
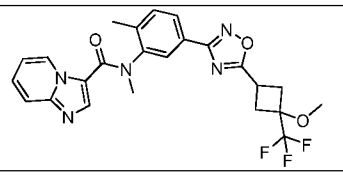
Representative compounds of Formula (I) and Formula (II) with c-kit inhibition IC_{50} values greater than 100 nM and prepared following the procedures described above, are set forth in Table 2.

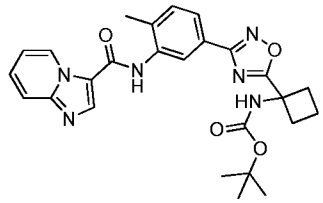
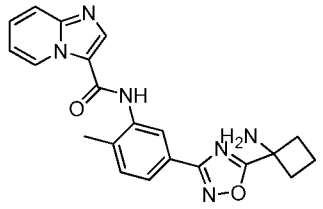
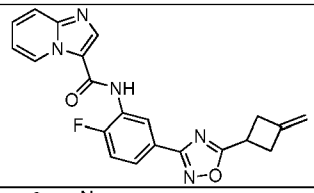
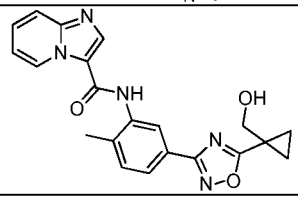
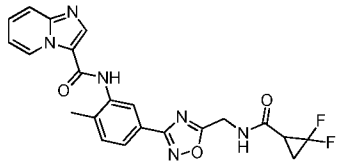
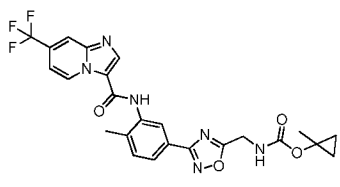
Table 2

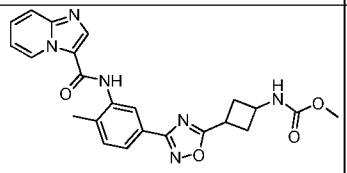
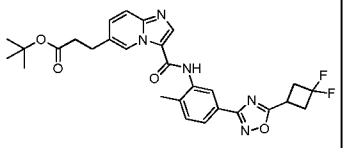
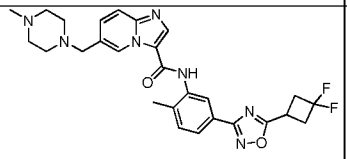
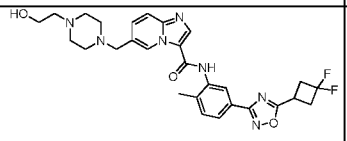
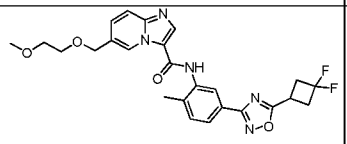
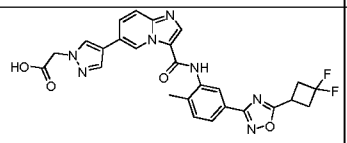
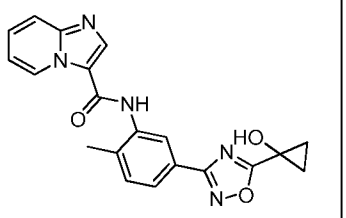
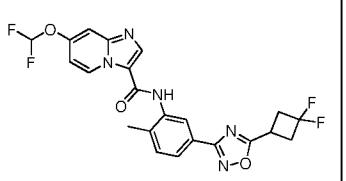
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F114		^{1}H NMR (400MHz, d_6-DMSO) δ 10.11 (s, 1H), 9.47 (d, *J* = 7.2 Hz, 1H), 8.63, (s, 1H), 8.13 (d, *J* = 1.6 Hz, 1H), 7.87 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 1H), 7.58 (bt, *J* = 7.2 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.23 (t, *J* = 7.2 Hz, 1H), 2.40 (s, 3H), 2.24 – 2.17 (m, 1H), 1.14 – 1.01 (m, 2H), 1.01 – 0.97 (m, 2H). MS *m/z* 360.1 $(M+1)^+$.	0.322*

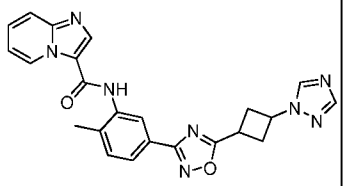
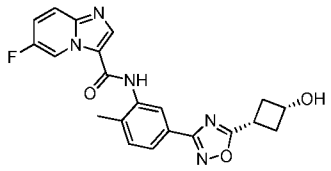
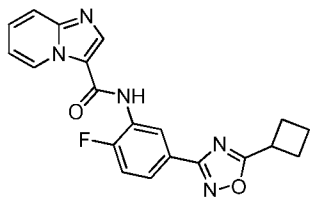
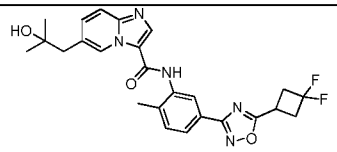
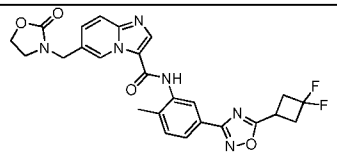
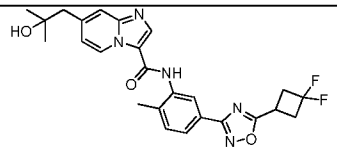
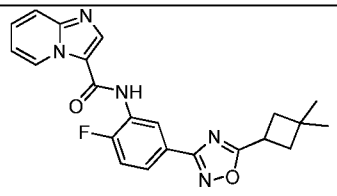
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F115		^{1}H NMR (400MHz, d_6-DMSO) δ 10.23 (s, 1H), 9.53 –9.51 (m, 1H), 8.72 (s, 1H), 8.05 (d, *J* = 2.0 Hz, 1H), 7.92 – 7.89 (m, 1H), 7.83 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.74 –7.69 (m, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.36 –7.32 (m, 1H), 3.83 – 3.78 (m, 1H), 3.20 –3.06 (m, 4H), 2.38 (s, 3H). MS *m/z* 409.14 $(M+1)^+$.	0.162
F116		MS *m/z* 404.2 $(M+1)^+$.	0.182*
F117		^{1}H NMR (400MHz, d_4-MeOH) δ 9.77 (d, J = 7.2 Hz, 1 H), 8.78 (s, 1 H), 8.14 – 8.13 (m, 1 H), 8.04 – 8.03 (m, 2 H), 7.95 – 7.93 (m, 1 H), 7.57 (ddd, J = 6.8, 6.8, 1.2 Hz, 1 H), 7.50 (d, J = 8.0, 1 H), 3.83 (s, 3 H), 3.75 – 3.65 (m, 1 H), 3.14 – 2.81 (m, 2 H), 2.75 – 2.51 (m, 2 H), 2.43 (s, 3 H), 2.22 – 2.09 (m, 2 H). MS *m/z* 431.1 $(M+1)^+$.	0.203
F118		^{1}H NMR (400MHz, d_4-MeOH) δ 9.77 (d, J = 7.2 Hz, 1 H), 8.78 (s, 1 H), 8.14 – 8.13 (m, 1 H), 8.04 – 8.03 (m, 2 H), 7.95 – 7.93 (m, 1 H), 7.57 (ddd, J = 6.8, 6.8, 1.2 Hz, 1 H), 7.50 (d, J = 8.0, 1 H), 3.75 – 3.65 (m, 1 H), 3.14 – 2.81 (m, 2 H), 2.75 – 2.51 (m, 2 H), 2.43 (s, 3 H), 2.22 – 2.09 (m, 2 H). MS *m/z* 417.2 $(M+1)^+$.	0.147*
F119		MS *m/z* 428.1 $(M+1)^+$.	0.162
F120		^{1}H NMR (400MHz, d_4-MeOH) δ 9.53 (d, J = 7.2 Hz, 1 H), 8.49 (s, 1 H), 8.13 – 8.12 (m, 1 H), 7.90 (dd, J = 8.2, 2.0 Hz, 1 H), 7.75 (d, J = 9.6 Hz, 1 H), 7.60 – 7.55 (m, 1 H), 7.48 (d, J = 8.0 Hz, 1H), 7.18 (ddd, J = 7.2, 7.2, 1.2 Hz, 1 H), 3.48 – 3.40 (m, 1 H), 2.58 – 2.54 (m, 4 H), 2.42 (s, 3 H), 1.46 (s, 3 H). MS *m/z* 404.1 $(M+1)^+$.	0.119

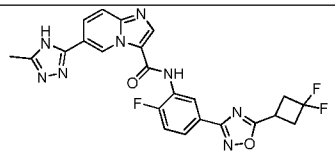
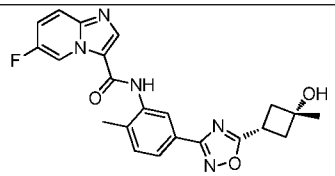
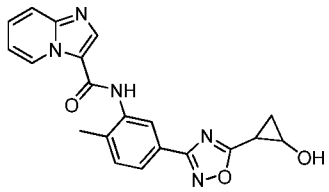
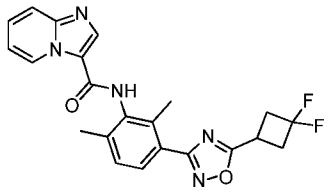
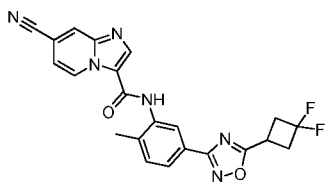
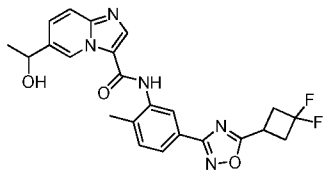
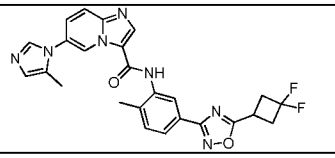
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F121		MS *m/z* 388.1 $(M+1)^+$.	0.14
F122		MS *m/z* 390.1 $(M+1)^+$.	0.135
F123		MS *m/z* 457.2 $(M+1)^+$.	0.345
F124		^{1}H NMR (400MHz, d_4-MeOH) δ 9.75 (d, J = 7.2 Hz, 1 H), 8.79 (s, 1 H), 8.18 (d, J = 2.0 Hz, 1 H), 8.02 (m, 2 H), 7.93 (dd, J = 8.2, 2.1 Hz, 1 H), 7.56 – 7.50 (m, 2H), 4.10 – 4.09 (m, 2 H), 3.93 – 3.86 (m, 1 H), 3.80 – 3.73 (m, 2 H), 3.49 – 3.40 (m, 2 H), 3.14 – 3.05 (m, 2 H), 2.99 – 2.93 (m, 2 H), 2.81 – 2.73 (m, 2 H), 2.44 (s, 3 H). MS *m/z* 459.1 $(M+1)^+$.	0.257
F125		MS *m/z* 472.2 $(M+1)^+$.	0.393
F126		MS *m/z* 516.24 $(M+1)^+$.	0.213
F127		^{1}H NMR (400MHz, d_6-DMSO) δ 10.24 (s, 1 H), 9.55 – 9.51 (m, 1 H), 8.73 (s, 1 H), 8.07 (d, J = 1.6 Hz, 1 H), 7.92 – 7.88 (m, 1 H), 7.85 (dd, J = 1.2, 7.6 Hz, 1 H), 7.74 – 7.69 (m, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.42 (d, J = 8.0 Hz, 1 H), 7.35 – 7.32 (m, 1 H), 4.37 – 4.30 (m, 1 H), 3.75 – 3.70 (m, 1 H), 2.61 – 2.54 (m, 2 H), 2.50 – 2.47 (m, 2 H), 2.37 (s, 3 H), 1.38 (s, 9 H). MS *m/z* 489.54 $(M+1)^+$.	0.353

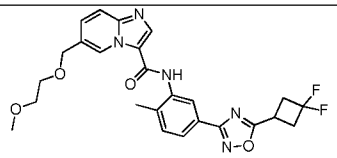
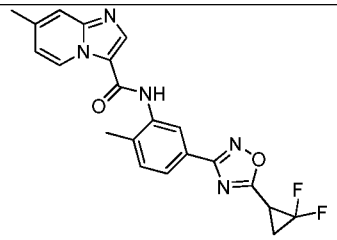
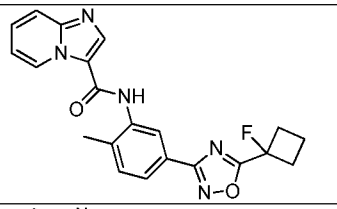
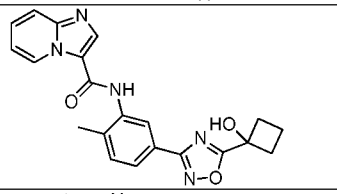
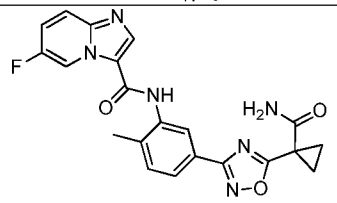
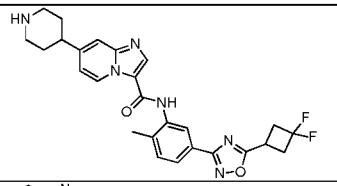
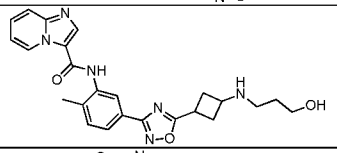
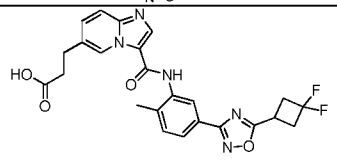
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F128		^{1}H NMR (400MHz, d_6-DMSO) δ 10.16 (s, 1 H), 9.50 – 9.47 (m, 1 H), 8.69 (s, 1 H), 8.24 (d, J = 4.8 Hz, 2 H), 8.08 (d, J = 1.6 Hz, 1 H), 7.86 – 8.72 (m, 2 H), 7.63 – 7.58 (m, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.27 – 7.23 (m, 1 H), 4.07 – 3.95 (m, 2 H), 2.76 – 2.63 (m, 4 H), 2.37 (s, 3 H). MS *m/z* 389.54 $(M+1)^+$.	0.109
F129		MS *m/z* 467.51 $(M+1)^+$.	0.143
F130		MS *m/z* 461.49 $(M+1)^+$.	0.106
F131		^{1}H NMR (400MHz, DMSO) δ 10.37 (s, 1H), 9.52 (d, *J*= 6.8 Hz, 1H), 8.88 (s, 1H), 8.08 (s, 1H), 7.92 (d, *J*= 9.1 Hz, 1H), 7.84 (d, *J*= 7.6 Hz, 1H), 7.74 (m, 1H), 7.54 (m, 1H), 7.36 (m, 1H), 2.39 (s, 3H), 1.77 (m, 4H). MS *m/z* 375.2 $(M+1)^+$.	0.311
F132		^{1}H NMR (400MHz, $CDCl_3$) δ 9.79 (d, *J*=6.9 Hz, 1H), 8.91 (s, 1H), 8.14 (t, *J*=8.8 Hz,1H), 8.08 (d, *J*=8.1 Hz, 1H), 8.06 (s, 1H), 7.83 (dd, *J*=7.6, 1.9 Hz, 1H), 7.63 (t, *J*=6.9 Hz,1H), 7.45 (t, *J*=8 Hz,1H), 4.00 (s, 2H), 3.45 (s, 3H), 2.42 (s, 3H), 1.79 (dd, *J*=8.6, 5.5 Hz, 2H), 1.55 (dd, *J*=8, 4.9 Hz,2H). MS *m/z* 447.2 $(M+1)^+$.	0.554
F133		MS *m/z* 447.2 $(M+1)^+$.	0.451
F134		MS *m/z* 414.1 $(M+1)^+$.	0.144
F135		^{1}H NMR (400MHz, d_6-DMSO) δ MS *m/z* 486.46 $(M+1)^+$.	0.999

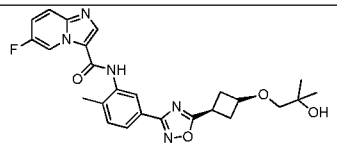
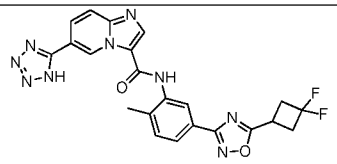
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F136		^{1}H NMR (400MHz, d_6-DMSO) δ 10.21 (s, 1 H), 9.53 (d, J = 6.8 Hz, 1 H), 8.71 (s, 1), 8.20 (s, 1 H), 8.077 (s, 1 H), 7.89 (d, J = 8.8 Hz, 1 H), 7.85 – 7.83 (m, 1 H), 7.72 – 7.68 (m, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.34 – 7.31 (m, 1 H), 2.70 – 2.63 (m, 2 H), 2.46 – 2.39 (m, 2 H), 2.37 (s, 3 H), 2.05 – 2.03 (m, 2 H), 1.37 (s, 9 H). MS *m/z* 489.54 $(M+1)^+$.	0.171
F137		^{1}H NMR (400MHz, d_6-DMSO) δ 10.11 (s, 1H), 9.47 (d, *J*=6.9, 1H), 9.19 (s, 3H), 8.66 (s, 1H), 8.14 (d, *J*=1.7, 1H), 7.91 – 7.82 (m, 2H), 7.63 – 7.58 (m, 1H), 7.55 (d, *J*=8.2, 1H), 7.25 (t, *J*=6.9, 1H), 4.41 (br s, 2H),2.74-2.85 (m, 3H), 2.66 – 2.70 (m, 2H), 2.39 (s, 3H), 2.12-2.24 (m, 2H). MS *m/z* 389.42 $(M+1)^+$.	0.197
F138		MS *m/z* 390.0 $(M+1)^+$.	0.103
F139		MS *m/z* 390.1 $(M+1)^+$.	0.137
F140		^{1}H NMR (400MHz, d_6-DMSO) δ 10.17 (s, 1 H), 9.53 – 9.51 (m, 1 H), 9.25 (t, J = 5.6 Hz, 1 H), 8.70 (s, 1 H), 8.07 (d, J = 1.6 Hz, 1 H), 7.90 – 7.87 (m, 1 H), 7.82 (dd, J = 1.6, 8.0 Hz, 1 H), 7.71 – 7.67 (m, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 7.33 – 7.29 (m, 1 H), 4.77 – 4.65 (m, 2 H), 2.76 – 2.68 (m, 1 H), 2.37 (s, 3 H), 1.96 – 1.89 (m, 2 H). MS *m/z* 453.41 $(M+1)^+$.	0.132
F141		^{1}H NMR (400MHz, d_6-DMSO) δ 10.23 (s, 1 H), 9.63 – 9.61 (m, 1 H), 8.75 (s, 1 H), 8.32 – 8.30 (m, 1 H), 8.09 (d, J = 1.6 Hz, 1 H), 7.93 (t, J= 5.6 Hz, 1 H), 7.82 (dd, J = 1.6, 8.0 Hz, 1 H), 7.52 (d, J = 8.4 Hz, 1 H), 7.46 (dd, J = 2.0, 7.2 Hz, 1 H), 4.53 (d, J = 6.0 Hz, 2 H), 2.38 (s, 3 H), 1.46 (s, 3 H), 0.795 – 0.764 (m, 2 H), 0.620 – 0.588 (m, 2 H). MS *m/z* 515.46 $(M+1)^+$.	0.391

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F142		MS *m/z* 447.1 $(M+1)^+$.	0.148
F143		1H NMR (400MHz, d6-DMSO) δ 10.10 (s, 1 H), 9.36 (s, 1 H), 8.62 (s, 1 H), 8.08 (d, J = 1.6 Hz, 1 H), 7.83 (dd, J = 1.6, 8.0 Hz, 1 H), 7.78 (d, J = 9.2 Hz, 1 H), 7.59 – 7.56 (m, 1 H), 7.51 (d, J = 8.0 Hz, 1 H), 3.93 – 3.82 (m, 1 H), 3.23 – 3.02 (m, 4 H), 2.91 (t, J = 7.2 Hz, 2 H), 2.60 (t, J = 7.2 Hz, 2 H), 2.36 (s, 3 H), 1.33 (s, 9 H). MS m/z 538.22 (M+1)+.	0.237
F144		MS *m/z* 522.2 $(M+1)^+$.	0.249
F145		MS *m/z* 552.2 $(M+1)^+$.	0.238
F146		MS *m/z* 498.1 $(M+1)^+$.	0.105
F147		MS *m/z* 534.1 $(M+1)^+$.	0.351
F148		^{1}H NMR (400MHz, d_6-DMSO) δ 10.13 (s, 1 H), 9.50 – 9.47 (m, 1 H), 8.66 (s, 1 H), 8.02 (d, *J* = 1.6 Hz, 1 H), 7.86 – 7.83 (m, 1 H), 7.79 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.64 – 7.60 (m, 1 H), 7.49 (d, *J* = 8.4 Hz, 1 H), 7.28 – 7.24 (m, 1 H), 2.36 (s, 3 H), 1.42 – 1.34 (m, 4 H). MS *m/z* 376.13 $(M+1)^+$.	0.305
F149		^{1}H NMR (400MHz, d_6-DMSO) δ 10.18 (s, 1 H), 9.32 (dd, *J* = 0.8, 6.8 Hz, 1 H), 8.61 (s, 1 H), 8.06 (d, *J* = 1.6 Hz, 1 H), 7.84 (dd, *J* = 1.6, 7.6 Hz, 1 H), 7.80 – 7.43 (m, 1 H), 7.51 (d, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 7.6 Hz, 1 H), 7.17 (t, *J* = 7.2 Hz, 1 H), 3.92 – 3.82 (m, 1 H), 3.24 –	0.378

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
		3.02 (m, 4 H), 2.36 (s, 3 H). MS *m/z* 476.13 $(M+1)^+$.	
F150		^{1}H NMR (400MHz, d_6-DMSO) δ 10.20 (s, 1 H), 9.54 – 9.50 (m, 1 H), 8.70 – 8.66 (m, 2 H), 8.11 – 8.04 (m, 2 H), 7.89 – 7.84 (m, 2 H), 7.70 – 7.66 (m, 1 H), 7.54 – 7.51 (m, 1 H), 7.33 – 7.29 (m, 1 H), 5.19 – 5.10 (m, 1 H), 3.88 – 3.79 (m, 1 H), 3.10 – 2.90 (m, 4 H), 2.38 (s, 3 H). MS *m/z* 441.17 $(M+1)^+$.	0.167
F151		^{1}H NMR (400MHz, d_4-MeOH) δ 9.55 (dd, J = 4.4, 2.0 Hz, 1 H), 8.52 (s, 1 H), 8.12 (m, 1 H), 7.92 (dd, J = 8.0, 2.0 Hz, 1 H), 7.79 (dd, J = 9.6, 4.8 Hz, 1 H), 7.58 (m, 1 H), 7.48 (d, J = 8.0 Hz, 1 H), 4.30 (m, 1 H), 3.35 (m, 1 H), 2.81 (m, 2 H), 2.42 (s, 3 H), 2.37 (m, 2 H). MS *m/z* 408.1 $(M+1)^+$	0.181
F152		NMR (400 MHz, d_2-CH_2Cl_2) δ 9.82 (d, *J*=7.0, 1H), 9.35 (s, 1H), 9.13 (s,1H), 8.79 (dd, *J*=3.7, 7.2, 1H), 8.17 (dd, *J*=8.8, 1H), 7.98 (ddd, *J*=2.1, 4.9, 8.6, 1H), 7.95 – 7.89 (m, 1H), 7.48 (td, *J*=1.1, 7.0, 1H), 7.34 (dd, *J*=1.6, 10.3, 1H), 3.87 (quintet of doublets, *J*=1.2, 8.8, 1H), 2.69 – 2.41 (m, 4H), 2.29 – 2.05 (m, 2H). MS *m/z* 378.1 $(M+1)^+$.	0.151
F153		MS *m/z* 482.1 $(M+1)^+$.	0.165
F154		MS *m/z* 509.0 $(M+1)^+$.	0.365
F155		MS *m/z* 482.1 $(M+1)^+$.	0.39
F156		NMR (400 MHz, d_6-DMSO) δ 10.58 (s, 1H), 9.57 (s, 1H), 8.87 (s, 1H), 8.37 (s, 1H), 7.87 (m, 3H), 7.48 (m, 2H), 3.90 (s, 1H), 2.23 (s, 4H), 1.24 (s, 3H), 1.14 (s, 3H). MS *m/z* 406.1 $(M+1)^+$.	0.125

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F157		MS *m/z* 495.1 $(M+1)^+$.	0.154
F158		MS *m/z* 422.1 $(M+1)^+$.	0.175
F159		NMR (400 MHz, d_2-CH_2Cl_2) δ 9.91 (d, *J*=13.1, 1H), 9.84 (t, *J*=8.6, 1H), 9.09 (s, 1H), 8.91 (s, 1H), 8.28 (d, *J*=1.4, 1H), 8.15 (d, *J*=9.0, 1H), 8.06 – 7.97 (m, 1H), 7.90 (dd, *J*=1.6, 7.9, 1H), 7.55 (t, *J*=6.9, 1H), 7.44 (d, *J*=8.0, 1H), 3.30 – 3.21 (m, 2H), 3.19 – 3.09 (m, 2H), 2.51 – 2.34 (m, 3H). MS *m/z* 376.1 $(M+1)^+$.	0.218
F160		^{1}H NMR (400MHz, d_4-MeOH) δ 9.77 (d, *J* = 7.2 Hz, 1 H), 8.82 (s, 1 H), 8.06 (m, 2 H), 7.88 (d, *J* = 8.0 Hz, 1 H), 7.58 (dt, *J* = 2.0, 6.8 Hz, 1 H), 7.37 (d, *J* = 8.0 Hz, 1 H), 3.81 (m, 1 H), 3.14 (m, 4 H), 2.56 (s, 3 H), 2.40 (s, 3 H). MS *m/z* 424.1 $(M+1)^+$.	0.293
F161		^{1}H NMR (400MHz, d_6-DMSO) δ 10.29 (s, 1H), 9.55 – 9.52 (m, 1H), 8.77 (s, 1H), 8.59 – 8.57 (m, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.85 (dd, *J* = 1.6, 7.6 Hz, 1H), 7.51 (d, *J*= 8.4 Hz, 1H), 7.48 (dd, *J* = 2.0, 7.6 Hz, 1H), 3.90 – 3.85 (m, 1H), 3.23 – 3.03 (m, 4H), 2.36 (s, 3H). MS *m/z* 434.13 $(M+1)^+$.	0.104
F162		^{1}H NMR (400MHz, d_6-DMSO) δ 10.15 (s, 1H), 9.49 (s, 1H), 8.67 (s, 1H), 8.08 (d, *J* = 1.6 Hz, 1H), 7.85 – 7.82 (m, 2H), 7.66 (dd, *J* = 1.2, 9.2 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 1H), 4.90 – 4.86 (m, 1H), 3.91 – 3.84 (m, 1H), 3.23 –3.04 (m, 4H), 2.37 (s, 3H), 1.40 (d, *J* = 6.4 Hz, 3H). MS *m/z* 453.16 $(M+1)^+$.	0.157
F163		MS *m/z* 490.2 $(M+1)^+$.	0.139

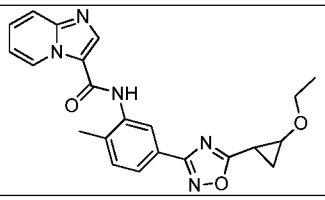
Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F164		MS *m/z* 498.2 $(M+1)^+$.	0.101
F165		MS *m/z* 410.14 $(M+1)^+$.	0.107
F166		MS *m/z* 392.15 $(M+1)^+$.	0.111
F167		MS *m/z* 390.16 $(M+1)^+$.	0.144
F168		MS *m/z* 421.14 $(M+1)^+$.	0.516
F169		MS *m/z* 493.22 $(M+1)^+$.	0.539
F170		MS *m/z* 433.19 $(M+1)^+$.	4.28
F171		MS *m/z* 482.16 $(M+1)^+$.	>10

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F172		MS *m/z* 480.2 $(M+1)^+$.	>10
F173		MS *m/z* 478.15 $(M+1)^+$.	>10

***20% FBS instead of 1% FBS**

A representative compound of Formula (I) and Formula (II) which was also prepared following the procedures described above, is set forth in Table 3.

Table 3

Cmpd No.	Structure	Physical Data	c-kit (Mo7e) μM
F174		MS *m/z* 404.2 $(M+1)^+$.	----

Assays

Compounds of Formula (I) and Formula (II) provided herein were assayed to measure their capacity to inhibit c-kit and PDGFR kinases using the appropriate assay described below: c-Kit inhibition was evaluated using the Mo7e cell proliferation assay, and PDGFR inhibition was evaluated using the Rat A10 cell proliferation assay and the Human TG/HA-VSMC cell proliferation assay.

Mo7e cell proliferation assay

The compounds of Table 1 and Table 2 were tested for inhibition of SCF dependent proliferation using human Mo7e cells which endogenously express c-kit in a 384 well format. Three-fold serially diluted test compounds (Cmax=10 mM) were evaluated for their antiproliferative activity of Mo7e cells stimulated with human recombinant SCF. After 48 hours of incubation at 37 °C, cell viability was measured by adding 25 uL of CellTiter Glo (Promega) to the cells and the luminescence was measured by a CLIPR CCD camera (Molecular Devices).

Rat A10 cell proliferation assay

Rat A10 cells (ATCC) were resuspended in DMEM supplemented with 1% FBS or 20% FBS and 10 ng/mL recombinant rat PDGF-BB at 20,000 cells/mL. The cells were aliquoted into 384 well plates at 50 µL/well and incubated for 4 hours at 37°C. 0.5 µL of test compound 3-fold serially diluted in DMSO was added to each well. The plates were returned to the incubator for a further 68 hours. 25 µL of CellTiter-Glo (Promega) was added to each well and the plates were incubated on the bench for 15 minutes. Luminescence was then read using a CLIPR CCD camera (Molecular Devices).

Human TG/HA-VSMC cell proliferation assay

Human TG/HA-VSMC cells (ATCC) were resuspended in DMEM supplemented with 1% FBS and 30 ng/mL recombinant human PDGF-BB at 60,000 cells/mL. The cells were aliquoted into 384 well plates at 50 µL/well and incubated for 4 hours at 37°C. 0.5 µL of test compound 3-fold serially diluted in DMSO was added to each well. The plates were returned to the incubator for a further 68 hours. 25 µL of CellTiter-Glo (Promega) was added to each well and the plates were incubated on the bench for 15 minutes. Luminescence was then read using a CLIPR CCD camera (Molecular Devices).

Certain Assay Results

Various compounds of Formula (I) and Formula (II) in free form or in pharmaceutically acceptable salt form, exhibit pharmacological properties, for example, as indicated by the tests described herein and presented in Table 1 and Table 2. The IC_{50} value is given as that concentration of the test compound in question that provoke a response halfway between the baseline and maximum responses. Certain compounds of Formula (I) or Formula (II) having specific IC_{50} for c-kit inhibition values of less than or equal to 100 nM are listed in Table 1, while certain compounds of Formula (I) or Formula (II) having specific IC_{50} for c-kit inhibition values greater than 100 nM are listed in Table 2.

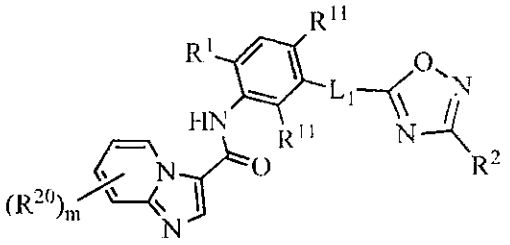
In other embodiments, compounds of Formula (I) or Formula (II) have IC_{50} values for c-kit inhibition in the range from 1 nM to 1 µM. In other embodiments, compounds of Formula (I) or Formula (II) have IC_{50} values for c-kit inhibition in the range from 1 nM to 500 nM. In other embodiments, compounds of Formula (I) or Formula (II) have IC_{50} values for c-kit inhibition in the range from 1 nM to 200 nM. In other embodiments, compounds of Formula (I) or Formula (II) have IC_{50} values for c-kit inhibition in the range from 1 nM to 100 nM. In other embodiments, compounds of Formula (I) or Formula (II) have IC_{50} values for c-kit inhibition in the range from 1 nM to 50 nM. In other embodiments, compounds of Formula (I) or Formula (II) have IC_{50} values for c-kit inhibition in the range from 1 nM to 25 nM. In other embodiments, compounds of

Formula (I) or Formula (II) have IC_{50} values for c-kit inhibition in the range from 1 nM to 10 nM. In other embodiments, compounds of Formula (I) or Formula (II) have IC_{50} values for c-kit inhibition in the range from 1 nM to 5 nM. In other embodiments, compounds of Formula (I) or Formula (II) have IC_{50} values for c-kit inhibition in the range from 1 nM to 2.5 nM.

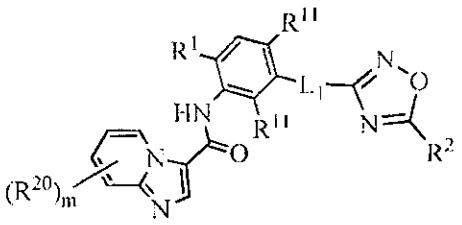
It is understood that the examples and embodiments described herein are for illustrative purposes only and that various modifications or changes in light thereof will be suggested to persons skilled in the art and are to be included within the spirit and purview of this application and scope of the appended claims.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A compound of Formula (I) or Formula (II), or pharmaceutically acceptable salt thereof:



Formula (I)



Formula (II)

wherein:

m is 1 and R^{20} is selected from H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, deuterium, deuterated C_1-C_6alkyl, -CN, $-(CR^9_2)_nOR^4$, $-C(O)R^4$, $-(CR^9_2)_nC(=O)OR^4$, R^{10}, $-(CR^9_2)_nR^{10}$, $-((CR^9_2)_nO)_tR^4$, $-(CR^9_2)_nO(CR^9_2)_nR^7$, $-(CR^9_2)_nC(=O)R^4$, $-C(=O)N(R^4)_2$, $-OR^4$ and $-(CR^9_2)_nCN$;

or m is 4 and R^{20} is deuterium;

R^1 is selected from C_1-C_6alkyl and halo;

each R^{11} is independently selected from H, halo, and C_1-C_6alkyl;

L_1 is a bond, –NH- or -C(=O)NH-;

L_2 is $-(CR^9_2)_n$-, $-CHR^6$-, $-(CR^9_2)_nO$-, -NH-, $-(CR^9_2)_nC(=O)$-, $-C(=O)O(CR^9_2)_n$-, $-(CR^9_2)_nOC(=O)NR^4$-, $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_n$ -, $-(CR^9_2)_nNR^4C(=O)$- or $-(CR^9_2)_nNR^4C(=O)O$- ;

R^2 is R^3 or L_2R^3;

R^3 is selected from an unsubstituted C_3-C_8cycloalkyl, a cyclobutanone, a cyclopentanone and a substituted C_3-C_8cycloalkyl,

wherein the substituted C_3-C_8cycloalkyl of R^3 is substituted with 1-4 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, $-OR^4$, -CN, $-C(=O)OR^4$, $-C(=O)R^4$, $-C(=O)R^7$, $-C(=O)OR^5$, $-(CR^9_2)_nOR^4$, $-O(CR^9_2)_nOR^4$, $-C(=O)O(CR^9_2)_nOR^4$, $-N(R^4)_2$, $=N-OR^4$, $=N-O-(CR^9_2)_nR^5$, $-C(=O)NR^4_2$, $-NR^4C(=O)OR^4$, $-NR^4C(=O)(CR^9_2)_nOR^4$, $-NR^4(CR^9_2)_nOR^4$, $-NR^4S(=O)_2R^4$, $-N(C(=O)OR^4)_2$, $=CH_2$, $=CH(CR^9_2)_nOR^4$, R^8, $-(CR^9_2)_nR^8$, deuterated C_1-C_6alkoxy, $-S(=O)_2R^4$, $-S(=O)_2R^7$, $-S(=O)_2R^8$, $-S(=O)_2N(R^4)_2$, $-S(=O)_2NHC(=O)OR^4$, $-S(=O)_2(CR^9_2)_rC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nOR^4$, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with C_1-C_6alkyl, a spiro attached dioxane, a spiro attached tetrahyrofuranly, a spiro attached oxetane, a spiro attached

cyclobutanone, a spiro attached cyclobutanol, a C_1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S, a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S substituted with 1-3 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, $-OR^4$ and R^8;

each R^4 is independently selected from H and C_1-C_6alkyl;

R^5 is an unsubstituted C_3-C_8cycloalkyl , an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N or O or a C_3-C_8cycloalkyl substituted with 1-3 substituents independently selected from C_1-C_6alkyl;

each R^6 is independently selected from $-NHC(O)OR^4$, $-OR^4$ and $-(CR^9_2)_nOR^4$;

each R^7 is independently selected from C_1-C_6haloalkyl;

R^8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^8 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$, $-C(O)OR^4$ and $-S(O)_2R^4$;

each R^9 is independently selected from H and C_1-C_6alkyl;

R^{10} is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently

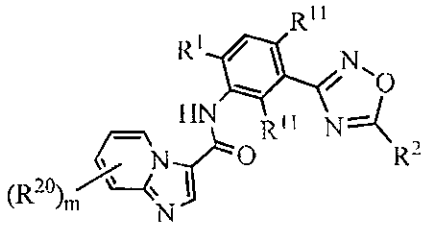
selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^{10} are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$ and $-S(O)_2R^4$;

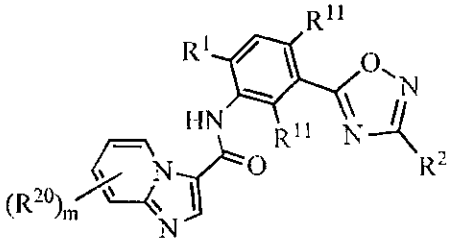
t is 1, 2 or 3, and

each n is independently selected from 1, 2, 3 and 4.

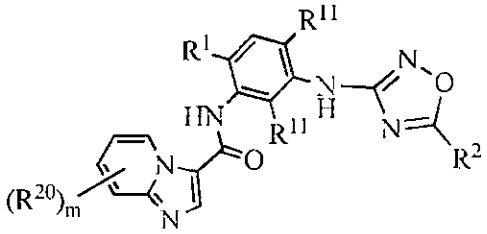
2. The compound of claim 1, wherein the compound is a compound of Formula (Ia), Formula (IIa), Formula (Ib) or Formula (IIb):



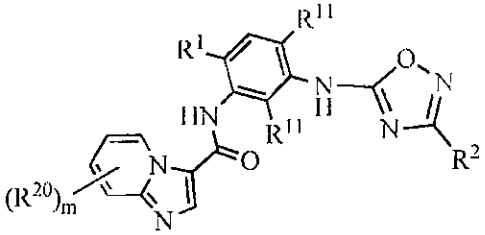
Formula (Ia)



Formula (IIa)



Formula (Ib)



Formula (IIb)

wherein:

m is 1 and R^{20} is selected from H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, deuterium, deuterated C_1-C_6alkyl, -CN, $-(CR^9_2)_nOR^4$, $-C(O)R^4$, $-(CR^9_2)_nC(=O)OR^4$, R^{10}, $-(CR^9_2)_nR^{10}$, $-((CR^9_2)_nO)_tR^4$, $-(CR^9_2)_nO(CR^9_2)_nR^7$, $-(CR^9_2)_nC(=O)R^4$, $-C(=O)N(R^4)_2$, $-OR^4$ and $-(CR^9_2)_nCN$;

or m is 4 and R^{20} is deuterium;

R^1 is selected from C_1-C_6alkyl and halo;

each R^{11} is independently selected from H, halo, and C_1-C_6alkyl;

L_2 is $-(CR^9_2)_n-$, $-CHR^6-$, $-(CR^9_2)_nO-$, $-NH-$, $-(CR^9_2)_nC(=O)-$, $-C(=O)O(CR^9_2)_n-$, $-(CR^9_2)_nOC(=O)NR^4-$, $-(CR^9_2)_nNR^4C(=O)(CR^9_2)_n-$, $-(CR^9_2)_nNR^4C(=O)-$ or $-(CR^9_2)_nNR^4C(=O)O-$;

R^2 is R^3 or L_2R^3;

R^3 is selected from an unsubstituted C_3-C_8cycloalkyl, a cyclobutanone, a cyclopentanone and a substituted C_3-C_8cycloalkyl,

wherein the substituted C_3-C_8cycloalkyl of R^3 is substituted with 1-4 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, $-OR^4$, -CN, $-C(=O)OR^4$, $-C(=O)R^4$, $-C(=O)R^7$, $-C(=O)OR^5$, $-(CR^9_2)_nOR^4$, $-O(CR^9_2)_nOR^4$, $-C(=O)O(CR^9_2)_nOR^4$, $-N(R^4)_2$, $=N-OR^4$, $=N-O-(CR^9_2)_nR^5$, $-C(=O)NR^4_2$, $-NR^4C(=O)OR^4$, $-NR^4C(=O)(CR^9_2)_nOR^4$, $-NR^4(CR^9_2)_nOR^4$, $-NR^4S(=O)_2R^4$, $-N(C(=O)OR^4)_2$, $=CH_2$, $=CH(CR^9_2)_nOR^4$, R^8, $-(CR^9_2)_nR^8$, deuterated C_1-C_6alkoxy, $-S(=O)_2R^4$, $-S(=O)_2R^7$, $-S(=O)_2R^8$, $-S(=O)_2N(R^4)_2$, $-S(=O)_2NHC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nC(=O)OR^4$, $-S(=O)_2(CR^9_2)_nOR^4$, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with C_1-C_6alkyl, a spiro attached dioxane, a spiro attached tetrahyrofuranly, a spiro attached oxetane, a spiro attached cyclobutanone, a spiro attached cyclobutanol, a C_1 alkyl bridge, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S, a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O and S substituted with 1-3 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, $-OR^4$ and R^8;

each R^4 is independently selected from H and C_1-C_6alkyl;

R^5 is an unsubstituted C_3-C_8cycloalkyl , an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N or O or a C_3-C_8cycloalkyl substituted with 1-3 substituents independently selected from C_1-C_6alkyl;

each R^6 is independently selected from $-NHC(O)OR^4$, $-OR^4$ and $-(CR^9_2)_nOR^4$;

each R^7 is independently selected from C_1-C_6haloalkyl;

R^8 is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently

selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-3 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^6 are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$, $-C(O)OR^4$ and $-S(O)_2R^4$;

each R^9 is independently selected from H and C_1-C_6alkyl;

R^{10} is selected from an unsubstituted phenyl, unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-C_8cycloalkyl, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, a substituted phenyl, a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, a substituted C_3-C_8cycloalkyl, a oxazolidin-2-one, pyrrolidinone and a pyrrolidin-2-one,

wherein the substituted phenyl, the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, substituted C_3-C_8cycloalkyl and substituted 4-6 membered heterocycloalkyl of R^{10} are substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(C(R^9)_2)_nOR^4$, $-(C(R^9)_2)_nR^5$, $-(C(R^9)_2)_nC(O)OR^4$ and $-S(O)_2R^4$;

t is 1, 2 or 3, and

each n is independently selected from 1, 2, 3 and 4.

3. The compound of claim 1 or claim 2, wherein R^1 is selected from $-CH_3$ and F.

4. The compound of any one of claims 1 to 3, wherein R^1 is $-CH_3$.

5. The compound of any one of claims 1 to 4, wherein each R^{11} is independently selected from H, F and $-CH_3$.

6. The compound of any one of claims 1 to 5, wherein each R^{11} is H.

7. The compound of any one of claims 1 to 6, wherein R^3 is selected from an unsubstituted C_3-C_8cycloalkyl, a cyclobutanone, a cyclopentanone and a substituted C_3-C_8cycloalkyl, wherein the substituted C_3-C_8cycloalkyl of R^3 is substituted with 1-4 substituents independently selected from C_1-C_6alkyl, halo, C_1-C_6haloalkyl, $-OR^4$, $-(CR^9_2)_nOR^4$, $-O(CR^9_2)_nOR^4$, $-N(R^4)_2$, $=N-OR^4$, $=N-O-(CR^9_2)_nR^5$, $-NR^4C(=O)OR^4$, $-NR^4C(=O)(CR^9_2)_nOR^4$, $-NR^4(CR^9_2)_nOR^4$, $-NR^4S(=O)_2R^4$, $-N(C(=O)OR^4)_2$, $=CH_2$, $=CH(CR^9_2)_nOR^4$, R^8, deuterated C_1-C_6alkoxy, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with C_1-C_6alkyl, a spiro attached dioxane, a spiro attached tetrahyrofuranly, a spiro attached cyclobutanone, a spiro attached cyclobutanol, an unsubstituted 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N and O and a 5-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N and O substituted with 1-3 substituents independently selected from C_1-C_6alkyl.

8. The compound of any one of claims 1 to 7, wherein each R^4 is independently selected from H, methyl, ethyl, propyl, butyl, i-propyl and t-butyl.

9. The compound of any one of claims 1 to 8, wherein R^5 is independently selected from cyclopropyl or morpholinyl.

10. The compound of any one of claims 1 to 9, wherein each R^7 is independently selected from CH_2F, $-CHF_2$, $-CH_2CHF_2$, $-CH_2CF_3$ and $-CF_3$.

11. The compound of any one of claims 1 to 10, wherein each R^9 is independently selected from H, methyl and ethyl.

12. The compound of any one of claims 1 to 11, wherein R^8 is selected from an an unsubstituted C_3-C_8cycloalkyl and an unsubstituted 5 membered heteroaryl with 1-4 heteroatoms selected from N.

13. The compound of any one of claims 1 to 12, wherein

R^3 is selected from cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl, , each of which is unsubstituted or each of which is substituted with 1-4 substituents independently selected from -F, $-CH_3$, $-CH_2CH_3$, $-CF_3$, -OH, $-OCH_3$, $-CH_2OCH_3$, $-NH_2$, $-N(CH_3)_2$, $-OCH_2CH_2OCH_3$, $=N-OCH_3$, $=N-OCH_2CH_3$, $=N-OCH(CH_3)_2$, =N-OH, $=N-O-CH_2R^5$, $=N-O-CH_2CH_2R^5$, $-NHC(=O)OC(CH_3)_3$, $-NHC(=O)OCH_3$, $-NHC(=O)CH_2OCH_3$, $-NHCH_2CH_2OCH_3$, $-NHCH_2CH_2OH$, $-NHS(=O)_2CH_3$, $-N(C(=O)OCH_3)_2$, $=CH_2$, $=CHCH_2CH_2OH$, $-OCD_3$, cyclopropyl, triazolyl, pyrazolyl, a spiro attached dioxolane, a spiro attached dioxolane which is substituted with a $-CH_3$, a spiro attached dioxane, a spiro

attached tetrahyrofuranly, a spiro attached cyclobutanone, a spiro attached cyclobutanol, piperidinyl and piperazinyl substituted with a $-CH_3$,

or R^3 is a cyclobutanone or a cyclopentanone.

14. The compound of any one of claims 1 to 13, wherein:

R^3 is cyclopropyl substituted with 1 or 2 F,

or

R^3 is cyclobutyl substituted with 2 F.

15. The compound of any one of claims 1 to 14, wherein m is 1 and R^{20} is selected from H, halo, C_1-C_6alkyl, C_1-C_6haloalkyl, C_1-C_6haloalkoxy, deuterated C_1-C_6alkyl, -CN, $-(CR^9_2)_nOR^4$, $-(CR^9_2)_rC(=O)OR^4$, R^{10}, $-(CR^9_2)_rR^{10}$, $-((CR^9_2)_nO)_tR^4$, $-(CR^9_2)_nO(CR^9_2)_nR^7$, $-(CR^9_2)_nC(=O)R^4$, and $-C(=O)N(R^4)_2$.

16. The compound of any one of claims 1 to 15, wherein m is 1 and R^{20} is selected from H, -F, $-CH_3$, $-CF_3$, $-CD_3$, -CN, $-OCHF_2$, $-C(CH_3)OH$, $-CH_2CH_2C(=O)OC(CH_3)_3$, $-CH_2OCH_2CH_2OH$, $-CH_2OCH_2CF_3$, $-C(=O)NH_2$, $-CH_2CH_2C(CH_3)_2OH$, $-CH_2OCH_2CH_2OCH_3$, $-CH_2OCH_2CH_2F$, $-CH_2CH_2C(=O)CH_3$, $-CH_2OH$ and $-CH_2OCH_3$.

17. The compound of any one of claims 1 to 16, wherein m is 1 and R^{20} is $-CH_3$.

18. The compound of any one of claims 1 to 16, wherein m is 1 and R^{20} is H.

19. The compound of any one of claims 1 to 18, wherein:

R^{10} is selected from morpholinyl, piperidinyl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazinyl, piperazin-1-yl, pyrazolyl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, triazolyl, 1H-1,2,3-triazol-4-yl, 4H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, thiazolyl, thiazol-4-yl, thiazol-5-yl, imidazolyl, imidazol-1-yl, imidazol-2-yl, each of which is unsubstituted or each of which is substituted with 1-3 substituents independently selected from C_1-C_6alkyl, $-(CR^9_2)_nOR^4$, $-(C(R^9)_2)_nC(O)OR^4$, $-(C(R^9)_2)_rR^5$ and $-S(=O)_2R^4$,

or R^{10} is selected from a oxazolidin-2-one and a pyrrolidin-2-one.

20. The compound of any one of claims 1 to 19, wherein:

R^{10} is selected from morpholinyl, piperidinyl, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperazinyl, piperazin-1-yl, pyrazolyl, pyrazol-1-yl, pyrazol-3-yl, pyrazol-4-yl, triazolyl, 1H-1,2,3-triazol-4-yl, 4H-1,2,4-triazol-3-yl, 1H-1,2,4-triazol-5-yl, thiazolyl, thiazol-4-yl, thiazol-5-yl, imidazolyl, imidazol-1-yl, imidazol-2-yl, each of which is unsubstituted or each of which is substituted with 1-3 substituents independently selected from $-CH_3$, $-CH_2CH_2OH$, $-CH_2C(O)OH$, $-CH_2CH_2OH$, $-CH_2C(CH_3)_2OH$, $-S(O)_2CH_3$ and $-CH_2CH_2$-R_5.

21. The compound of any one of claims 1 to 14, wherein m is 4 and R^{20} is deuterium.

22. The compound of claim 1 selected from the group consisting of:

N-{5-[3-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-5-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{2-methyl-5-[5-(3-oxocyclopentyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3-hydroxy-3-methylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[3-(hydroxyimino)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(4,4-difluorocyclohexyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3-hydroxy-3-methylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[3-(methoxyimino)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-[5-(5-{5,8-dioxaspiro[3.4]octan-2-yl}-1,2,4-oxadiazol-3 yl) 2 methylphenyl]imidazo[1,2 a]pyridine-3-carboxamide;

N-(2-methyl-5-{5-[(6R)-6-methyl-5,8-dioxaspiro[3.4]octan-2-yl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-[5-(5-{5,9-dioxaspiro[3.5]nonan-2-yl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{2-methyl-5-[5-(3-oxocyclobutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-(2-methyl-5-{5-[(6S)-6-methyl-5,8-dioxaspiro[3.4]octan-2-yl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[3-(ethoxyimino)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-[5-(5-{3-[(cyclopropylmethoxy)imino]cyclobutyl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-[2-methyl-5-(5-{3-[(propan-2-yloxy)imino]cyclobutyl}-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3-aminocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[3-(2-methoxyethoxy)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3-methoxycyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[1-(methoxymethyl)cyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

tert-butyl N-{1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclopropyl}carbamate;

N-{5-[5-(1-methanesulfonamidocyclopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

methyl N-{1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclopropyl}-N-(methoxycarbonyl)carbamate;

methyl N-{1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclopropyl}carbamate;

N-(5-{5-[3-hydroxy-3-(trifluoromethyl)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

1-methylcyclopropyl N-{[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]methyl}carbamate;

methyl N-{1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclobutyl}carbamate;

N-{5-[5-(1-methanesulfonamidocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[1-(dimethylamino)cyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{2-methyl-5-[5-(3-methylidenecyclobutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3-cyclopropyl-3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[3-(3-hydroxypropylidene)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-[2-methyl-5-(5-{5-oxaspiro[3.4]octan-2-yl}-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-[5-(5-{[(3,3-difluorocyclobutyl)amino]methyl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-(2-methyl-5-{5-[(2,2,3,3-tetrafluorocyclobutoxy)methyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3-fluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(hydroxymethyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2-hydroxyethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(methoxymethyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[1-(2-hydroxyethyl)-1H-pyrazol-4-yl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(1-methyl-1H-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl]imidazo[1,2-a]pyridine-3-carboxamide;

N-(2-methyl-5-{5-[3-(1H-pyrazol-1-yl)cyclobutyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(1,3-thiazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-fluorophenyl}-6-(1-methyl-1H-pyrazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-fluorophenyl}-6-[1-(2-hydroxy-2-methylpropyl)-1H-pyrazol-4-yl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(1-methanesulfonylpiperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-4-yl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-fluorophenyl}-6-{1-[2-(morpholin-4-yl)ethyl]-1H-pyrazol-4-yl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2,2,2-trifluoroethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(3-oxobutyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(3-hydroxy-3-methylbutyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[2-(1-hydroxycyclopropyl)ethyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[2-(morpholin-4-yl)ethyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-[5-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-dimethylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(morpholin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide;

6-cyano-N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-fluorophenyl}-6-(5-methyl-4H-1,2,4-triazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide;

3-N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3,6-dicarboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[2-(4-methylpiperazin-1-yl)ethyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(2,2-difluorocyclopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(1H-1,2,3-triazol-4-yl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-[1-(2-hydroxyethyl)-1H-1,2,3-triazol-4-yl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2,4-dimethylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(2-oxo-1,3-oxazolidin-3-yl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-methylimidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-methylimidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-fluoroimidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-fluoroimidazo[1,2-a]pyridine-3-carboxamide;

7-cyano-N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-[5-(5-cyclopentyl-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-[2-methyl-5-(5-{6-oxospiro[3.3]heptan-2-yl}-1,2,4-oxadiazol-3-yl)phenyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(2-oxopyrrolidin-1-yl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2,2-difluoroethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3-ethylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(5-methyl-4H-1,2,4-triazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-methylimidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(morpholin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(1H-imidazol-1-yl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2-fluoroethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[3-(methoxymethyl)-1H-1,2,4-triazol-5-yl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(2,2-difluorocyclopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2,2,2-trifluoroethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-[5-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-2-methylphenyl]-6-[(2,2,2-trifluoroethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[(1R)-2,2-difluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[(1S)-2,2-difluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[3-hydroxy-3-(trifluoromethyl)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide;

6-fluoro-N-(5-{5-[3-hydroxy-3-(trifluoromethyl)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[(1R,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-5,6,7,8-tetradeuteroimidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[(3,3-difluorocyclobutyl)carbamoyl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

7-fluoro-N-(5-{5-[3-hydroxy-3-(trifluoromethyl)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(4-methyl-1H-imidazol-1-yl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2R,6S)-2,6-dimethylmorpholin-4-yl]imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[3-methoxy-3-(trifluoromethyl)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

6-fluoro-N-(5-{5-[1-(methoxymethyl)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[1-(2-methoxyethyl)-5-methyl-1H-1,2,4-triazol-3-yl]imidazo[1,2-a]pyridine-3-carboxamide;

N-[5-(5-{6-hydroxyspiro[3.3]heptan-2-yl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[(1S,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

7-methyl-N-(2-methyl-5-{5-[(2,2,3,3-tetrafluorocyclobutoxy)methyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;

6-methyl-N-(2-methyl-5-{5-[(2,2,3,3-tetrafluorocyclobutoxy)methyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-[5-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(cyclopropylmethyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[(1R,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[(1S,2R)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[(1R)-2,2-difluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2,4-dimethylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[(1S)-2,2-difluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2,4-dimethylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[(1R,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3-fluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-methylimidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3-fluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-methylimidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[(1S,2R)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

methyl N-{3,3-difluoro-1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclobutyl}carbamate;

methyl N-{3,3-difluoro-1-[3-(4-methyl-3-{7-methylimidazo[1,2-a]pyridine-3-amido}phenyl)-1,2,4-oxadiazol-5-yl]cyclobutyl}carbamate,

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2-fluoroethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-[5-(3-cyclopropyl-1,2,4-oxadiazol-5-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,3,4-oxadiazol-2-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3-hydroxy-3-methylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[(3Z)-3-(methoxyimino)cyclopentyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[(3Z)-3-(hydroxyimino)cyclopentyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-(2-methyl-5-{5-[1-(trifluoromethyl)cyclopropyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3-hydroxy-3-methylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{2-methyl-5-[5-(3-oxocyclobutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-(2-methyl-5-{5-[3-(piperidin-1-yl)cyclobutyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-(2-methyl-5-{5-[3-(morpholin-4-yl)cyclobutyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-(2-methyl-5-{5-[3-(4-methylpiperazin-1-yl)cyclobutyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{2-methyl-5-[5-(3-{[2-(morpholin-4-yl)ethoxy]imino}cyclobutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;

tert-butyl N-{3-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclobutyl}carbamate;

N-{5-[5-(3-aminocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3-methanesulfonamidocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

1-methylcyclopropyl N-{2-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]ethyl}carbamate;

N-{5-[5-(1-aminocyclopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[1-(2-methoxyacetamido)cyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-[5-(5-{3-[(2-methoxyethyl)amino]cyclobutyl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-fluorophenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[3-methoxy-3-(trifluoromethyl)cyclobutyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)-N-methylimidazo[1,2-a]pyridine-3-carboxamide;

tert-butyl N-{1-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclobutyl}carbamate;

N-{5-[5-(1-aminocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{2-fluoro-5-[5-(3-methylidenecyclobutyl)-1,2,4-oxadiazol-3-yl]phenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[1-(hydroxymethyl)cyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-[5-(5-{[(2,2-difluorocyclopropyl)formamido]methyl}-1,2,4-oxadiazol-3-yl)-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide;

1-methylcyclopropyl N-[(3-{4-methyl-3-[7-(trifluoromethyl)imidazo[1,2-a]pyridine-3-amido]phenyl}-1,2,4-oxadiazol-5-yl)methyl]carbamate;

methyl N-{3-[3-(3-{imidazo[1,2-a]pyridine-3-amido}-4-methylphenyl)-1,2,4-oxadiazol-5-yl]cyclobutyl}carbamate;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(4-methylpiperazin-1-yl)methyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-{[4-(2-hydroxyethyl)piperazin-1-yl]methyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2-methoxyethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide;

2-{4-[3-({5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}carbamoyl)imidazo[1,2-a]pyridin-6-yl]-1H-pyrazol-1-yl}acetic acid;

N-{5-[5-(1-hydroxycyclopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(difluoromethoxy)imidazo[1,2-a]pyridine-3-carboxamide;

N-(2-methyl-5-{5-[3-(1H-1,2,4-triazol-1-yl)cyclobutyl]-1,2,4-oxadiazol-3-yl}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;

6-fluoro-N-{5-[5-(3-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-[5-(5-cyclobutyl-1,2,4-oxadiazol-3-yl)-2-fluorophenyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(2-hydroxy-2-methylpropyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2-oxo-1,3-oxazolidin-3-yl)methyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(2-hydroxy-2-methylpropyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-dimethylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-fluorophenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-fluorophenyl}-6-(5-methyl-4H-1,2,4-triazol-3-yl)imidazo[1,2-a]pyridine-3-carboxamide;

6-fluoro-N-{5-[5-(3-hydroxy-3-methylcyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(2-hydroxycyclopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{3-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2,6-dimethylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

7-cyano-N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(1-hydroxyethyl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-(5-methyl-1H-imidazol-1-yl)imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-[(2-methoxyethoxy)methyl]imidazo[1,2-a]pyridine-3-carboxamide;

N-(5-{5-[(1S)-2,2-difluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(1-fluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

N-{5-[5-(1-hydroxycyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;

tert-butyl 3-[3-({5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}carbamoyl)imidazo[1,2-a]pyridin-6-yl]propanoate;

N-{5-[5-(1-carbamoylcyclopropyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-6-fluoroimidazo[1,2-a]pyridine-3-carboxamide and

N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}-7-(piperidin-4-yl)imidazo[1,2-a]pyridine-3-carboxamide.

23. The compound of claim 1 selected from the group consisting of:
N-{5-[5-(3,3-difluorocyclobutyl)-1,2,4-oxadiazol-3-yl]-2-methylphenyl}imidazo[1,2-a]pyridine-3-carboxamide;
N-(5-{5-[(1R)-2,2-difluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(5-{5-[(1S)-2,2-difluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(5-{5-[(1S,2R)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide, and
N-(5-{5-[(1R,2S)-2-fluorocyclopropyl]-1,2,4-oxadiazol-3-yl}-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide.

24. A pharmaceutical composition comprising a therapeutically effective amount a compound of any one of claims 1 to 23 and a pharmaceutically acceptable carrier.

25. Use of a compound of any one of claims 1 to 23 in the manufacture of a medicament for treating a disease or disorder in a patient where modulation of a kinase is implicated, wherein the kinase is selected from c-kit, PDGFRα and PDGFRβ, and wherein the disease is selected from the group consisting of a mast-cell associated disease, a respiratory disease, an inflammatory disorder, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), an autoimmune disorder, a metabolic disease, a fibrosis disease, a dermatological disease, pulmonary arterial hypertension (PAH) and primary pulmonary hypertension (PPH).

26. The use of claim 25, wherein the disease is selected from the group consisting of asthma, allergic rhinitis, pulmonary arterial hypertension (PAH), pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), uticaria, dermatosis, atopic dermatitis, allergic contact dermatitis, rheumatoid arthritis, multiple sclerosis, melanoma, a gastrointestinal stromal tumor, a mast cell tumor, mastocytosis, anaphylactic syndrome, type I diabetes or type II diabetes.