Abstract:
The invention provides compounds and pharmaceutical compositions thereof, which are useful as protein kinase inhibitors, as well as methods for using such compounds to treat, ameliorate or prevent a condition associated with abnormal or deregulated kinase activity. In some embodiments, the invention provides methods for using such compounds to treat, ameliorate or prevent diseases or disorders that involve abnormal activation of PDGFR (PDGFRα, PDGFRβ) kinases or c-kit and PDGFR (PDGFRα, PDGFRβ) kinases.
COMPOUNDS AND COMPOSITIONS AS PDGFR KINASE INHIBITORS

FIELD OF THE INVENTION
The invention relates to inhibitors of PDGFR kinases or PDGFR and 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 PDGFR (PDGFRa and PDGFRp) kinases, or inhibitors of c-kit and PDGFR (PDGFRa and PDGFRP) 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):
wherein:

- m is 1 and R^{20} is selected from H, halo, C_1-C_6 alkyl, R^8, R^{10}, -OR^4, C_1-C_6 haloalkyl and -(CR^2_n)OR^11;
- or m is 4 and R^{20} is deuterium;
- R^1 is selected from H, d-C_alkyl and halo;
- each R^2 is independently selected from H, halo, and C_1-C_6 alkyl;
- R^3 is selected from -C(R^5)^2_n(CR^9)^2_nOH, -(C(R^5)^2_nR^9)^2_nOH, -(CR^9)^2_nC(R^9)^2_nR^10, C_5-C_alkyl substituted with 1-3 R^6, -(CR^9)^2_nC(R^9)^2_nR^12, -(CR^3)^2_nR^9, -(CR^3)^2_nR^10, -(CR^9)^2_nSR^4, -(CR^9)^2_nC(R^9)^2_nR^12, -(CR^3)^2_nC(R^9)^2_nR^12, benzyl substituted with R^{10}, C_5-C_alkyl substituted with 1-3 substituents independently selected from R^6, halo and C_1-C_6 alkyl;
- each R^4 is independently selected from H and C_1-C_6 alkyl;
- R^5 is C_alkyl, -(CR^9)^2_nR^{10}, phenyl or benzyl;
- each R^6 is independently selected from -OH or -(CR^9)^2_nOH;
- each R^7 is independently selected from H, -OR^4, and halo;
- R^8 is selected from 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, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S and a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, wherein the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, and the substituted 5 membered
heteroaryl with 1-4 heteroatoms selected from N of R⁹ are substituted with 1-3 substituents independently selected from d-dalkyl and \(-\text{O}(\text{R}^{8})_{2}\)ₙ₁NR⁴₂;

each R⁹ is independently selected from H and C₁-C₆alkyl;

R¹₀ is selected from an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C₃-C₆cycloalkyl, an unsubstituted adamantine, a substituted adamantine, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted C₃-C₆cycloalkyl,

wherein the substituted C₃-C₆cycloalkyl, substituted adamantine and substituted 4-6 membered heterocycloalkyl of R¹₀ are substituted with 1-3 R⁶ or substituted with 1-3 substituents independently selected from R⁶ and d-C₆alkyl;

R¹¹ is d-C₆haloalkyl;

R¹² is an unsubstituted phenyl or phenyl substituted with 1-3 substituents independently selected from halo and -SR⁴;

R¹³ is \(-\text{O}(\text{R}^{9})_{2}\)ₙ₁OR⁴,

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

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

![Formula (I)](image)

wherein:

m is 1 and R²⁰ is selected from H, halo, d-dalkyl, \(R^8\), \(R^{10}\), \(-\text{OR}^4\), \(\text{d-haloalkyl}\) and \(-(\text{R}^{9})_{n}\)OR¹¹;

or m is 4 and R²⁰ is deuterium;

R¹ is selected from H, d-dalkyl and halo;

each R² is independently selected from H, halo, and d-dalkyl;
R3 is selected from -(CR\textsuperscript{9}R\textsuperscript{2})\textsubscript{n}OH, -(CR\textsuperscript{9}R\textsuperscript{2})\textsubscript{n}C(R\textsuperscript{9}R\textsuperscript{6}R\textsuperscript{11}), -(CR\textsuperscript{9}R\textsuperscript{2})\textsubscript{n}R\textsuperscript{10}, C\textsubscript{5-6}.

C\textsubscript{scycloalkyl} substituted with 1-3 R\textsuperscript{6}, benzyl substituted with R\textsuperscript{10},

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<th>R\textsuperscript{6} is selected from -C(R\textsuperscript{9}R\textsuperscript{2})\textsubscript{n}OH, -(CR\textsuperscript{9}R\textsuperscript{2})\textsubscript{n}C(R\textsuperscript{9}R\textsuperscript{6}R\textsuperscript{11}), -(CR\textsuperscript{9}R\textsuperscript{2})\textsubscript{n}R\textsuperscript{10}, C\textsubscript{5-6}.</th>
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wherein each R\textsuperscript{4} is independently selected from H and C\textsubscript{1-3}dalkyl;

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<th>R\textsuperscript{6} is d-C\textsubscript{alkyl}, -(CR\textsuperscript{9}R\textsuperscript{2})\textsubscript{n}, phenyl or benzyl;</th>
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<th>R\textsuperscript{6} is selected from 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, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S and a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N, wherein the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, and the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N of R\textsuperscript{8} are substituted with 1-3 substituents independently selected from d-dalkyl and -O(C(R\textsuperscript{9}R\textsuperscript{2})\textsubscript{n}R\textsuperscript{4}2;</th>
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| each R\textsuperscript{9} is independently selected from H and d-dalkyl; |

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<th>R\textsuperscript{10} is selected from an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C\textsubscript{3-4}</th>
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<th>C\textsubscript{4}cycloalkyl, an unsubstituted adamantane, a substituted adamantane, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted C\textsubscript{3-4}cycloalkyl of R\textsuperscript{10}, wherein the substituted C\textsubscript{3-4}cycloalkyl, substituted adamantane and substituted 4-6 membered heterocycloalkyl of R\textsuperscript{10} are substituted with 1-3 R\textsuperscript{6};</th>
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| R\textsuperscript{11} is d-C\textsubscript{ehaloalkyl}; and |

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

In certain embodiments of compounds of Formula (I) 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) is a compound having a structure of Formula (la), Formula (lb), Formula (lc) or Formula (ld):
In certain embodiments of compounds of Formula (I) and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, \( R^3 \) is \(-\text{CH}(R^5)\text{CH}_2\text{OH}\) or benzyl substituted with \( R^{10} \). In certain embodiments of compounds of Formula (I) and the pharmaceutically acceptable salts, pharmaceutically acceptable solvates (e.g. hydrates), the N-oxide derivatives, protected derivatives, individual isomers and mixture of isomers thereof, \( R^3 \) is \( -(\text{CR}^9\text{R}^{10})\text{C}(\text{R}^8\text{R}^6\text{R}^{12}) \).

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (la), Formula (lb), Formula (lc) or Formula (Id), each \( R^9 \) is independently selected from H and methyl.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (la), Formula (lb), Formula (lc) or Formula (Id), each \( R^9 \) is independently selected from H and methyl.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (la), Formula (lb), Formula (lc) or Formula (Id), \( R^1 \) is selected from \(-\text{CH}_3\) and F.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (la), Formula (lb), Formula (lc) or Formula (Id), \( R^1 \) is \(-\text{CH}_3\).

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (la), Formula (lb), Formula (lc) or Formula (Id), each \( R^2 \) is H.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (la), Formula (lb), Formula (lc) or Formula (Id), each \( R^6 \) is independently selected from H and methyl.
selected from -OH andr -CH₂OH.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (la), Formula (lb), Formula (lc) or Formula (ld), each R⁷ is independently selected from H, -F and -Cl;

5 In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (la), Formula (lb), Formula (lc) or Formula (ld), each R⁵ is independently selected from benzyl, phenyl, methyl, ethyl, propyl, and, i-propyl.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (la), Formula (lb), Formula (lc) or Formula (ld), m is 1 and R⁴ is selected from H, halo, d-alkyl, R⁸, -OR₄.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (la), Formula (lb), Formula (lc) or Formula (ld), m is 1 and R⁴ is deuterium.

10 In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (la), Formula (lb), Formula (lc) or Formula (ld), R⁸ is selected from pyridyl and pyrazolyl, each of which is unsubstituted or each of which is substituted with 1-2 substituents independently selected from d-alkyl and -O(C(R₃)₂)nNR₄₂.

15 In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (la), Formula (lb), Formula (lc) or Formula (ld), m is 1 and R⁴ is -CH₃.

In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (la), Formula (lb), Formula (lc) or Formula (ld), m is 1 and R⁴ is H.

20 In certain embodiments of any of the aforementioned compounds of Formula (I), Formula (la), Formula (lb), Formula (lc) or Formula (ld), each R⁴ is H or methyl.

Certain embodiments of the compounds of Formula (I) are selected from: N-[5-[[1-hydroxy-3-phenylpropan-2-yl]carbamoyl]-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[5-[[2-hydroxy-1-phenylethyl]carbamoyl]-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[5-[[1-hydroxy-3-methylbutan-2-yl]carbamoyl]-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[2-fluoro-5-[[2-hydroxy-1-phenylethyl]carbamoyl]phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[2-fluoro-5-[[1 R,2S]-2-hydroxy-2,3-dihydro-1 H-inden-1-yl]carbamoyl]phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-[2-fluoro-5-[[1 S,2R]-2-hydroxy-2,3-dihydro-1 H-inden-1- -
a) pyridine-3-carboxamide; N-5-[[2-(3-hydroxypropylidin-1-yl)phenyl]methyl]carbamoyl]-
2-methyl]phenyl]imidazo[1,2-a]pyridine-3-carboxamide; 7-{6-[[3-(
(dimethylamino)propoxy]pyridin-3-yl]-N-(2-fluoro-5-[[1 R,2S]-1-hydroxy-2,3-dihydro-1 H-
inden-2-yl]carbamoyl]phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-5-[[1 R,2S]-6-
chloro-2-hydroxy-2,3-dihydro-1 H-inden-1-yl]carbamoyl]-2-fluorophenyl]-6-
methylimidazo[1,2-a]pyridine-3-carboxamide, and N-(2-fluoro-5-[[3R,4R]-3-hydroxy-3,4-

Certain other embodiments of the compounds of Formula (I) are selected from: N-(2-
fluoro-5-[[1 S,2R]-2-hydroxy-2,3-dihydro-1 H-inden-1-yl]carbamoyl]phenyl]-6-
methoxyimidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-[[1 S,2R]-2-hydroxy-2,3-
dihydro-1 H-inden-1-yl]carbamoyl]phenyl]-6-methylimidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[[1 R,2R]-1-hydroxy-2,3-dihydro-1 H-inden-2-yl]carbamoyl]phenyl]imidazo[1,2-a]pyridine-3-
carboxamide; 7-{6-[[3-(dimethylamino)propoxy]pyridin-3-yl]-N-(2-fluoro-5-[[1 S,2R]-1-
hydroxy-2,3-dihydro-1 H-inden-2-yl]carbamoyl]phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-
(2-fluoro-5-[[1 S,2R]-5-chloro-2-hydroxy-2,3-dihydro-1 H-inden-1-yl]carbamoyl]phenyl]-2-fluorophenyl]-6-
methylimidazo[1,2-a]pyridine-3-carboxamide; N-5-[[1 R,2S]-6-chloro-2-hydroxy-2,3-
dihydro-1 H-inden-1-yl]carbamoyl]-2-fluorophenyl]-6-fluorimidazo[1,2-a]pyridine-3-
carboxamide; N-(2-fluoro-5-[[1 R,2R]-2-(hydroxymethyl)cyclohexyl]carbamoyl]phenyl]imidazo[1,2-a]pyridine-3-carboxamide; N-(3-[[1 S]-2-hydroxy-1-phenylethyl]carbamoyl]phenyl]imidazo[1,2-a]pyridine-3-
carboxamide; N-(2-fluoro-5-[[1 R,2S]-2-hydroxy-6-methoxy-2,3-dihydro-1 H-inden-1-
-yl]carbamoyl]phenyl]-6-methylimidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-
-[[1 R,2S]-1-hydroxy-2,3-dihydro-1 H-inden-2-yl]carbamoyl]phenyl]imidazo[1,2-a]pyridine-3-
carboxamide; N-3-[[1 R,2S]-2-hydroxy-2,3-dihydro-1 H-inden-1-yl]carbamoyl]phenyl]imidazo[1,2-a]pyridine-3-
carboxamide; N-(2-fluoro-5-[[2S]-1-hydroxypentan-2-yl]carbamoyl]phenyl]imidazo[1,2-a]pyridine-3-
carboxamide; N-(2-fluoro-5-[[2S]-1-hydroxypentan-2-yl]carbamoyl]phenyl]imidazo[1,2-a]pyridine-3-
carboxamide; N-(2-fluoro-5-[[1 S,2R]-2-hydroxycyclohexyl]carbamoyl]phenyl]imidazo[1,2-a]pyridine-3-
carboxamide; N-(2-fluoro-5-[[1 S,2R]-2-(hydroxymethyl)cyclohexyl]carbamoyl]phenyl]imidazo[1,2-a]pyridine-3-
(2-fluoro-5-(((1 R,2S)-2-hydroxy-2,3-dihydro-1 H-inden-1 -yl)carbamoyl)phenyl)-6-
(morpholin-4-yl)imidazo[1 ,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-(((1 S,2R)-2-hydroxy-
2,3-dihydro-1 H-inden-1 -yl)carbamoyl)phenyl)-5,6,7,8-tetrahydrogeniomidazo[1 ,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-(((1 R,2R)-2-
hydroxy-2,3-dihydro-1 H-inden-1 -yl)carbamoyl)phenyl)-6-
(trifluoromethyl)imidazo[1 ,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-(((1 S,2R)-2-
hydroxycyclohexyl)carbamoyl)phenyl)imidazo[1 ,2-a]pyridine-3-carboxamide; 7-
fluoro-N-(2-fluoro-5-(((1 S,2R)-2-hydroxy-2,3-dihydro-1 H-inden-1 -yl)carbamoyl)phenyl)-6-
(trifluoroethoxy)methyl]imidazo[1 ,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-(((1 S,2R)-2-
hydroxycyclohexyl)carbamoyl)phenyl)imidazo[1 ,2-a]pyridine-3-carboxamide; N-(2-fluoro-
5-((3,3,3-trifluoro-2-hydroxypropyl)carbamoyl)phenyl)imidazo[1 ,2-a]pyridine-3-
carboxamide; N-(3-(((1-hydroxycyclobutyl)methyl)carbamoyl)phenyl)imidazo[1 ,2-a]pyridine-3-
carboxamide; N-(3-(((2S)-1-hydroxypropan-2-yl)carbamoyl)phenyl)imidazo[1 ,2-a]pyridine-3-
carboxamide; N-(3-(((2R)-1-hydroxy-3-methylbutan-2-yl)carbamoyl)phenyl)imidazo[1 ,2-a]pyridine-3-
carboxamide; N-(3-(((2S)-1-hydroxy-2,3-dihydro-1 H-inden-1 -yl)carbamoyl)phenyl)-6-
(morpholin-4-yl)imidazo[1 ,2-a]pyridine-3-carboxamide; N-(3-(((2S)-1-hydroxybutan-2-yl)carbamoyl)phenyl)imidazo[1 ,2-a]pyridine-3-
carboxamide; N-(3-(((2S)-1-hydroxypropan-2-yl)carbamoyl)phenyl)imidazo[1 ,2-a]pyridine-3-
carboxamide; N-(3-(((2S)-1-hydroxybutan-2-yl)carbamoyl)phenyl)imidazo[1 ,2-a]pyridine-3-
carboxamide; N-(3-(((2R)-1-hydroxy-3-methylbutan-2-yl)carbamoyl)phenyl)imidazo[1 ,2-a]pyridine-3-
carboxamide;
N-(2-fluoro-5-\{(1S,2R)-2-(2-hydroxypropan-2-yl)cyclohexyl\}carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-\{(1 R,2R)-1,3-dihydroxy-1-phenylprop-2-yl\}carbamoyl)-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-\{(1 S,2R)-1,3-dihydroxy-3-methyl-1-phenylbutan-2-yl\}carbamoyl)-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-\{(2S,3S,6R)-3-hydroxy-2,6-dimethylpiperidin-1-yl\}ethyl)carbamoyl)phenyl)-7-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-\{(1 R,2S)-2-hydroxy-6-methoxy-2,3-dihydro-1H-inden-1-yl\}carbamoyl)phenyl)-6-methylimidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-\{(1 S)-2-hydroxy-1-phenylethyl\}carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-\{(2-fluorophenyl)-6-methylimidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-\{(3S,4S)-3-hydroxythian-4-yl\}carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-\{(1 S,2S)-2-hydroxy-3-methoxy-1-phenylpropan-2-yl\}carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-\{(1 S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl\}carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-\{(3S,4S)-3-hydroxythian-4-yl\}carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-\{(3S,4S)-3-hydroxythian-4-yl\}carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-\{(1 S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl\}carbamoyl)-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-\{(1 S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl\}carbamoyl)-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-\{(1 S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl\}carbamoyl)-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-\{(2S,3S,6R)-3-hydroxy-2,6-dimethylpiperidin-1-yl\}ethyl)carbamoyl)phenyl)-7-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-(2-fluoro-5-\{(1 S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl\}carbamoyl)phenyl)-7-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-\{(1 R,2R)-1,3-dihydroxy-1-phenylpropan-2-yl\}carbamoyl)-2-fluorophenyl)-7-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-\{(1 R,2R)-1,3-dihydroxy-1-phenylpropan-2-yl\}carbamoyl)-2-fluorophenyl)-7-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-a]pyridine-3-carboxamide; N-(5-\{(1 R,2R)-1,3-dihydroxy-1-phenylpropan-2-yl\}carbamoyl)-2-fluorophenyl)-7-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-a]pyridine-3-carboxamide;
dihydroxy-1-phenylpropan-2-yl\[carbamoyl]-2-fluorophenyl\)-7-(1-methyl-1 H-pyrazol-5-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 (la), Formula (lb), Formula (lc), or Formula (Id), and a pharmaceutically acceptable carrier. In certain embodiments of such pharmaceutical compositions, the pharmaceutical composition is formulated for intravenous administration, intravitreal 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, an eye drop or an 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 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 (la), Formula (lb), Formula (lc), or Formula (Id). In certain embodiments of this aspect the disease is age-related macular degeneration (AMD), 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 age-related macular degeneration (AMD), asthma, allergic rhinitis, pulmonary arterial hypertension (PAH), pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), urticaria, dermatosis, type I diabetes or type II diabetes.

Another aspect provided herein are medicaments for treating a disease mediated by 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 (la), Formula (lb), Formula (lc), or Formula (Id), and the disease is age-related macular degeneration (AMD), 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 age-related macular
degeneration (AMD), asthma, allergic rhinitis, pulmonary arterial hypertension (PAH),
pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel
syndrome (IBS), inflammatory bowel disease (IBD), urticaria, dermatosis, type I diabetes
or type II diabetes.

Another aspect provided herein is the use of a compound of Formula (I), Formula
(la), Formula (lb), Formula (lc), or Formula (ld) in the manufacture of a medicament for
treating a disease or disorder in a patient where PDGFR kinase activity, or c-kit and
PDGFR kinase activity is implicated, wherein the disease is age-related macular
degeneration (AMD), 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 age-related macular
degeneration (AMD), asthma, allergic rhinitis, pulmonary arterial hypertension (PAH),
pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel
syndrome (IBS), inflammatory bowel disease (IBD), urticaria, dermatosis, type I diabetes
or type II diabetes.

Another aspect provided herein includes methods for treating a disease or disorder
where 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 (la), Formula (lb), Formula (lc),
or Formula (ld), 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 age-related macular degeneration (AMD), 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 age-related macular degeneration (AMD), 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 (la), Formula (lb), Formula (lc), or Formula (Id) for use in treating a disease mediated by PDGFR kinases (PDGFRα and PDGFRβ) or PDGFR kinases (PDGFRα and PDGFRβ) and c-kit kinase, wherein the disease is selected from age-related macular degeneration (AMD), 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 age-related macular degeneration (AMD), 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 age-related macular degeneration (AMD), asthma, allergic rhinitis, pulmonary arterial hypertension (PAH), pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), urticaria, dermatosis, type I diabetes or type II diabetes.

**DETAILED DESCRIPTION OF THE INVENTION**

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 “Ci-C₃alkyl”, “C₁-C₄alkyl”, “Ci-C₅alkyl”, “Ci-C₆alkyl” and “Ci-C₇alkyl” 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 C₁-C₆ 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 -ORₐ, where Rₐ is an alkyl group as defined herein. As used herein, the terms “Ci-C₃alkoxy”, “C₁-C₄alkoxy”, “C₁-C₅alkoxy”, “C₁-C₆alkoxy”, “CVCalkoxy”, “CVCalkoxy” and “CVCalkoxy” refer to an alkoxy group wherein the alkoxy 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, isoproxy, n-butyloxy, t-butyloxy, pentoxy, hexyloxy, heptyloxy, octyloxy, nonyloxy, deocyloxy 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 "C₃-C₅ cycloalkyl", "C₃-C₆ cycloalkyl", "C₃-C₇ cycloalkyl", "C₃-C₈ cycloalkyl", "C₃-C₉ cycloalkyl" and "C₃-C₁₀ 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. Dihaloalkyl 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 referred to herein as "d-dhaloalkyl", "C₁-C₄ haloalkyl", "d-dhaloalkyl", "d-dhaloalkyl", "d-dhaloalkyl" and "d-dhaloalkyl" 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-oxadiazone; 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-benzoazoxylyl; 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-benzoazoxyn; 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 8-carbazolyl; 3-, 4-, 5-, 6-, 7-, or 8-cinnolinyl; 2-, 4-, or 5-4H-imidazo[4,5-d]thiazolyl; 2-, 3-, 4-, or 6-imidazo[2,1-b]thiazolyl; 2-, 3-, 4-, or 7-imidazo[1,2-b][1,2,4]triazinyl; 1-, 2-4-, 5-, 6-, or 7-indazolyl; 1-, 2-, 3-, 5-, 6-, 7-, or 8-isindolyl; 1-, 2-, 3-, 4-, 5-, 6-, or 7-isoindolyl; 1-, 3-, 4-, 5-, 6-, or 8-isooquinolyl; 2-, 3-, 4-, 5-, 6-, or 7-naphthyridinyl; 1-, 2-, 4-, 5-, 6-, 7-, 8-, or 9-perimidinyl; 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-phenanthridinyl; 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-phenathroinyl; 1-, 2-, 3-, 4-, 5-, 6-, or 7-phenazinyl; 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-phenothiazinyl; 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, or 10-phenoxazinyl; 1-, 2-, 4-, 5-, 6-, 7-, or 8-phthalazinyl; 1-, 2-, 4-, or 6-, 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 5-1 H-pyrazolo[4,3-d]-oxazolyl; 2-, 3-, 5-, or 8-pyrazino[2,3-d]pyrindazinyl; 1-, 2-, 3-, 4-, 5-, or 8-5H-pyrdo[2,3-d]-o-oxazinyl; 1-, 2-, 3-, 4-, 5-, 6-, 7-, or 9-quinolinyl; 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinoloinyl; 2-, 3-, 4-, 5-, 6-, or 7-oxyazoloinyl; 2-, 3-, 4-, or 5-thieno[2,3-b]furanyl, and 1-, 3-, 6-, 7-, 8-, or 9-furo[3,4-c]cininolyl.

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, C1-C4alkyl 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, thiranyl, thiiran-2-yl, thiiran-3-yl, azetadnyl, azetadn-1-yl, azetadn-2-yl, azetadn-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, pyrrolidn-3-yl, pyrrolidin-4-yl, pyrrolidin-5-yl, tetrahydrofuranyl, tetrahydrofurani-2-yl, tetrahydrofurani-3-yl, tetrahydrofurani-4-yl, tetrahydrofurani-5-yl, tetrahydrothienyl, tetrahydrothien-2-yl, tetrahydrothien-3-yl, tetrahydrothien-4-yl, tetrahydrothien-5-yl, piperidiny1, piperidin-1-yl, piperidin-2-yl, piperidin-3-yl, piperidin-4-yl, piperidin-5-yl, piperidin-6-yl, tetrahydropropynyl, tetrahydropropyn-2-yl, tetrahydropropyn-3-yl, tetrahydropropyn-4-yl, tetrahydropropyn-5-yl, tetrahydropropyn-6-yl, tetrahydrothiopyryl, tetrahydrothiopyryl-2-yl, tetrahydrothiopyryl-3-yl, tetrahydrothiopyryl-4-yl, tetrahydrothiopyryl-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, dithiolanyl, dithia-2-yl, dithia-3-yl,
dithia-5-yl, dithia-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, imidazolinyll, 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, pyrazolinyll, 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-tetrahydroprydinyl, 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-pyrryl.

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), 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,
alopexia, 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, ophalmia sympatica, phakogene uveitis, chronic agressive
hepatitis, primary biliary 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, obliterator, 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) 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) 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) 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, urticaria, pulmonary arterial hypertension (PAH), primary pulmonary hypertension (PPH), dermatitis, 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 Formula (I), and subformulae thereof (such as Formula (Ia), Formula (Ib), Formula (Ic) and Formula (Id)), 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 Formula (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 PDGFR kinases or c-kit and PDGFR kinases. Certain embodiments of compounds provided herein have an IC\textsubscript{50} for c-kit inhibition to IC\textsubscript{50} for PDGFR inhibition ratio (IC\textsubscript{50 c-kit}/IC\textsubscript{50 PDGFR}) in the range of 750 to 1000. Certain embodiments of compounds provided herein have an IC\textsubscript{50} for c-kit inhibition to IC\textsubscript{50} for PDGFR inhibition ratio (IC\textsubscript{50 c-kit}/IC\textsubscript{50 PDGFR}) in the range of 500 to 750. Certain embodiments of compounds provided herein have an IC\textsubscript{50} for c-kit inhibition to IC\textsubscript{50} for PDGFR inhibition ratio (IC\textsubscript{50 c-kit}/IC\textsubscript{50 PDGFR}) in the range of 250 to 500. Certain embodiments of compounds provided herein have an IC\textsubscript{50} for c-kit inhibition to IC\textsubscript{50} for PDGFR inhibition ratio (IC\textsubscript{50 c-kit}/IC\textsubscript{50 PDGFR}) in the range of 100 to 250. Certain embodiments of compounds provided herein have an IC\textsubscript{50} for c-kit inhibition to IC\textsubscript{50} for PDGFR inhibition ratio (IC\textsubscript{50 c-kit}/IC\textsubscript{50 PDGFR}) in the range of 75 to 100. Certain embodiments of compounds provided herein have an IC\textsubscript{50} for c-kit inhibition to IC\textsubscript{50} for PDGFR inhibition ratio (IC\textsubscript{50 c-kit}/IC\textsubscript{50 PDGFR}) in the range of 25 to 75.
PDGFR inhibition ratio (IC_{50, c-kit}/IC_{50, PDGFR}) in the range of 50 to 75. Certain embodiments of compounds provided herein have an IC_{50} for c-kit inhibition to IC_{50} for PDGFR inhibition ratio (IC_{50, c-kit}/IC_{50, PDGFR}) in the range of 25 to 50. Certain embodiments of compounds provided herein have an IC_{50} for c-kit inhibition to IC_{50} for PDGFR inhibition ratio (IC_{50} c-kit/IC_{50, PDGFR}) in the range of 10 to 25. Certain embodiments of compounds provided herein have an IC_{50} for c-kit inhibition to IC_{50} for PDGFR inhibition ratio (IC_{50} c-kit/IC_{50, PDGFR}) in the range of 7.5 to 10. Certain embodiments of compounds provided herein have an IC_{50} for c-kit inhibition to IC_{50} for PDGFR inhibition ratio (IC_{50} c-kit/IC_{50, PDGFR}) in the range of 5 to 7.5. Certain embodiments of compounds provided herein have an IC_{50} for c-kit inhibition to IC_{50} for PDGFR inhibition ratio (IC_{50} c-kit/IC_{50, PDGFR}) in the range of 2.5 to 5. Certain embodiments of compounds provided herein have an IC_{50} for c-kit inhibition to IC_{50} for PDGFR inhibition ratio (IC_{50} c-kit/IC_{50, PDGFR}) in the range of 1 to 2.5. Certain embodiments of compounds provided herein have an IC_{50} for c-kit inhibition to IC_{50} for PDGFR inhibition ratio (IC_{50} c-kit/IC_{50, PDGFR}) in the range of 0.25 to 1.

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 PDGFR kinases or c-kit and PDGFR kinases using such compounds and pharmaceutical compositions.

The PDGFR kinase, c-kit and PDGFR kinase, inhibitors of the present invention are compounds having the structure of Formula (I), 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)](image)

wherein:

- m is 1 and R^{20} is selected from H, halo, d-C_{ealkyl}, R^8, R^10, -OR^4, d-C_{ehaloalkyl} and -(CR^8_{2}R^1)_{n}OR^{11};

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

- R^1 is selected from H, d-C_{ealkyl} and halo;

- each R^2 is independently selected from H, halo, and d-C_{ealkyl};
R³ is selected from -C(R²R³)(CR²)ₙOH, -(CR²)ₙC(R³R⁴R⁵)ᵣ, -(CR²)ₙR⁶, C₅₋C₈ cycloalkyl

substituted with 1-3 R⁶, benzyl substituted with R¹⁰,

each R⁴ is independently selected from H and C₁₋C₆ alkyl;

R⁵ is Ci-C₆ alkyl, -(CR²)ₙ R¹⁰, phenyl or benzyl;

each R⁶ is independently selected from -OH or -(CR²)ₙOH;

each R⁷ is independently selected from H, -OR⁴, and halo;

R⁸ is selected from unsubstituted 5-6 membered heteroaryl with 1-2 heteroatoms

1-4 heteroatoms selected from N, O or S, an unsubstituted 5 membered heteroaryl with

heteroatoms independently selected from N, O or S and a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N,

wherein the substituted 5-6 membered heteroaryl with 1-2 heteroatoms

independently selected from N, O or S, and the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N of R⁸ are substituted with 1-3 substituents independently selected from d-dalkyl and -0(C(R³)₂)ₙNR⁴₂;

each R⁹ is independently selected from H and d-dalkyl;

R¹⁰ is selected from an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C₃₋dycycloalkyl, an unsubstituted adamantane, a substituted adamantine, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted d-dycycloalkyl of R¹⁰,

wherein the substituted d-dycycloalkyl, substituted adamantane and substituted 4-6 membered heterocycloalkyl of R¹⁰ are substituted with 1-3 R⁶;

R¹¹ is d-dhaloalkyl; and

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

In certain embodiments of compounds of Formula (I), 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) is a compound having a structure of
Formula (la), Formula (lb), Formula (lc) or Formula (Id):

Formula (la)

Formula (lb)

Formula (lc)

Formula (Id)

m is 1 and R^{20} is selected from H, halo, C_1-C_6 alkyl, R^8, R^8', -OR^4, C_i-C_6 haloalkyl and - (CR^9_n)R^11;

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

10 R^1 is selected from H, d-Calkyl and halo;

each R^2 is independently selected from H, halo, and C_1-C_6 alkyl;

each R^4 is independently selected from H and C_1-C_6 alkyl;

R^5 is C_1-C_6 alkyl, -(CR^9_n)R^10, phenyl or benzyl;

each R^6 is independently selected from -OH or -(CR^9_n)OH;

15 each R^7 is independently selected from H, -OR^4, and halo;

R^8 is selected from 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, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S and a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N,

wherein the substituted 5-6 membered heteroaryl with 1-2 heteroatoms

independently selected from N, O or S, and the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N of R^8 are substituted with 1-3 substituents independently selected from C_i-C_6 alkyl and -0(C(R^9_n))_2NR^4;

25 each R^9 is independently selected from H and C_1-C_6 alkyl;

R^8' is selected from an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C_3-

C_6 cycloalkyl, an unsubstituted adamantine, a substituted adamantine, a substituted...
4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted C_{3-8} cycloalkyl of R^1; wherein the substituted C_{3-8} cycloalkyl, substituted adamantine and substituted 4-6 membered heterocycloalkyl of R^1 are substituted with 1-3 R^6;

R^1 is d-C6h6alkyl; and each n is independently selected from 1, 2, 3 and 4.

The compounds of Formula (I), 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 {sup 2}H, {sup 3}H, {sup 11}C, {sup 12}C, {sup 13}C, {sup 14}C, {sup 15}N, {sup 16}F, {sup 31}P, {sup 32}P, {sup 33}S, {sup 34}S, {sup 35}S, {sup 36}S, {sup 37}Cl, {sup 38}Cl, {sup 39}K, respectively. The invention includes various isotopically labeled compounds as defined herein, for example those into which radioactive isotopes, such as {sup 3}H and {sup 14}C, or those into which non-radioactive isotopes, such as {sup 2}H and {sup 13}C are present. Such isotopically labelled compounds are useful in metabolic studies (with {sup 14}C), reaction kinetic studies (with, for example {sup 2}H or {sup 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 {sup 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., {sup 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$_2$O, de-
acetone, d$_{6}$-DMSO.

Compounds of the invention, i.e. compounds of Formula (I) 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 2004/0781 63. Hence the invention further provides co-crystals comprising a
compound of Formula (I) and Formula (II).

**Processes for Making Compounds of Formula (I)**

General procedures for preparing compounds of Formula (I) 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

In certain embodiments, the compounds of Formula (I) provided herein are prepared
as a pharmaceutically acceptable acid addition salt by reacting the free base form of the
compound of Formula (I) 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) is prepared by reacting the free acid form of the compound of
Formula (I) 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) are prepared using salts of the starting materials or intermediates. In certain embodiments, the compounds of Formula (I) 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) include, but are not limited to, a hydrobromide, hydrochloride, sulfate, nitrate, succinate, maleate, formate, acetate, adipate, besylate, bicarbonate/carbonate, propionate, fumarate, citrate, tartrate, lactate, benzoate, salicylate, glutamate, aspartate, p-toluene sulfonate, benzenesulfonate, methanesulfonate, ethanesulfonate, ethanedisulfonate, camphorsulfonate, chloroethylphthalonate, naphthalenesulfonate (e.g. 2-naphthalenesulfonate), hexanoate salt, bisulfate/sulphate, borate, camsylate, cyclamate, edisylate, esylate, gluceptate, gluconate, glucuronate, hexafluorophosphosphate, hibenzoate, 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, pyrogulamate, saccharate, stearate, subsalicylate, 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) include, but are not limited to, hydrobromic acid, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid, succinic acid, malic 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, 4-hydroxybenzoic acid, salicylic acid, glutamic acid, aspartic acid, toluenesulfonic acid, sulfosalicylic acid, L-glutamic acid, hippuric acid, nicotinic acid, adipic acid, saccharin, 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) 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) 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) 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).


In certain embodiments, compounds of Formula (I) in unoxidized form are prepared from N-oxides of compounds Formula (I) 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) 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) are prepared or formed, as solvates (e.g., hydrates). In certain embodiments, hydrates of compounds of Formula (I) 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-toluyl tartaric acid, mandelic acid, malic acid or camphor-1 0-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) are prepared as their individual stereoisomers. In other embodiments, the compounds of Formula (I) 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 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, diastereomeric 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) 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)-(II). The R₁, R₂, R₂₀ and R₃ 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 oxalyl chloride and the base is pyridine.

\[
\text{Scheme (I)}
\]

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.

\[
\text{Scheme (II)}
\]

The examples provided herein are offered to illustrate, but not to limit, the compounds of Formula (I) 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, Blk, 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/ErB-1, ErB-2/NEU/H ER-2, ErB-3 and ErB-4), FAK, FGFR1 R (also FGFR1 or FGR-1), FGFR2 R (also FGR-2), MET (also Met-1 or c-MET), PDGFR (a 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, 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.), SAPK2a, SAPK23, Ark, ATM (1-3), CamK (1-IV), CamKK, Chk1 and 2 (Checkpoint kinases), CK1, CK2, Erk, IKK-1 (also IKK-a 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 (a 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.


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 leukotrienes), and various cytokines (IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-8, TNF-a, GM-CSF, MIP-La, MIP-\(\beta\), MIP-2 and IFN-\(\gamma\)). The liberation by activated mast cells of mediators (TNF-a, 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-a 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 FcsRI 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 neurtensin, 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 inclined 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.


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: 1026-1 034, 2003; Berlin et al., "Treatment of Cockroach Allergen Asthma Model with Imatinib Attenuates Airway Responses", American Journal of Respiratory and Critical care

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 hematopoiesis, melanogenesis, genetogenesis, 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 vasculitis 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(1): 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., "Abi 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 M07e 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 2004/01 903) 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/PDG receptor tyrosine kinase inhibitor, improves disease control in severe corticosteroid-dependent asthmatics", 64, 1194-1 201, 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-a 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 (PLCy) 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 hydrolyses 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-a kinase domain are associated with gastrointestinal stromal tumors (GIST).

Compounds of Formula (I) provided herein inhibit PDGF receptor (PDGFRαa and PDGFRβ) activity, are useful for the treatment of diseases, which respond to an inhibition of the PDGF receptor kinase. Therefore, compounds of Formula (I) 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 compounds of Formula (I) provided herein are useful to treat disorders, such as thrombosis, psoriasis, scleroderma, fibrosis, asthma, metabolic diseases (such as diabetes: Type 1 diabetes or Type 2 diabetes) and hypereosinophilia. Compounds of Formula (I) provided herein are also effective against diseases associated with vascular smooth-muscle cell
migration and proliferation, such as restenosis and atherosclerosis.

Compounds of Formula (I) provided herein inhibit PDGF receptor (PDGFRA and PDGFRP) activity, are useful for the treatment of age-related macular degeneration (AMD)

Patients with obliterator 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) 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) 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) 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 PDGFR (α and β) 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) 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. Such compounds of Formula (I) 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 PDGFR (α and/or β) 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, dermatological 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 sclerosis, cytopenias (by way of example only, anemia, leucopenia, neutropenia, thrombocytopenia, granulocytopenia, pancytopenia 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), myelodysplastic 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, hyperesinophilic, 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) 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 PDGFR (a and/or b) 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 sclerosis, cytopenias (by way of example only, anemia, leucopenia, neutropenia, thrombocytopenia, granulocytopenia, pancytopenia 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), myelodysplastic 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 syndrome, carcinoma, syndrome, thrombocytopenia, cytopenias, diabetes, type I diabetes, type II diabetes, rheumatoid arthritis, multiple sclerosis, cytopenias (by way of example only, anemia, leucopenia, neutropenia, thrombocytopenia, granulocytopenia, pancytopenia and idiopathic thrombocytopenic purpura), systemic lupus erythematosus, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohn's disease, psoriasis, lymphomas (by way of example only, B and T cell lymphomas), myelodysplastic 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) 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 (a 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 sclerosis, cytopenias (by way of example only, anemia, leucopenia, neutropenia, thrombocytopenia, granulocytopenia, pancytopenia and idiopathic thrombocytopenic purpura), systemic lupus erythematosus, chronic obstructive pulmonary disease (COPD), adult respiratory distress syndrome (ARDS), ulcerative colitis, Crohn's disease, psoriasis, lymphomas (by way of example only, B and T cell lymphomas), myelodysplastic 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.
disease, comprising administering to a system or subject in need of such treatment an effective amount of a compound of Formula (I), 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), 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), 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; seborrheic 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), 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, Crohn's 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), 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), 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 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 PDGFR (a and/or β) kinase activity, or c-kit kinase and PDGFR (a and/or β) kinase activity, and thereby are used to in the prevention or treatment of diseases and/or disorders associated with PDGFR (a and/or β) kinase activity, or c-kit kinase and PDGFR (a 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 PDGFR (a 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 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 (a 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 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 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 PDGFR (α and/or β) kinase activity. Also provided herein is the use of a compound of Formula (I), 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 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 PDGFR (α and/or β) kinase, or c-kit and PDGFR (α and β) kinases.

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 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), 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 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), 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), administered by inhalation, is in the range from 0.05 micrograms per kilogram body weight \(^\text{g/kg}\) to 100 micrograms per kilogram body weight \(^\text{g/kg}\). In other embodiments, the daily dosage of a compound of Formula (I), administered orally, is in the range from 0.01 micrograms per kilogram body weight \(^\text{g/kg}\) 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), 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 pharmaceutically acceptable salts, solvates, N-oxides or isomers thereof. In certain embodiments, such processes include admixing a compound of the Formula (I), 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) 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 compositions optionally 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) are adapted for oral administration for the treatment of
diseases and/or disorders associated with PDGFR (α and/or β) kinase activity. In other
embodiments, the pharmaceutical compositions comprising at least one compound of
Formula (I) are adapted for oral administration for the treatment of diseases and/or
diseases 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) are adapted for inhalation administration, including pulmonary
administration, inhalation administration or intranasal administration, for the treatment of
diseases and/or disorders associated with PDGFR (α and/or β) kinase activity. In other
embodiments, the pharmaceutical compositions comprising at least one compound of
Formula (I) are adapted for inhalation administration, including pulmonary administration,
inhalation administration or intranasal administration, for the treatment of diseases and/or
diseases 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) are adapted for inhalation administration, 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) are adapted for inhalation
administration, 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) are adapted for parenteral or intravenous administration, for the
treatment of diseases and/or disorders associated with PDGFR (α and/or β) kinase
activity. In other embodiments, the pharmaceutical compositions comprising at least one
compound of Formula (I) are adapted for parenteral or intravenous administration, for the
treatment of diseases and/or disorders associated with c-kit kinase and PDGFR
(a and/or β) kinase activity.

Oral Dosage Forms

In certain embodiments, the pharmaceutical compositions containing at least one
compound of Formula (I) 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) are prepared by admixing at least one compound of Formula (I) (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 cellulosics, 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 xerogel silica gel (AEROSIL 200, manufactured by W.R. Grace Co. of Baltimore, Md.), a coagulated aerosol of synthetic
silica (marketed by Degussa Co. of Piano, 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) (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) 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), reduce dosage frequency, and increase patient compliance.

Administration of compounds of Formula (I) 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 polyoxyethylene 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) 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 lyophilized 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) are administered transdermally. 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) or Formula (II) include an effective amount of a compound of Formula (I), 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) to the tissue. Such penetration enhancers include, but are not limited to, acetone; various alcohols such as ethanol, oleyl, and tetrahydrofurfuryl; alkyl sulfides such as dimethyl sulfide; 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) 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) are used to further adjust the properties of the resulting composition.

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

**Topical Dosage Forms.**

In certain embodiments at least one compound of Formula (I) is administered by topical application of pharmaceutical composition containing at least one compound of Formula (I) 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) 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) 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 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) in a pharmaceutically acceptable aqueous or non-aqueous solvent/propellant. Suitable propellants include halocarbons, hydrocarbons, and other liquified gases. Representative propellants include: trichlorofluoromethane (propellant 11), dichlorofluoromethane (propellant 12), dichlorotetrafluoroethane (propellant 14), tetrafluoroethane (HFA-134a), 1,1,1,2-trifluoroethane (HFA-152a), difluoromethane (HFA-32), pentafluoroethane (HFA-12), heptafluoropropane (HFA-227a), perfluoro propane, 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) 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 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-heptafluoro-n-propane and mixtures thereof.

In certain embodiments, suspensions and solutions comprising at least one compound of Formula (I), 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) 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) and a powder base such as lactose or starch. In certain embodiments, compounds of Formula (I) 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) 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) 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 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 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), 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) is administered once daily by inhalation administration, while in other embodiments a compound of Formula (I) 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 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-p-D-maltopyranoside, EDTA, and mixed micelles.

In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) 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) 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.

**Ophthalmic Administration**

In certain embodiments pharmaceutical compositions containing at least one compound of Formula (I) are administered ophthalmically 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) 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) 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) 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) provided herein, is administered alone (without an additional therapeutic agent) for the treatment of a disease or disorder associated with PDGFR (α and/or β) kinase activity.

In certain embodiments, a compound of Formula (I) 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) 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 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), is administered in combination with one or more additional therapeutic agents, for the treatment of a disease or disorder associated with PDGFR (α and/or β) kinase activity.

In other embodiments, a compound of Formula (I), 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), is formulated in combination with one or more additional therapeutic agents and administered for the treatment of a disease or disorder associated with PDGFR (α and/or β) kinase activity.

In other embodiments, a compound of Formula (I), 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), 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 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), is administered sequentially with one or more additional therapeutic agents, for the treatment of a disease or disorder associated with PDGFR (α and/or β) kinase activity.

In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I), 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), prior to administration of one or more additional therapeutic agents, for the treatment of a disease or disorder associated with PDGFR (α and/or β) kinase activity.

In other embodiments, the combination treatments provided herein include administration of a compound of Formula (I), 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), 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 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), subsequent to administration of one or more additional therapeutic agents, for the treatment of a disease or disorder associated with PDGFR (α and/or β) kinase activity.

In other embodiments, the combination treatments provided herein include
administration of a compound of Formula (I), 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), 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 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), 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, the combination treatments provided herein include
administration of a compound of Formula (I), 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 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) 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 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 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, metoclopramide, domperidone, prochlorperazine, promethazine, chlorpromazine, trimethobenzamide, ondansetron, granisetron, hydroxyzine, acetylmethylecaine monoethanolamine, alizapride, azasetron, benzquinamide, bietanautine, bromopride, buclizine, clebopride, cyclizine, dimenhydrinate, diphenidol, dolasetron, meclizine, methallatal, metopimazine, nabilone, oxypernydyl, pipamazine, scopolamine, sulpiride, tetrahydrocannabinols, thiethylperazine, thioproperazine, tropisetron, and combinations thereof.

The anti-inflammatory agents used in combination with compounds of Formula (I), 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, flurbiprofen, oxaprozin, piroxicam, meloxicam, ampiroxicam, droxicam, pivoxicam, tenoxicam, nabumetone, phenylbutazone, oxyphenbutazone, antipyrine, aminopyrine, apazone and nimesulide, leukotriene antagonists including, but not limited to, zileuton, aurothioglucose, gold sodium thiomolate and auranofin, steroids including, but not limited to, aclometasone dipropionate, aminonide, beclomethasone dipropionate, betametasone, betamethasone benzoate, betamethasone dipropionate, betamethasone sodium phosphate, betamethasone valerate, clobetasol propionate, clocortolone pivalate, hydrocortisone, hydrocortisone derivatives, desonide, desoximetasone, dexamethasone, flunisolide, flucinolone, flurandrenolide, halcinocide, medrysone, methylprednisolone, methylprednisolone 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 benz bromarone.

The immunomodulatory agents used in combination with compounds of Formula (I), 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 methotrexate, leflunomide, corticosteroids, cyclophosphamide, cyclosporine A, cyclosporin G, mycophenolate mofetil, ascomycin, rapamycin (sirolimus), FK-506, mizoribine, deoxyspergualin, brequinar, mycophenolic acid, malononitriiloamindes (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(abwe)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 Rituaxan (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-CD1 1a 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-a receptor or a fragment thereof, the extracellular domain of an IL-1 ß 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-a, interferon (IFN)-a, IFN-ß, 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-a 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 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, mechloretamine, cis-platin, oxaliplatin, carboplatin, cyclophosphamide, ifosfamide, melphalan, chlorambucil, hexamethylmelamine, thiotepa, busulfan, carmustine, streptozocin, dacarbazine and temozolomide.

The antimetabolites used in combination with compounds of Formula (I), 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, cytarabine, 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 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 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 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 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-lipoxigenase (5-LO) inhibitor or 5-lipoxigenase activating protein (FLAP) antagonist such as; zileuton; ABT-761; fenleutin; tepoxalin; Abbott-85761; a N-(5-substituted)-thiophene-2-alkylsulfonamide; 2,6-di-tert-butylphenolhydrozones; a methoxytetrahydroprans 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 BAYx7195.

In other embodiments, the combinations described herein include combination of a compound of Formula (I), 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-Is such as L-651,392; amidino compounds such as CGS-25019c; benzoxalamines such as ontazolast; benzeneacarboximidamides such as BIIL 284/260; and compounds such as zafirlukast, ablukast, montelukast, SINGULAIR™, pranlukast, verlukast (MK-679), RG-12525, Ro-245913, irlukast (CGP 4571 5A), and BAYx7195.

In other embodiments, the combinations described herein include combination of a compound of Formula (I), 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 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 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), 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 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-1/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 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 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 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, ethylenamines, 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, trimethylolmelamine, chlorambucil, chlorambazine, 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, peptomycin, plicamycin, porfiromycin, puromycin, streptonigrin, streptozocin, tubercidin, urethane, vinblastine, vincristine, and vindesine.

In certain embodiments, the combination treatments provided herein include administration of a compound of Formula (I), 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) 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, tadalafil, digoxin, furosemide, spironolactone, warfarin, epoprostenol, treprostinil, bosentan and ambrisentan.

Examples

The following examples were offered to illustrate, but not to limit, the compounds of Formula (I) 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 NaHCO₃, 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 3M LiOH (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 3M HCl (17.5 mL). 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. ¹H NMR (400MHz, d₆-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 methyl 3-amino-4-fluorobenzoate (7)
A solution of 4-fluoro-3-nitrobenzoic acid (5) (20 g, 108.11 mmol) and conc. H₂SO₄ (20 ml) in methanol (300 ml) was heated to 80 °C and stirred overnight. The resulting mixture was cooled and concentrated under vacuum. The resulting solution was diluted with ice water (600 ml). The solids were collected by filtration and dried to give of methyl 4-fluoro-3-nitrobenzoate (6) as a white solid.

Into a solution of methyl 4-fluoro-3-nitrobenzoate (6) (13 g, 65.33 mmol) in methanol (250 ml) under a nitrogen atmosphere, was added Pd/C (5 g). The suspension was stirred under a H₂ atmosphere overnight at room temperature. The reaction mixture was filtered and concentrated under vacuum to give of methyl 3-amino-4-fluorobenzoate (7) as yellow oil.

**Synthesis of 4-fluoro-3-(imidazo[1,2-a]pyridine-3-carboxamido)benzoic acid (9)**

To a solution of imidazo[1,2-a]pyridine-3-carboxylic acid (1) (10 g, 61.73 mmol) in dichloromethane (300 ml) was added DMF (2 ml) and oxalyl chloride (18 g, 141.73 mmol) at 0-10 °C. The resulting solution was stirred overnight at room temperature and concentrated under vacuum. The solid obtained was added into a solution of methyl 3-amino-4-fluorobenzoate (7) (10 g, 59.17 mmol) and TEA (20 g, 198.02 mmol) in dichloromethane portionwise. The resulting solution was stirred overnight at room temperature. The resulting mixture was concentrated under vacuum and diluted with of methanol (250 ml). The solids were collected by filtration and washed with sat. Na₂CO₃ (2x200 ml) and methanol (2x50 ml) to yield methyl 4-fluoro-3-(imidazo[1,2-a]pyridine-3-carboxamido)benzoate (8) as a light yellow solid.

A solution of methyl 4-fluoro-3-(imidazo[1,2-a]pyridine-3-carboxamido)benzoate (8) (9.2 g, 29.39 mmol) and LiOH·H₂O (6.2 g, 147.62 mmol) in THF:MeOH:H₂O (4:1:1, 150 ml) was stirred for 2 hours at 70 °C. The resulting solution was diluted with ice water
(600 ml) and the pH value was adjusted to 2-3 with cone. HCl. The solids were collected by filtration and washed with H₂O (2x100 ml) and methanol (2x50 ml). The solid was dried to give 4-fluoro-3-(imidazo[1,2-a]pyridine-3-carboxamido)benzoic acid (9) as an off-white solid. 

\[ ^{1}H \text{NMR (400MHz, d}_{6}\text{-DMSO)} \delta 13.10 \text{ (bs, 1 H), 10.27 (s, 1 H), 9.44 (d, J=6.9 Hz, 1H), 8.62 (s, 1 H), 8.27 (dd, J}=7.5, 2.1 Hz, 1H), 7.78-7.87 (m, 2H), 7.42-7.58 (m, 2H), 7.17-7.23 (m, 1H).} 

Synthesis of 7-methylimidazo[1,2-a]pyridine-3-carboxylic acid (13)

\[
\begin{array}{c}
Cl^\text{OMe} \quad + \quad H^\text{OEt} \\
KOT-Bu \quad i-Pr_2O
\end{array}
\]

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 (10) was vacuum dried and used directly in the following step.

To a stirring suspension of 4-methylpyridin-2-amine (11) (10 g, 92.5 mmol) and potassium 2-chloro-3-ethoxy-3-oxoprop-1-en-1-olate (10) (43.46 g, 231.3 mmol) in EtOH (200 ml) at room temperature was added sulfuric acid (7.66 ml, 115.6 mmol) dropwise. The reaction mixture was stirred at room temperature overnight then heated at 78 °C for 3 hours. Pyridine (20 ml) was then added to the mixture and reaction was heated at reflux overnight. The reaction was cooled to room temperature and the solvent was concentrated. The residue was taken in water and the pH value was adjusted to 6-8 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 was purified by silica gel chromatography to afford 7-methylimidazo[1,2-a]pyridine-3-carboxylate (12). MS m/z 178.6 (M+1)^+.

To a stirring solution of ethyl 7-methylimidazo[1,2-a]pyridine-3-carboxylate (12) (10 g, 38.7 mmol) in THF:MeOH (4:1, 50 ml) was added 2M LiOH (25 ml). The reaction was
heated at 60 °C for 1 hour. The solvent was evaporated and the solid was redissolved in water. The pH value was adjusted to 4-5 with solid NaHSO₄. The precipitate was collected by filtration to give 7-methylimidazo[1,2-a]pyridine-3-carboxylic acid (13). 

\[ ^1H \text{NMR (400MHz, } d_6\text{-DMSO)} \delta 9.15 (d, J = 8.0 \text{ Hz, 1H}), 8.15 (s, 1H), 7.57 (s, 1H), 7.06 (dd, J = 6.8, 1.6 \text{ Hz, 1H}). \text{ MS } m/z 177.6 (M+1)^+. \]

The following compounds were prepared according to the protocol described for 7-methylimidazo[1,2-a]pyridine-3-carboxylic acid (13).

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<th>Intermediate number</th>
<th>Structure</th>
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<td>MS m/z 181.2 (M+1)^+.</td>
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<tr>
<td>13b</td>
<td><img src="13b.png" alt="Structure" /></td>
<td>MS m/z 181.2 (M+1)^+.</td>
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<td>[ ^1H \text{NMR (400MHz, } d_6\text{-DMSO)} \delta 8.94 (d, J = 2.0 \text{ Hz, 1H}), 8.13 (s, 1H), 7.70 (d, J = 9.6 \text{ Hz, 1H}), 7.31 (dd, J = 2.8, 9.8 \text{ Hz, 1H}), 3.85 (s, 3H). \text{ MS } m/z 193.1 (M+1)^+. ]</td>
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<tr>
<td>13f</td>
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</tr>
<tr>
<td>13g</td>
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<tr>
<td>13h</td>
<td><img src="13h.png" alt="Structure" /></td>
<td>[ ^1H \text{NMR (400MHz, } d_6\text{-DMSO)} \delta 9.29 (d, J = 1.6 \text{ Hz, 1H}), 9.15 (dd, J = 1.6, 4.4 \text{ Hz, 1H}), 8.4 (s, 1H), 8.20 (d, J = 4.4 \text{ Hz, 1H}). \text{ MS } m/z 164.1 (M+1)^+. ]</td>
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</table>
Synthesis of 3-amino-4-fluoro-N-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (16)

To a solution of 3-amino-4-fluorobenzoic acid (14) (1.0 g, 6.4 mmol) in DMF (20 ml) was added diisopropylethylamine (3.4 ml, 19.3 mmol) and HATU (2.45 g, 6.4 mmol). The reaction was stirred at room temperature for 30 minutes then (1R,2S)-1-amino-2,3-dihydro-1H-inden-2-ol (15) (0.96 g, 0.64 mmol) was added and the stirring continued for 1.5 hours. The reaction mixture was diluted with ethyl acetate and washed with sat NaHCO₃, water and brine. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The crude product was purified by preparative mass trigger LCMS to afford 3-amino-4-fluoro-N-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (16) as a white yellow solid. ¹H NMR (400MHz, d₆-MeOH) δ 8.74 (dd, J = 4.8, 1.6 Hz, 1H), 8.44 (dd, J = 4.4, 1.2 Hz, 1H), 7.98 (s, 1Hz), 7.15-7.55 (m, 4H), 5.55 (d, J = 5.2 Hz, 1H), 4.69 (td, J = 8.4, 2.0 Hz, 1H), 3.23 (dd, J = 16, 5.2 Hz,1 H), 3.01 (dd, J = 16.4, 2.0 Hz,1 H), (MS m/z 287.1 (M+1)⁺).

Synthesis of (1R,2S)-1-amino-5-fluoro-2,3-dihydro-1H-inden-2-ol (21a)
5-fluoro-1-indanone (17) (1 g, 6.7 mmol) was dissolved in methanol (15 mL) at room temperature. Sodium borohydride powder (8.0 mmol) was added in portions over several minutes with stirring. After 2 hours of stirring at room temperature, the reaction mixture was diluted with distilled water (10 mL) and acidified with 1M hydrochloric acid (10 mL) then extracted with ether (3 x 15 mL). The combined ether extracts were washed with brine (15 mL), dried over anhydrous sodium sulfate and concentrated to give 5-fluoro-1-indanol (18) as a clear oil.

The 5-fluoro-1-indanol (18) (6.5 mmol) and 4-toluenesulfonic acid (0.03 mmol) were dissolved in toluene (20 mL). The mixture was refluxed under a Dean-Stark water collector for 3 hours then washed with 5% sodium sulfate (3 x 10 mL) and brine (1 x 15 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and the solvent evaporated to give crude product 5-fluoro-1 H-indene (19) as a brown oil used directly in the following step.

A stirred mixture of 5-fluoro-1 H-indene (19) (2.4 mmol), (R,R)-Jacobsen’s catalyst (0.24 mmol) and 4-phenylpyridine N-oxide (0.24 mmol) in dichloromethane (2.0 mL) was cooled to 0 °C. A cold aqueous solution of sodium hypochlorite (2 mL) was added in slowly with vigorous stirring while maintaining the reaction temperature between 0 - 2 °C. Upon complete addition of the bleach, the reaction mixture was stirred for another one hour at 0 °C. At this point, hexane (10 mL) was added in one portion with stirring and the reaction mixture was filtered through a pad of Celite™ on a large buchner funnel. The filtrate brown organic layer was washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give crude epoxide (20) as a brown liquid (250 mg) used directly in the following step.

A three-necked flask under nitrogen atmosphere was charged with indene oxide (20) (1.7 mmol), acetonitrile (5 mL) then stirred and cooled to -40 °C. To this slurry was added trifluoromethanesulfonic acid (3.4 mmol) while maintaining the reaction temperature at -30 °C. The reaction mixture was warmed to room temperature and
stirred for 1 hour. Water (10 mL) was added and stirred for 15 minutes. After removal of acetonitrile under reduced pressure, the reaction mixture was heated at reflux for 3 hours. After cooling to room temperature, dichloromethane (10 mL) was added and stirred for 10 minutes. The two phases were separated and the aqueous layer containing the amino indanol was collected. The aqueous solution was basified with 1M sodium hydroxide (5 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layer was concentrated under reduced pressure to give the desired (1R,2S)-cis-amino alcohol (21a) as light yellow solid. $^1$H NMR (400MHz, $d_6$-MeOH) δ 7.20-7.24 (m, 1H), 7.12 (dd, $J = 8.4, 2.4$ Hz, 1H), 6.99 (dd, $J = 8.8, 2.4$ Hz, 1H), 4.61 -4.67 (m, 1H), 4.50 (d, $J = 6.0$ Hz, 1H), 3.10 (dd, $J = 16.4, 2.4$ Hz, 1H), 2.87 (dd, $J = 16.4, 2.8$ Hz, 1H). MS m/z 168.1 (M+1)⁺.

The following compounds were prepared according to the protocol described for (1R,2S)-1-amino-5-fluoro-2,3-dihydro-1H-inden-2-ol (21a).

<table>
<thead>
<tr>
<th>Intermediate number</th>
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<td>21b</td>
<td><img src="image" alt="Structure" /></td>
<td>MS m/z 168.1 (M+1)⁺.</td>
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Synthesis of (S)-3,3,3-trifluoro-N-((1R,2S)-6-fluoro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-methoxy-2-phenylpropanamide (22) to determine the chiral purity via (S)-Mosher amide of (21b)

To a solution of (S)-(-)-MTPA [(S)-a-methoxy-a-trifluoromethylphenylacetic Acid] (14 mg, 0.06 mmol) in DMF (2 mL) was added diisopropylethylamine (20 µl, 0.11 mmol) and HATU (30 mg, 0.079 mmol). The reaction was stirred at room temperature for 30 minutes then (1R,2S)-1-amino-2,3-dihydro-1H-inden-6-fluoro-2-ol (21b) (10 mg, 0.06 mmol) was added and stirring continued for 1.5 hours. The reaction mixture was diluted with ethyl acetate and washed with sat NaHCO₃, water and brine. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The crude product was purified by preparative mass trigger LCMS to afford (S)-3,3,3-trifluoro-N-((1R,2S)-6-fluoro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)-2-methoxy-2-phenylpropanamide (22). $^{19}$F
NMR (400MHz, $d_6$-MeOH) $\delta$ -70.3 (3F), -118.5 (1 F), showing enantiomeric ratio is 90%.

MS m/z 384.1 (M+1)+.

Synthesis of 3-amino-4-fluoro-N-((1R,2S)-5-fluoro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (23a)

To a solution of 3-amino-4-fluorobenzoic acid (14) (80 mg, 0.52 mmol) in DMF (20 ml) was added diisopropylethylamine (270 ml, 1.6 mmol) and HATU (290 mg, 0.78 mmol). The reaction was stirred at room temperature for 30 minutes then (1R,2S)-1-amino-2,3-dihydro-1H-inden-5-fluoro-2-ol (21a) (85 mg, 0.52 mmol) was added and stirring continued for 1.5 hours. The reaction mixture was diluted with ethyl acetate and washed with sat NaHCO$_3$, water and brine. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The crude product was purified by preparative mass trigger LCMS to afford 3-amino-4-fluoro-N-((1R,2S)-5-fluoro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (23a) as a white yellow solid. $^1$H NMR (400MHz, $d_6$-MeOH) $\delta$ 7.44 (dd, J = 8.4, 2.4 Hz, 1H), 7.30 (m, 1H), 7.13 (dd, J = 8.4, 5.2 Hz, 1H), 7.03 (m, 1H), 6.88 (dd, J = 8.8, 2.0 Hz, 1H), 6.81 (dd, J = 8.8, 2.4 Hz, 1H), 5.36 (d, J = 5.21 Hz, 1H), 4.82 (td, J = 8.4, 2.0 Hz, 1H), 3.09 (dd, J = 16, 5.2 Hz, 1H), 3.04 (dd, J = 16.4, 2.0 Hz, 1H). MS m/z 305.1 (M+1)+.

The following compounds were prepared according to the protocol described for (1R,2S)-1-amino-5-fluoro-2,3-dihydro-1H-inden-2-ol (23a).

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<tr>
<td>23b</td>
<td><img src="image" alt="Structure" /></td>
<td>MS m/z 305.1 (M+1)+</td>
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</table>
A solution of 4-fluoro-3-nitrobenzoic acid (5) (20 g, 108.11 mmol) and cone. H₂SO₄ (20 ml) in methanol (300 ml) was heated to 80 °C and stirred overnight. The resulting mixture was cooled and concentrated under vacuum. The resulting solution was diluted with ice water (600 ml). The solids were collected by filtration and dried to give of methyl 4-fluoro-3-nitrobenzoate (6) as a white solid.

Into a solution of methyl 4-fluoro-3-nitrobenzoate (6) (13 g, 65.33 mmol) in methanol (250 ml) under a nitrogen atmosphere, was added Pd/C (5 g). The suspension was stirred under a H₂ atmosphere overnight at room temperature. The reaction mixture was filtered and concentrated under vacuum to give of methyl 3-amino-4-fluorobenzoate (7) as yellow oil.

Synthesis of 4-fluoro-3-(imidazo[1,2-a]pyridine-3-carboxamido)benzoic acid (9)

To a solution of imidazo[1,2-a]pyridine-3-carboxylic acid (1) (10 g, 61.73 mmol) in dichloromethane (300 ml) was added DMF (2 ml) and oxalyl chloride (18 g, 141.73 mmol) at 0-10 °C. The resulting solution was stirred overnight at room temperature and concentrated under vacuum. The solid obtained was added into a solution of methyl 3-amino-4-fluorobenzoate (7) (10 g, 59.17 mmol) and TEA (20 g, 198.02 mmol) in dichloromethane portionwise. The resulting solution was stirred overnight at room temperature.
temperature. The resulting mixture was concentrated under vacuum and diluted with of methanol (250 mL). The solids were collected by filtration and washed with sat. Na$_2$CO$_3$ (2x200 mL) and methanol (2x50 mL) to yield methyl 4-fluoro-3-(imidazo[1,2-a]pyridine-3-carboxamido)benzoate (8) as a light yellow solid.

5 A solution of methyl 4-fluoro-3-(imidazo[1,2-a]pyridine-3-carboxamido)benzoate (8) (9.2 g, 29.39 mmol) and LiOH·H$_2$O (6.2 g, 147.62 mmol) in THF:MeOH::H$_2$O (4:1, 150 mL) was stirred for 2 hours at 70 °C. The resulting solution was diluted with ice water (600 mL) and the pH value was adjusted to 2.3 with cone. HCl. The solids were collected by filtration and washed with H$_2$O (2x100 mL) and methanol (2x50 mL). The solid was dried to give 4-fluoro-3-(imidazo[1,2-a]pyridine-3-carboxamido)benzoic acid (9) as an off-white solid. $^1$H NMR (400MHz, $d_6$-DMSO) δ 13.10 (bs, 1 H), 10.27 (s, 1 H), 9.44 (d, $J$=6.9 Hz, 1H), 8.62 (s, 1H), 8.27 (dd, $J$=7.5, 2.1 Hz, 1H), 7.78-7.87 (m, 2H), 7.42-7.58 (m, 2H), 7.17-7.23 (m, 1H).

Synthesis of 7-methylimidazo[1,2-a]pyridine-3-carboxylic acid (13)

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 (10) was vacuum dried and used directly in the following step.

To a stirring suspension of 4-methylpyridin-2-amine (11) (10 g, 92.5 mmol) and potassium 2-chloro-3-ethoxy-3-oxoprop-1-en-1-olate (10) (43.46 g, 231.3 mmol) in EtOH (200 mL) at room temperature was added sulfuric acid (7.66 mL, 115.6 mmol) dropwise. The reaction mixture was stirred at room temperature overnight then heated at 78 °C for 3 hours. Pyridine (20 mL) was then added to the mixture and reaction was heated at reflux overnight. The reaction was cooled to room temperature and the solvent was
concentrated. The residue was taken in water and the pH value was adjusted to 6-8 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 was purified by silica gel chromatography to afford ethyl 7-methylimidazo[1,2-a]pyridine-3-carboxylate (12). MS m/z 178.6 (M+1)⁺.

To a stirring solution of ethyl 7-methylimidazo[1,2-a]pyridine-3-carboxylate (12) (10 g, 38.7 mmol) in THF:MeOH (4:1, 50 mL) was added 2M LiOH (25 mL). The reaction was heated at 60 °C for 1 hour. The solvent was evaporated and the solid was redissolved in water. The pH value was adjusted to 4-5 with solid NaHSO₄. The precipitate was collected by filtration to give 7-methylimidazo[1,2-a]pyridine-3-carboxylic acid (13). ¹H NMR (400MHz, d₆-DMSO) δ 9.15 (d, J = 8.0 Hz, 1H), 8.15 (s, 1H), 7.57 (s, 1H), 7.06 (dd, J = 6.8, 1.6 Hz, 1H). MS m/z 177.6 (M+1)⁺.

The following compounds were prepared according to the protocol described for 7-methylimidazo[1,2-a]pyridine-3-carboxylic acid (13).

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<td>¹H NMR (400MHz, d₆-DMSO) δ 8.94 (d, J = 2.0 Hz, 1H), 8.13 (s, 1H), 7.70 (d, J = 9.6 Hz, 1H), 7.31 (dd, J = 2.8, 9.8 Hz, 1H), 3.85 (s, 3H). MS m/z 193.1 (M+1)⁺.</td>
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<td>13f</td>
<td><img src="image" alt="Structure 13f" /></td>
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Synthesis of 3-amino-4-fluoro-N-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (16)

To a solution of 3-amino-4-fluorobenzoic acid (14) (1.0 g, 6.4 mmol) in DMF (20 ml) was added diisopropylethylamine (3.4 ml, 19.3 mmol) and HATU (2.45 g, 6.4 mmol). The reaction was stirred at room temperature for 30 minutes then (1R,2S)-1-amino-2,3-dihydro-1H-inden-2-ol (15) (0.96 g, 0.64 mmol) was added and the stirring continued for 1.5 hours. The reaction mixture was diluted with ethyl acetate and washed with sat. NaHCO₃, water and brine. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The crude product was purified by preparative mass trigger LCMS to afford 3-amino-4-fluoro-N-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (16) as a white yellow solid. ¹H NMR (400MHz, d₆-MeOH) δ 8.74 (dd, J = 4.8, 1.6 Hz, 1H), 8.44 (dd, J = 4.4, 1.2 Hz, 1H), 7.98 (s, 1Hz), 7.15-7.55 (m, 4H), 5.55 (d, J = 5.2 Hz, 1H), 4.69 (td, J = 8.4, 2.0 Hz, 1H), 3.23 (dd, J = 16, 5.2 Hz, 1H), 3.01 (dd, J = 16.4, 2.0 Hz, 1H). (MS m/z 287.1 (M+1)+).

Synthesis of (1R,2S)-1-amino-5-fluoro-2,3-dihydro-1H-inden-2-ol (21a)
5-fluoro-1-indanone (17) (1 g, 6.7 mmol) was dissolved in methanol (15 mL) at room temperature. Sodium borohydride powder (8.0 mmol) was added in portions over several minutes with stirring. After 2 hours of stirring at room temperature, the reaction mixture was diluted with distilled water (10 mL) and acidified with 1M hydrochloric acid (10 mL) then extracted with ether (3 x 15 mL). The combined ether extracts were washed with brine (15 mL), dried over anhydrous sodium sulfate and concentrated to give 5-fluoro-1-indanol (18) as a clear oil.

5-fluoro-1-indanol (18) (6.5 mmol) and 4-toluenesulfonic acid (0.03 mmol) were dissolved in toluene (20 mL). The mixture was refluxed under a Dean-Stark water collector for 3 hours then washed with 5% sodium sulfate (3 x 10 mL) and brine (1 x 15 mL). The organic phase was dried over anhydrous sodium sulfate, filtered and the solvent evaporated to give crude product 5-fluoro-1 H-indene (19) as a brown oil used directly in the following step.

A stirred mixture of 5-fluoro-1 H-indene (19) (2.4 mmol), (R,R)-Jacobsen’s catalyst (0.24 mmol) and 4-phenylpyridine N-oxide (0.24 mmol) in dichloromethane (2.0 mL) was cooled to 0 °C. A cold aqueous solution of sodium hypochlorite (2 mL) was added in slowly with vigorous stirring while maintaining the reaction temperature between 0 - 2 °C. Upon complete addition of the bleach, the reaction mixture was stirred for another one hour at 0 °C. At this point, hexane (10 mL) was added in one portion with stirring and the reaction mixture was filtered through a pad of Celite™ on a large buchner funnel. The filtrate brown organic layer was washed with brine (2 x 10 mL), dried over anhydrous sodium sulfate, filtered and concentrated to give crude epoxide (20) as a brown liquid (250 mg) used directly in the following step.

A three-necked flask under nitrogen atmosphere was charged with indene oxide (20) (1.7 mmol), acetonitrile (5 mL) then stirred and cooled to -40 °C. To this slurry was added trifluromethanesulfonic acid (3.4 mmol) while maintaining the reaction temperature at -30 °C. The reaction mixture was warmed to room temperature and
stirred for 1 hour. Water (10 mL) was added and stirred for 15 minutes. After removal of
acetonitrile under reduced pressure, the reaction mixture was heated at reflux for 3
hours. After cooling to room temperature, dichloromethane (10 mL) was added and
stirred for 10 minutes. The two phases were separated and the aqueous layer containing
the amino indanol was collected. The aqueous solution was basified with 1M sodium
hydroxide (5 mL) and extracted with ethyl acetate (3 x 15 mL). The organic layer was
concentrated under reduced pressure to give the desired (1R,2S)-cis-amino alcohol
(21a) as light yellow solid. \(^1\)HNMR (400MHz, d6-MeOH) \(\delta\) 7.20-7.24 (m, 1H), 7.1 2 (dd, \(J = 8.4, 2.4\) Hz, 1H), 6.99 (dd, \(J = 8.8, 2.4\) Hz, 1H), 4.51 - 4.67 (m, 1H), 2.87 (dd, \(J = 16.4, 2.4\) Hz, 1H). MS m/z 168.1
(M+1). The following compounds were prepared according to the protocol described for
(1R,2S)-1-amino-5-fluoro-2,3-dihydro-1 H-inden-2-ol (21a).

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<td>21b</td>
<td><img src="image" alt="Structure" /></td>
<td>MS m/z 168.1 (M+1)*.</td>
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Synthesis of (S)-3,3,3-trifluoro-N-((1 R,2S)-6-fluoro-2-hydroxy-2,3-dihydro-1 H-inden-1-yl)-2-methoxy -2-phenylpropanamide (22) to determine the chiral purity via (S)- Mosher amide of (21b)

To a solution of (S)-(-)-MTPA [(S)-a-methoxy-a-trifluoromethylphenylacetic Acid] (14 mg, 0.06 mmol) in DMF (2 mL) was added diisopropylethylamine (20 \(\mu\)I, 0.11 mmol) and HATU (30 mg, 0.079 mmol). The reaction was stirred at room temperature for 30
minutes then (1R,2S)-1-amino-2,3-dihydro-1 H-inden-6-fluoro-2-ol (21b) (10 mg, 0.06
mmol) was added and stirring continued for 1.5 hours. The reaction mixture was diluted
with ethyl acetate and washed with sat NaHCO\(_3\), water and brine. The organic layer was
dried over magnesium sulfate, filtered and reduced to dryness. The crude product was
purified by preparative mass trigger LCMS to afford (S)-3,3,3-trifluoro-N-((1 R,2S)-6-fluoro-2-hydroxy-2,3-dihydro-1 H-inden-1-yl)-2-methoxy -2-phenylpropanamide (22). \(^{19}\)F
NMR (400MHz, $d_6$-MeOH) $\delta$ -70.3 (3F), -118.5 (1 F), showing enantiomeric ratio is 90%. MS m/z 384.1 (M+1)$^+$.  

Synthesis of 3-amino-4-fluoro-N-((1R,2S)-5-fluoro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (23a)

To a solution of 3-amino-4-fluorobenzoic acid (14) (80 mg, 0.52 mmol) in DMF (20 ml) was added diisopropylethylamine (270 ml, 1.6 mmol) and HATU (290 mg, 0.78 mmol). The reaction was stirred at room temperature for 30 minutes then (1R,2S)-1-amino-2,3-dihydro-1H-inden-5-fluoro-2-ol (21a) (85 mg, 0.52 mmol) was added and stirring continued for 1.5 hours. The reaction mixture was diluted with ethyl acetate and washed with sat NaHCO$_3$, water and brine. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The crude product was purified by preparative mass trigger LCMS to afford 3-amino-4-fluoro-N-((1R,2S)-5-fluoro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (23a) as a white yellow solid. $^1$H NMR (400MHz, $d_6$-MeOH) $\delta$ 7.44 (dd, $J = 8.4$, 2.4 Hz, 1H), 7.30 (m, 1H), 7.13 (dd, $J = 8.4$, 5.2 Hz, 1H), 7.03 (m, 1H), 6.88 (dd, $J = 8.8$, 2.0 Hz, 1H), 6.81 (dd, $J = 8.8$, 2.4 Hz, 1H), 5.36 (d, $J = 5.2$ Hz, 1H), 4.82 (td, $J = 8.4$, 2.0 Hz, 1H), 3.09 (dd, $J = 16$, 5.2 Hz, 1H), 3.04 (dd, $J = 16.4$, 2.0 Hz, 1H). MS m/z 305.1 (M+1)$^+$.  

The following compounds were prepared according to the protocol described for (1R,2S)-1-amino-5-fluoro-2,3-dihydro-1H-inden-2-ol (23a).

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<td>MS m/z 305.2 (M+1)$^+$.</td>
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Synthesis of (+/-)-1-(2-(aminomethyl)phenyl)piperidin-3-ol (27a)

A mixture of 2-fluorobenzonitrile (24) (401 mg, 3.31 mmol), (+/-)-piperidin-3-ol hydrochloride (25) (500 mg, 3.65 mmol) and potassium carbonate (1.37 g, 9.9 mmol) in 10 ml DMSO was stirred at 110°C for 12 hours. The reaction mixture was diluted with ethyl acetate and washed with sat. NaHCO₃, water and brine. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The crude product was purified by silica gel chromatography to afford (+/-)-2-(3-hydroxypiperidin-1-yl)benzonitrile (26). ¹H NMR (400MHz, CDCl₃) δ 7.56 (dd, J = 8.0, 2.0 Hz, 1H), 7.51 - 7.46 (m, 1H), 7.05-7.01 (m, 2H), 4.02 (brs, 1H), 3.31 (dd, J = 11.6, 3.2 Hz, 1H), 3.13-3.05 (m, 3H), 2.06-1.98 (m, 1H), 1.87-1.60 (m, 4H). MS m/z 203.1 (M+1)⁺.

(+/-)-2-(3-hydroxy-piperidin-1-yl)benzonitrile (26) (320 mg, 1.58 mmol) was dissolved in MeOH (1OmL) at room temperature. Raney Nickel was added, the flask sealed and charged with H₂(g). The reaction mixture was stirred at room temperature for 12 hours. The reaction mixture was filtered through a celite plug and solvent was removed in vacuo to afford (+/-)-1-(2-(aminomethyl)phenyl)piperidin-3-ol (27a). MS m/z 207.1 (M+1)⁺.

The following compounds were prepared according to the protocol described for (+/-)-1-(2-(aminomethyl)phenyl)piperidin-3-ol (27a).

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<th>Intermediate number</th>
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Synthesis of (>ac)-cis-4-aminochroman-3-ol hydrobromic acid salt (30)

A 1-L 1-neck round bottom flask equipped with a magnetic stir bar was charged with KOH (13.6 g, 243 mmol), MeOH (200 mL), and the solution was cooled in an ice bath for 30 minutes. An addition funnel was charged with 4-chromanone (12 g, 81 mmol), MeOH (400 mL), and the solution was dropped into the reaction mixture over 10 minutes. Diacetoxyiodobenzene (30 g, 93 mmol) was added to the reaction mixture portionwise over 5 minutes, and the solution was aged in the ice bath for 1 hour, removed from the bath and aged at room temperature for 19 hours. The reaction mixture was concentrated to near dryness on a roto-vap, and to the resultant slurry was added saturated K$_2$CO$_3$ (400 mL) and EtOAc (400 mL). The biphasic solution was stirred at room temperature for 1 hour, the phases were separated, the aqueous phase was extracted with EtOAc (2 x 200 mL), the organic extracts were combined and washed with brine (1 x 200 mL), dried over MgSO$_4$, filtered, and the filtrate was concentrated to dryness. The resultant pale brown solid (17 g) was taken-up in hot (40 °C) Et$_2$O (490 mL) over 1 hour, vacuum filtered while hot to remove insoluble particulates, the filtrate was cooled to room temperature over 25 minutes and then placed in an ice bath for 2 hours.

The resultant solids were vacuum filtered, washed with ice cold Et$_2$O (50 mL), and air dried to afford 7.03 g of an off-white crystalline solid. $^1$H NMR was consistent with the expected ketal intermediate (not shown). The filtrate was concentrated to dryness and the resultant solid (9.36 g) is crystallized from hot Et$_2$O (237 mL) as described above to afford an additional 4.28 g of an off-white crystalline solid. This was combined with the first batch and used in the next step (vida infra).

A 2-L 1-neck round bottom flask equipped with a magnetic stir bar was charged with the ketal intermediate from above (11.31 g), EtOH (300 mL), and to this stirred suspension was added 3N HCl (108 mL) over 2 minutes. The reaction mixture was
stirred at room temperature for 1 hour, H$_2$O (500 mL) was added, and the reaction mixture was stirred at room temperature for 20 minutes. K$_2$CO$_3$ (30 g) was added portionwise (CAUTION: GAS EVOLUTION) to neutralize the reaction mixture, EtOAc (500 mL) was added and the biphasic solution was stirred at room temperature for 10 minutes. The phases were separated, the aqueous phase was extracted with EtOAc (2 x 500 mL), the organic extracts were combined and washed with brine (1 x 250 mL), dried over MgSO$_4$, filtered, and the filtrate was concentrated to dryness to afford 7.75 g of a pale yellow powder. $^1$H NMR was consistent with the expected product (rac)-3-hydroxy-4-chromanone (28).

A 200-mL 1-neck round bottom flask equipped with a magnetic stir bar was charged with (rac)-3-hydroxy-4-chromanone (28) (794 mg, 4.8 mmol), (NH$_3$OH)$_2$SO$_4$ (1.59 g, 9.7 mmol), NaOAc (1.59 g, 19.4 mmol), and aqueous THF (24 mL, contains 1-2 % H$_2$O). The suspension was aged at room temperature for 19 hours, concentrated to dryness, the residue was dissolved in EtOAc (50 mL) and H$_2$O (50 mL), the phases were separated, the aqueous phase was extracted with EtOAc (3 x 50 mL), the organic extracts were combined and washed with brine (1 x 50 mL), dried over MgSO$_4$, filtered, and the filtrate was concentrated to dryness to afford 854 mg of a pale red solid. The solid was impregnated on SiO$_2$ (3 g) and purified by silica gel chromatography (12 g SiO$_2$, 0-100 % EtOAc:hexanes gradient). 755 mg of the oxime (29) so obtained and used without further analysis below (vida infra).

A 250-mL Parr vessel was charged with the oxime (29) from above (488 mg, 2.7 mmol), MeOH (10 mL), and the solution was cooled in an ice bath. An aqueous solution of HBr (0.38 mL, 48% aqueous) was added followed by 10% w/w dry Pd/C (200 mg). The resultant suspension was warmed to room temperature, the vessel was sealed and pressurized to 40 psig H$_2$ and shaken on a Parr shaker for 17 hours. The reaction mixture was vacuum filtered thru a plug of Celite, the filter cake was washed with MeOH (50 mL), and the filtrate is concentrated to dryness to afford 639 mg of a pale yellow powder. $^1$H NMR was consistent with the expected product (rac)-c/s-4-aminochroman-3-ol hydrobromic acid salt (30). $^1$H NMR (400MHz, d$_6$-DMSO) δ 8.32 (br s, 3H), 7.41 - 7.40 (m, 1H), 7.30 - 7.26 (m, 1H), 7.01 - 6.97 (m, 1H), 6.88 - 6.85 (m, 1H), 6.18 - 6.17 (m, 1H), 4.55 - 4.54 (m, 1H), 4.23 - 4.07 (m, 3H). MS m/z 166.08 (M+1)*

Synthesis of 4-fluoro-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)benzoic acid (32)
To a suspension of 7-methylimidazo[1,2-a]pyridine-3-carboxylic acid (13f) (1 g, 5.68 mmol) in dichloromethane (300 mL) oxalyl chloride (2.4 mL, 28.4 mmol) and catalytic amounts of DMF. The resulting solution was stirred overnight at room temperature and concentrated under vacuum. The solid obtained was added into a solution of methyl 3-amino-4-fluorobenzoate (7) (1.05 g, 6.24 mmol) in dry pyridine. The resulting solution was stirred (50°C) for 5 hours before it was poured into water. The solids were collected by filtration and used without further purification to yield methyl 4-fluoro-3-(7-

methylimidazo[1,2-a]pyridine-3-carboxamido)benzoate (31).

LiOH (1 g) was added in one portion to a stirred solution of the above methyl ester in THF (10 mL), MeOH (10 mL), and water (10 mL). After stirring 3 hours at room temperature, the solvent was evaporated and the solid re-suspended in water and neutralized with 1N HCl. The product 4-fluoro-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)benzoic acid was isolated by filtration (32). ¹H NMR (400MHz, d₆-DMSO)

δ 3.10 (bs, 1 H), 10.27 (s, 1 H), 9.44 (d, J=6.9 Hz, 1H), 8.62 (s, 1H), 8.27 (dd, J=7.5, 2.1 Hz, 1H), 7.78-7.87 (m, 1H), 7.42-7.58 (m, 2H), 7.17-7.23 (m, 1H), 2.43 (s, 3H) MS m/z 314.09 (M+1)⁺.

Synthesis of methyl 3-(7-bromoimidazo[1,2-a]pyridine-3-carboxamido)-4-fluorobenzoate (33)

A mixture comprising 7-bromoimidazo[1,2-a]pyridine-3-carboxylic acid (13c) (1.8 g, approximately 7.47 mmol) and thionyl chloride (10 mL, 137 mmol) under N₂ was heated at reflux for 1.5 hours. The reaction mixture was concentrated in vacuo and azeotroped...
with toluene. Methyl 3-amino-4-fluorobenzoate (7) (1.263 g, 7.47 mmol) (pre-dried at 45 °C) was added followed by pyridine and the mixture was stirred at room temperature under N₂ overnight. The reaction mixture was diluted with EtOAc and washed with H₂O. The resulting solid was collected by filtration. The filtrate was dried (MgSO₄) and concentrated in vacuo and triturated with ether to afford a cream solid. The solids were combined and dried at 45 °C to afford the title compound (33). ¹H NMR (400MHz, d-DMSO) δ 10.3 (1H, s), 9.4 (1H, d), 8.6 (1H, s), 8.3 (1H, m), 8.2 (1H, s), 7.9 (1H, m), 7.5 (1H, t), 7.4 (1H, d), 3.9 (3H, s). MS m/z 392 (M+H)⁺.

Synthesis of 4-fluoro-3-(7-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-a]pyridine-3-carboxamido)benzoic acid (34)

Methyl 3-(7-bromoimidazo[1,2-a]pyridine-3-carboxamido)-4-fluorobenzoate (33) (7 g, 17.99 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (4.49 g, 21.58 mmol) and cesium carbonate (23.44 g, 71.9 mmol) were stirred in 1,2-dimethoxyethane (60 ml) and water (25 ml). The mixture was degassed thoroughly refilling with nitrogen. PdCl₂(dppf).DCM adduct (0.350 g, 0.429 mmol) was added and the mixture was degassed thoroughly refilling with nitrogen. The mixture was stirred at 100 °C for 7 hours and then cooled to 50 °C and filtered through glass-fiber paper. The filtrate was acidified to pH 5 by the addition of 2M HCl and filtered. The foam residue was dissolved in DCM/MeOH (1:1) and azeotroped with toluene (x2). The resulting solid was dried in a vacuum oven to afford the title compound (34). MS m/z 380 (M+H)⁺.

Synthesis of final compounds

Synthesis of N-(5-((1-hydroxy-3-phenylpropan-2-yl)carbamoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide (F1)
To a solution of 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoic acid (4) (60 mg, 0.2 mmol) in DMF (2 mL) was added diisopropylethylamine (70 µL, 0.4 mmol) and HATU (76 mg, 0.2 mmol). The reaction was stirred at room temperature for 15 minutes then 2-amino-3-phenylpropan-1-ol (30 mg, 0.2 mmol) was added and stirring continued for 6 hours. The reaction mixture was diluted with ethyl acetate and washed with sat NaHCO₃, water and brine. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The crude product was purified by preparative mass trigger LCMS to afford N-(5-((1-hydroxy-3-phenylpropan-2-yl)carbamoyl)-2-fluoro-5-((1-hydroxy-indan-2-ylcarbamoyl)-phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F14) as a clear glassy solid. ¹H NMR (400 MHz, d6-DMSO) δ 10.11 (S, 1H), 9.49 (d, J = 6.8 Hz, 1H), 8.65 (s, 1H), 8.18 (d, J = 8.8 Hz, 1H), 7.85 (d, J = 8.8 Hz, 1H), 7.8 (d, J = 2.0 Hz, 1H), 7.67 (dd, J = 8.0, 2.0 Hz, 1H), 7.63 (bt, J = 8.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.29 - 7.25 (m, 5H), 7.18 - 7.14 (m, 1H), 4.29 - 4.14 (m, 2H), 3.52 - 3.40 (m, 2H), 2.97 - 2.77 (m, 1H), 2.30 (s, 3H). MS m/z 429.1 (M+1)⁺.

Synthesis of N-(2-fluoro-5-((1 R,2S)-1-hydroxy-2,3-dihydro-1-H-inden-2-ylcarbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F5)

To a solution of 4-fluoro-3-(imidazo[1,2-a]pyridine-3-carboxamido)benzoic acid (9) (40 mg, 0.14 mmol) in DMF (2 mL) was added HATU (53 mg, 0.14 mmol). The reaction was stirred at room temperature for 15 minutes then (1 R,2S)-2-amino-2,3-dihydro-1-H-inden-1-ol (15) (19 mg, 0.13 mmol) and diisopropylethylamine (24 µL, 0.14 mmol) were added and stirring continued for 2 hours. To the reaction mixture was added to 20 mL of water, sonicated and filtered to afford N-(2-fluoro-5-((1 R,2S)-1-hydroxy-2,3-dihydro-1-H-inden-2-ylcarbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F5) as a white solid. ¹H NMR (400 MHz, d6-DMSO) δ 10.28 (s, 1H), 9.45 (d, J = 6.8 Hz, 1H), 8.61 (s, 1H), 8.40 (d, J = 8.4 Hz, 1H), 8.24 (d, J = 7.2 Hz, 1H), 7.95 - 7.91 (m, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.53 (t, J = 6.8 Hz, 1H), 7.42 (t, J = 8.8 Hz, 1H), 7.28 - 7.16 (m, 5H), 5.47 - 5.43 (m, 1H), 5.15 - 5.13 (m, 1H), 4.54 - 4.52 (m, 1H), 3.11 (dd, J = 16.0, 4.8 Hz, 1H), 2.91 - 2.86 (m, 1H). MS m/z 430.4 (M+1)⁺.

Synthesis of 7-(2-methyl-2H-pyrazol-3-yl)-imidazo[1,2-a]pyridine-3-carboxylic acid [2-fluoro-5-(1-hydroxy-indan-2-ylcarbamoyl)-phenyl]-amide (F14)
To a solution of 7-Bromo-imidazo[1,2-a]pyridine-3-carboxylic acid [2-fluoro-5-(1-hydroxy-indan-2-ylcarbamoyl)-phenyl]-amide (F10) (120 mg, 0.236 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (49.0 mg, 0.236 mmol), and cesium carbonate (154 mg, 0.471 mmol) in DMF (2 mL) was added PdCl₂(dppf)₂CI₂. DCM adduct (19.24 mg, 0.024 mmol). Under anhydrous conditions the reaction was heated at 100 °C for 4 hours. The reaction mixture was diluted with 10% MeOH/EtOAc, washed with H₂O and sat NaHCO₃. The organic layer was dried over MgSO₄, filtered and concentrated. The product was purified by isco flash column chromatography using a 4 g silica flash column eluting on a gradient of 0-1 5% 2M NH₃ in MeOH/DCM. ¹H NMR (400MHz, CD₃OD) δ 9.5 (1H, d), 8.6 (1H, s), 8.4 (1H, m), 7.9 (1H, s), 7.8 (1H, m), 7.6 (1H, s), 7.5 (1H, d), 7.4-7.25 (5H, m), 6.65 (1H, s), 5.2 (1H, d), 4.2 (1H, m), 4.0 (3H, s), 3.35 (1H, s), 3.3-3.1 (2H, m).

7-(2-Methyl-2H-pyrazol-3-yl)-imidazo[1,2-a]pyridine-3-carboxylic acid [2-fluoro-5-(1-hydroxy-indan-2-ylcarbamoyl)-phenyl]-amide (F14) was separated into compounds 7-(2-Methyl-2H-pyrazol 3-yl)-imidazo[1,2-a]pyridine-3-carboxylic acid [2-fluoro-5-((1S,2R)-1-hydroxy-indan-2-ylcarbamoyl)-phenyl]-amide (F15) and 7-(2-Methyl-2Hpyrazol 3-yl)-imidazo[1,2-a]pyridine-3-carboxylic acid [2-fluoro-5-((1 R,2S)-1-hydroxy-indan-2-ylcarbamoyl)-phenyl]-amide (F16) by chiral supercritical fluid chromatography using Chiralpak IB, 250 x 10 mm, 5 μm column and 50% methanol / 50% C0₂ mobile phase at 10 mL/min.

Synthesis of N-(2-fluoro-5-(((1 R,2S)-2-hydroxy-2,3-dihydro-1 H-inden-1-yl)carbamoyl) phenyl)-6-methylimidazo[1,2-a]pyridine-3-carboxamide (F17)
To a solution of 6-methylimidazo[1,2-a]pyridine-3-carboxylic acid (13g) (75 mg, 0.43 mmol) in dichloromethane (5 mL) was added oxalyl chloride (75 µl, 0.84 mmol) and DMF (20 µl) at 0-10 °C. The resulting solution was stirred 30 minutes at room temperature and concentrated under vacuum. A solution of 3-amino-4-fluoro-2,3-dihydro-1H-inden-1-yl)benzamide (16) (122 mg, 0.43 mmol) in 3 mL pyridine was added into the above obtained solid. The resulting solution was stirred 30 minutes at room temperature. The above solution was purified by preparative mass trigger LCMS to afford N-(2-fluoro-5-(((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl) phenyl)-6-methylimidazo[1,2-a]pyridine-3-carboxamide (F17) as a light yellow solid. $^1$H NMR (400MHz, $d_6$-MeOH) δ 9.55 (s, 1 H), 8.72 (s, 1 H), 8.41 (dd, $J = 7.2$, 2.4 Hz, 1 H), 7.86 (m, 3H), 7.21 - 7.39 (m, 5H), 5.55 (d, $J = 5.2$ Hz, 1 H), 4.68 (td, $J = 8.4$, 2.0 Hz, 1 H), 3.22 (dd, $J = 16$, 5.2 Hz, 1 H), 3.00 (dd, $J = 16.4$, 2.0 Hz, 1 H), 2.52 (s, 3H). MS m/z 445.1 (M+1)$^+$. Synthesis of N-(2-fluoro-5-(((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl) phenyl)-7-fluoroimidazo[1,2-a]pyridine-3-carboxamide (F18)

To a solution of 7-fluoroimidazo[1,2-a]pyridine-3-carboxylic acid (13b) (13 mg, 0.069 mmol) in dichloromethane (2 mL) was added oxalyl chloride (20 µl, 0.23 mmol) and DMF (5 µl) at 0-10 °C. The resulting solution was stirred 30 minutes at room temperature and concentrated under vacuum. A solution of 3-amino-4-fluoro-2,3-dihydro-1H-inden-1-yl)benzamide (16) (20 mg, 0.069 mmol) in 1 mL pyridine was added into the above obtained solid. The resulting solution was stirred 30 minutes at room temperature. The above solution was purified by preparative mass trigger LCMS to afford N-(2-fluoro-5-(((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl) phenyl)-7-fluoroimidazo[1,2-a]pyridine-3-carboxamide (F18) as a light white solid. $^1$H NMR (400MHz, $d_6$-MeOH) δ 9.55 (t, $J = 6.4$ Hz, 1 H), 8.50 (s, 1 H), 8.36 (dd, $J = 7.2$, 2.4 Hz, 1 H), 7.80 - 7.85 (m, 1 H), 7.45 (d, $J = 6.4$ Hz, 1 H) 7.21 - 7.37 (m, 5H), 7.14 (td, $J = 7.6$, 2.0 Hz, 1 H) 5.57 (d, $J = 5.2$ Hz, 1 H), 4.69 (dt, $J = 8.4$, 2.0 Hz, 1 H), 3.22 (dd, $J = 16$, 5.2 Hz, 1 H).
Synthesis of N-(2-fluoro-5-(((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)phenyl)-6-methoxyimidazo[1,2-a]pyridine-3-carboxamide (F19)

To a solution of 6-methoxyimidazo[1,2-a]pyridine-3-carboxylic acid (13e) (70 mg, 0.36 mmol) in dichloromethane (5 mL) was added oxalyl chloride (95 µL, 1.1 mmol) and DMF (20 µL) at 0-10 °C. The resulting solution was stirred 30 minutes at room temperature and concentrated under vacuum. A solution of 3-amino-4-fluoro-N-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (16) (104 mg, 0.36 mmol) in 3 mL of pyridine was added into the above obtained solid. The resulting solution was stirred 30 minutes at room temperature. The above solution was purified by preparative mass trigger LCMS to afford N-(2-fluoro-5-(((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)phenyl)-6-methoxyimidazo[1,2-a]pyridine-3-carboxamide (F19) as a white powder. ¹H NMR (400MHz, d₆-MeOH) δ 9.09 (d, J = 2.4 Hz, 1H), 8.35 (s, 1H), 8.28 (dd, J = 7.2, 2.4 Hz, 1H), 7.73-7.77 (m, 1H), 7.56 (d, J = 4.8 Hz, 1H) 7.15-7.29 (m, 6H), 5.52 (d, J = 5.2 Hz, 1H), 4.64 (dt, J = 8.4, 2.0 Hz, 1H), 3.98 (s, 3H), 3.18 (dd, J = 16.4, 2.0 Hz, 1H). MS m/z 461.1 (M+1)+.

Synthesis of N-(5-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)-2-methylphenylimidazo[1,2-a]pyridine-3-carboxamide (F20)

To a solution of 3-(imidazo[1,2-a]pyridine-3-carboxamido)-4-methylbenzoic acid (4) (40 mg, 0.14 mmol) in DMF (2 mL) was added HATU (51 mg, 0.14 mmol). The reaction was stirred at room temperature for 15 minutes then (1R,2S)-2-amino-2,3-dihydro-1H-inden-1-ol (15) (18 mg, 0.12 mmol) and diisopropylethylamine (24 µL, 0.14 mmol) were added and stirring continued for 2 hours. The reaction mixture was added to 20 mL of water, sonicated and filtered to afford N-(5-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)-2-methylphenylimidazo[1,2-a]pyridine-3-carboxamide (F20) as a white solid. ¹H NMR (400MHz, d₆-DMSO) δ 10.05 (s, 1H), 9.46-9.44 (m, 1H), 8.59 (s, 1H), 8.23
Synthesis of N-(2-fluoro-5-(((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)phenyl)-5,6,7,8-tetradeuteriumimidazo[1,2-a]pyridine-3-carboxamide (F25)

To a solution of 5,6,7,8-tetradeuteriumimidazo[1,2-a]pyridine-3-carboxylic acid (13i) (70 mg, 0.43 mmol) in dichloromethane (5 mL) was added oxalyl chloride (12 µL, 1.3 mmol) and DMF (20 µL) at 0-10 °C. The resulting solution was stirred 30 minutes at room temperature and concentrated under vacuum. A solution of 3-amino-4-fluoro-N-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (16) (122 mg, 0.43 mmol) in 3 mL of pyridine was added into the above obtained solid. The resulting solution was stirred 30 minutes at room temperature. The above solution was purified by preparative mass trigger LCMS to afford N-(2-fluoro-5-(((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)phenyl)-5,6,7,8-tetradeuteriumimidazo[1,2-a]pyridine-3-carboxamide (F25) as a white solid. 1H NMR (400MHz, d6-MeOH) δ 8.49 (s, 1H), 8.37 (dd, J = 7.2, 2.4 Hz, 1H), 7.82 (m, 1H), 7.19-7.36 (m, 5H), 5.55 (d, J = 5.2 Hz, 1H), 4.68 (dt, J = 8.4, 2.0 Hz, 1H), 3.21 (dd, J = 16.6 Hz, 1H), 3.00 (dd, J = 16.4, 2.0 Hz, 1H). MS m/z 435.1 (M+1)+.

Synthesis of N-(2-fluoro-5-(((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)phenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide (F26)

To a solution of 7-methylimidazo[1,2-a]pyridine-3-carboxylic acid (13f) (80 mg, 0.45 mmol) in dichloromethane (5 mL) was added oxalyl chloride (90 µL, 1.0 mmol) and DMF (20 µL) at 0-10 °C. The resulting solution was stirred 30 minutes at room temperature and concentrated under vacuum. A solution of 3-amino-4-fluoro-N-((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (16) (122 mg, 0.43 mmol) in 3 mL of pyridine was added into the above obtained solid. The resulting solution was stirred 30 minutes at room temperature. The above solution was purified by preparative mass trigger LCMS to afford N-(2-fluoro-5-(((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)phenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide (F26) as a white solid. 1H NMR (400MHz, d6-MeOH) δ 8.50 (s, 1H), 8.38 (dd, J = 7.2, 2.4 Hz, 1H), 7.82 (m, 1H), 7.20-7.36 (m, 5H), 5.56 (d, J = 5.2 Hz, 1H), 4.68 (dt, J = 8.4, 2.0 Hz, 1H), 3.22 (dd, J = 16.6 Hz, 1H), 3.01 (dd, J = 16.4, 2.0 Hz, 1H). MS m/z 435.1 (M+1)+.
2,3-dihydro-1H-inden-1-yl)benzamide (16) (135 mg, 0.45 mmol) in 3 mL pyridine was added into the above obtained solid. The resulting solution was stirred 30 minutes at room temperature. The above solution was purified by preparative mass trigger LCMS to afford N-(2-fluoro-5-(((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)phenyl)-6-methylimidazo[1,2-a]pyridine-3-carboxamide (F28) as a light yellow solid. 1H NMR (400MHz, d6-MeOH) δ 9.78 (s, 1H), 8.95 (s, 1H), 8.40 (dd, J = 7.2, 2.4 Hz, 1H), 7.85-7.90 (m, 2H), 7.48 (d, J = 7.2 Hz, 1H), 7.20-7.40 (m, 5H), 5.56 (d, J = 5.2 Hz, 1H), 4.68 (td, J = 8.4, 2.0 Hz, 1H), 3.22 (dd, J = 16, 5.2 Hz, 1H), 3.00 (dd, J = 16.4, 2.0 Hz, 1H), 2.63 (s, 3H). MS m/z 445.1 (M+1)+.

Synthesis of N-(2-fluoro-5-(((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)phenyl)-6-fluorimidazo[1,2-a]pyridine-3-carboxamide (F27)

To a solution of 6-fluorimidazo[1,2-a]pyridine-3-carboxylic acid (13a) (210 mg, 1.2 mmol) in dichloromethane (8 mL) was added oxalyl chloride (250 µl, 2.8 mmol) and DMF (40 µl) at 0-1°C. The resulting solution was stirred 30 min at room temperature and concentrated under vacuum. A solution of 3-amino-4-fluoro-N-(((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (16) (350 mg, 1.2 mmol) in 3 mL of pyridine was added into the above obtained solid. The resulting solution was stirred 30 minutes at room temperature. The above solution was purified by preparative mass trigger LCMS to afford N-(2-fluoro-5-(((1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)phenyl)-6-fluorimidazo[1,2-a]pyridine-3-carboxamide (F27) as a light yellow solid. 1H NMR (400MHz, d6-MeOH) δ 9.57 (dd, J = 4.8, 2.4 Hz 1H), 8.60 (s, 1H), 8.35 (dd, J = 7.2, 2.4 Hz, 1H), 7.80-7.85 (m, 2H), 7.65-7.71 (m, 1H) 7.18-7.37 (m, 5H), 5.54 (d, J = 5.2 Hz, 1H), 4.65 (td, J = 8.4, 2.0 Hz, 1H), 3.18 (dd, J = 16, 5.2 Hz, 1H), 2.97(dd, J = 16.4, 2.0 Hz, 1H). (MS m/z 449.1 (M+1)+.

Synthesis of N-(2-fluoro-5-(((1R,2S)-5-fluoro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl)phenyl)-6-methyl imidazo[1,2-a]pyridine-3-carboxamide (F28)
To a solution of 6-methylimidazo[1,2-a]pyridine-3-carboxylic acid (13g) (12 mg, 0.066 mmol) in dichloromethane (2 mL) was added oxalyl chloride (10 µι, 0.23 mmol) and DMF (20 µι) at 0-10 °C. The resulting solution was stirred 30 min at room temperature and concentrated under vacuum. A solution of 3-amino-4-fluoro-N-((1R,2S)-5-fluoro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (23a) in 3 mL of pyridine (20 mg, 0.066 mmol) was added into the above obtained solid. The resulting solution was stirred 30 minutes at room temperature. The above solution was purified by preparative mass trigger LCMS to afford N-(2-fluoro-5-(((1R,2S)-5-fluoro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl) phenyl)-6-methylimidazo[1,2-a]pyridine-3-carboxamide (F28) as a white yellow solid. $^1$H NMR (400MHz, d$_6$-MeOH) δ 9.53 (s, 1H), 8.71 (s, 1H), 8.37 (dd, J = 7.2, 2.4 Hz, 1H), 7.78-7.87 (m, 3H), 7.30-7.38 (m, 2H), 7.01 (dd, J = 8.8, 2.0 Hz, 1H), 6.94 (td, J = 8.8, 2.4 Hz, 1H), 5.55 (d, J = 5.2 Hz, 1H), 4.70 (td, J = 8.4, 2.0 Hz, 1H), 3.20 (dd, J = 16.5, 2.4 Hz, 1H), 3.00 (dd, J = 16.4, 2.0 Hz, 1H), 2.53 (s, 3H). MS m/z 463.1 (M+1)$^+$.  

Synthesis of N-(2-fluoro-5-(((1R,2S)-5-fluoro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl) phenyl)-6-methylimidazo[1,2-a]pyridine-3-carboxamide (F29)

To a solution of 6-methylimidazo[1,2-a]pyridine-3-carboxylic acid (13g) (12 mg, 0.066 mmol) in dichloromethane (2 mL) was added oxalyl chloride (20 µι, 0.23 mmol) and DMF (20 µι) at 0-10 °C. The resulting solution was stirred 30 minutes at room temperature and concentrated under vacuum. A solution of 3-amino-4-fluoro-N-((1R,2S)-5-fluoro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (23b) in 3 mL of pyridine (20 mg, 0.066 mmol) was added into the above obtained solid. The resulting solution was stirred 30 minutes at room temperature. The above solution was purified by preparative mass trigger LCMS to afford N-(2-fluoro-5-(((1R,2S)-5-fluoro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)carbamoyl) phenyl)-6-methyl-imidazo[1,2-a]pyridine-3-carboxamide (F29) as a white
yellow solid. \(^1\)H NMR (400MHz, \(^{d}_6\)-MeOH) \(\delta\) 9.49 (s, 1H), 8.71 (s, 1H), 8.35 (dd, \(J = 7.2, 2.4 \text{ Hz}, 1\text{H}\)), 7.79-7.87 (m, 3H), 7.31 (m, 1H), 7.18 (m, 1H), 6.96 (dd, \(J = 8.8, 2.0 \text{ Hz}, 1\text{H}\)), 6.91 (td, \(J = 8.8, 2.4 \text{ Hz}, 1\text{H}\)), 5.48 (d, \(J = 5.2 \text{ Hz}, 1\text{H}\)), 4.64 (td, \(J = 8.4, 2.0 \text{ Hz}, 1\text{H}\)), 3.11 (dd, \(J = 16, 5.2 \text{ Hz}, 1\text{H}\)), 2.92 (dd, \(J = 16.4, 2.0 \text{ Hz}, 1\text{H}\)) 2.52 (s, 3H). MS m/z 463.1 (M+)\(^+\).

Synthesis of N-(2-fluoro-5-(((1R,2S)-6-chloro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)(carbamoyl)phenyl)-6-methylimidazo[1,2-a]pyridine-3-carboxamide (F33)

To a solution of 6-methyl imidazo[1,2-a]pyridine-3-carboxylic acid (13g) (20 mg, 0.11 mmol) in dichloromethane (2 mL) was added oxaly chloride (30 \(\mu\)l, 0.33mmol) and DMF (20 \(\mu\)l) at 0-1 0 \(^\circ\)C. The resulting solution was stirred 30 minutes at room temperature and concentrated under vacuum. A solution of 3-amino-4-fluoro-N-((1R,2S)-6-chloro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)benzamide (23c) in 3 mL pyridine (36 mg, 0.11 mmol) was added into the above obtained solid. The resulting solution was stirred 30 minutes at room temperature and then purified by preparative mass trigger LCMS to afford N-(2-fluoro-5-(((1R,2S)-6-chloro-2-hydroxy-2,3-dihydro-1H-inden-1-yl)(carbamoyl)phenyl)-6-methyl-imidazo[1,2-a]pyridine-3-carboxamide (F33) as a white yellow solid. \(^1\)H NMR (400MHz, \(^{d}_6\)-MeOH) \(\delta\) 9.47 (s, 1H), 8.69 (s, 1H), 8.33 (dd, \(J = 7.2, 2.4 \text{ Hz}, 1\text{H}\)), 7.77-7.83 (m, 3H), 7.29 (m, 1H), 7.16 (m, 1H), 6.94 (dd, \(J = 8.8, 2.0 \text{ Hz}, 1\text{H}\)), 6.89 (td, \(J = 8.8, 2.4 \text{ Hz}, 1\text{H}\)), 5.46 (d, \(J = 5.2 \text{ Hz}, 1\text{H}\)), 4.62 (td, \(J = 8.4, 2.0 \text{ Hz}, 1\text{H}\)), 3.09 (dd, \(J = 16, 5.2 \text{ Hz}, 1\text{H}\)), 2.90 (dd, \(J = 16.4, 2.0 \text{ Hz}, 1\text{H}\)) 2.53 (s, 3H). MS m/z 479.9 (M+)\(^+\).

Synthesis of N-(2-fluoro-5-(((rac-c/s-3-hydroxychroman-4-yl) carbamoyl)phenyl) imidazo[1,2-a]pyridine-3-carboxamide (F34)

To a solution of 4-fluoro-3-(imidazo[1,2-a]pyridine-3-carboxamido)benzoic acid (9) (20 mg, 0.067 mmol) in DMF (2 mL) was added HATU (51 mg, 0.13 mmol). The reaction was stirred at room temperature for 15 minutes then (ac)-c/s4-aminochroman-3-ol
hydrobromic acid salt (30) (16.3 mg, 0.067 mmol) and diisopropylethylamine (36 µL, 0.20 mmol) were added and stirring continued for 2 hours. The reaction mixture was added to 20 mL of water, sonicated and filtered to afford N-(2-fluoro-5-(((rac)-c/s-3-hydroxychroman-4-yl) carbamoyl) phenyl) imidazo[1,2-a]pyridine-3-carboxamide (F34) as a white solid. 

1H NMR (400MHz, d_4-MeOH) δ 9.61 (d, J = 8.0 Hz, 1H), 8.65 (s, 1H), 8.27 (dd, J = 8.4, 1.6, 1H), 7.16 (m, 1H), 7.07 (m, 1H), 6.82 (td, J = 7.6, 1.2 Hz, 1H), 6.73 (td, J = 8.0, 0.8 Hz, 1H), 5.45 (s, 1H), 4.13-4.19 (m, 3H). 

MS m/z 461.5 (M+1)^+.

Synthesis of N-(5-(((1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl)carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide (F123)

To a solution of 4-fluoro-3-(imidazo[1,2-a]pyridine-3-carboxamido)benzoic acid (9) (60 mg, 0.20 mmol) in DMF (2 mL) was added HATU (84 mg, 0.22 mmol). The reaction was stirred at room temperature for 15 minutes then (1S,2S)-2-amino-1-phenylpropane-1,3-diol (37 mg, 0.22 mmol) and diisopropylethylamine (70 µL, 0.40 mmol) were added and stirring continued for 1.5 hours. The reaction mixture was added to 20 mL of water, sonicated and filtered. The solid was dissolved in 2 mL methanol and purified by preparative mass trigger LCMS to afford N-(5-(((1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl)carbamoyl)-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide (F123). 

1H NMR (400MHz, d_4-CD_3OD) δ 9.41 (m, 1H), 8.39 (s, 1H), 8.14-8.11 (dd, J = 7.2, 2.4 Hz 1H), 7.64-7.61 (m, 1H), 7.57-7.53 (m, 1H), 7.49-7.44 (m, 1H), 7.35 (d, J = 7.2 Hz, 2H), 7.24-7.04 (m, 5H), 4.97 (d, J = 4.8 Hz, 1H), 4.29-4.24 (m, 1H), 3.74-3.69 (m, 1H), 3.55-3.50 (m, 1H), 3.25-3.23 (m, 1H), 3.23-3.11 (m, 1H) MS m/z 449.15 (M+1)^+.

Synthesis of N-(2-fluoro-5-(((1S,2S)-1-hydroxy-3-methoxy-1-phenylpropan-2-yl)carbamoyl)phenyl-7-methylimidazo[1,2-a]pyridine-3-carboxamide (F126)
To a solution of 4-fluoro-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)benzoic acid (32) (150 mg, 0.48 mmol) in DMF (5 ml) was added HATU (201 mg, 0.53 mmol). The reaction was stirred at room temperature for 15 minutes then (1S,2S)-2-amino-3-methoxy-1-phenylpropan-1-ol (87 mg, 0.48 mmol) and diisopropylethylamine (167 µL, 0.96 mmol) were added and stirring continued for 1 hour. The crude reaction mixture was purified by preparative mass trigger LCMS to afford N-(2-fluoro-5-(((1S,2S)-1-hydroxy-3-methoxy-1-phenylpropan-2-yl)carbamoyl)phenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide (F1 26). $^1$H NMR (400MHz, $d_6$-DMSO) $\delta$ 10.19 (s, 1H), 9.36 (d, J = 5.2 Hz, 1H), 8.49 (s, 1H), 8.09-8.05 (m, 2H), 7.67 (t, J = 1.2 Hz, 1H), 7.56 (s, 1H), 7.38-7.27 (m, 5H), 7.23-7.17 (m, 1H), 7.03 (dd, J = 6.8, 1.2 Hz, 1H), 5.60 (s, 1H), 4.83 (s, 1H), 4.37-4.30 (m, 1H), 3.56-3.51 (m, 1H), 3.29-3.24 (m, 1H), 3.23 (s, 3H), 2.43 (s, 3H) MS m/z 477.19 (M+1 $^+$).

Synthesis of N-(5-(((1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl)carbamoyl)-2-fluorophenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide (F1 27)

To a solution of 4-fluoro-3-(7-methylimidazo[1,2-a]pyridine-3-carboxamido)benzoic acid (32) (60 mg, 0.19 mmol) in DMF (2 ml) was added HATU (80 mg, 0.21 mmol). The reaction was stirred at room temperature for 15 minutes then (1S,2S)-2-amino-1-phenylpropane-1,3-diol (35 mg, 0.21 mmol) and diisopropylethylamine (66 µL, 0.38 mmol) were added and stirring continued for 48 hours. The crude reaction mixture was purified by preparative mass trigger LCMS to afford N-(5-(((1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl)carbamoyl)-2-fluorophenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide (F1 27). $^1$H NMR (400MHz, $d_6$-DMSO) $\delta$ 10.19 (s, 1H), 9.36 (d, J = 6.4 Hz, 1H), 8.50 (s, 1H), 8.09-8.07 (m, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.67 (t, J = 7.6 Hz, 2H), 7.22-7.17 (m, 1H), 7.04 (dd, J = 7.2, 1.6 Hz, 1H), 5.53 (brs, 1H), 4.92 (brs, 1H), 4.79 (brs, 1H), 4.21-4.14 (m, 1H), 3.63-3.57 (m, 1H), 3.40-3.34 (m, 1H), 2.43 (s, 3H) MS m/z 463.17 (M+1 $^+$).

Synthesis of 7-(2-Methyl-2H-pyrazol-3-yl)imidazo[1,2-a]pyridine-3-carboxylic acid [2-fluoro-5-((1R,2R)-2-hydroxy-1-hydroxymethyl-2-phenyl-ethylcarbamoyl)-phenyl]-amide (F1 28)
4-Fluoro-3-(7-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-a]pyridine-3-carboxamido)benzoic acid (50 mg, 0.132 mmol) (34), (1R,2R)-2-amino-1-phenylpropane-1,3-diol (24.24 mg, 0.145 mmol), HATU (55.1 mg, 0.145 mmol) and Huenig’s Base (25.3 µL, 0.145 mmol) were stirred in DCM (439 µL) for 18 hours. The reaction mixture was diluted with DCM and water. A precipitate formed in the layers and the resulting white solid was filtered off. The solid was dried under vacuum to afford the title compound (F128). 1H NMR (400MHz, d6-DMSO) δ 10.3 (1H, s), 9.5 (1H, d), 8.65 (1H, s), 8.1 (1H, d), 8 (1H, s), 7.9 (1H, d), 7.75 (1H, m), 7.55 (1H, s) 7.4 (2H, d), 7.35 (2H, d), 7.3 (1H, t), 7.25 (1H, t), 6.7 (1H, s), 5.5 (1H, d), 4.95 (1H, t), 4.75 (1H, t), 4.2 (1H, m), 4 (3H, s), 3.6 (1H, m). MS m/z 529.6 (M+H)+.

Representative compounds of Formula (I) with PDGFR inhibition IC_{50} values in the range of 1 nM to 200 nM, and prepared following the procedures described above, are set forth in Table 1.

### Table 1

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F2

$^1$H NMR (400MHz, $d_6$-DMSO) $\delta$ 10.16 (s, 1H), 9.50 (d, $J = 6.8$ Hz, 1H), 8.71 (d, $J = 6.8$ Hz, 1H), 8.66 (s, 1H), 7.92 (d, $J = 2.0$ Hz, 1H), 7.85 (d, $J = 9.2$ Hz, 1H), 7.79 (dd, $J = 8.0$, 2.0 Hz, 1H), 7.63 (t, $J = 7.6$ Hz, 1H), 7.43 – 7.39 (m, 3H), 7.34 – 7.22 (m, 4H), 5.11 – 5.06 (m, 1H), 3.74 – 3.63 (m, 2H), 2.32 (s, 3H).

MS $m/z$ 415.1 (M+)$^+$.  

0.146

F3

$^1$H NMR (400MHz, $d_6$-DMSO) $\delta$ 10.16 (s, 1H), 9.51 (d, $J = 6.8$ Hz, 1H), 8.67 (s, 1H), 7.96 (d, $J = 8.8$ Hz, 1H), 7.88 (s, 1H), 7.87 (d, $J = 9.0$ Hz, 1H), 7.75 (dd, $J = 8.0$, 2.0 Hz, 1H), 7.66 (bt, $J = 8.4$ Hz, 1H), 7.39 (d, $J = 8.4$ Hz, 1H), 7.29 (bt, $J = 6.4$ Hz, 1H), 3.84 – 3.81 (m, 1H), 3.52 – 3.51 (m, 2H), 2.32 (s, 3H), 1.92 (hept, 1H), 0.91 (d, $J = 6.8$ Hz, 1H), 0.88 (d, $J = 6.8$ Hz, 1H).

MS $m/z$ 381.1 (M+)$^+$.  

0.175

F4

$^1$H NMR (400MHz, $d_4$-CD$_3$OD) $\delta$ 9.50 (s, 1H), 8.54 (s, 1H), 8.32 (d, 1H), 7.84-7.82 (m, 1H), 7.77 (d, 1H), 7.62(m, 1H), 7.45 (m, 2H), 7.36-7.32 (m, 3H), 7.28-7.26-5 (m, 1H), 7.21 (t, 1H), 5.25 (t, 1H), 3.89 (d, 2H), 2.91-2.86 (m, 1H).

MS $m/z$ 419 (M+)$^+$.  

0.089

F5

$^1$H NMR (400MHz, $d_6$-DMSO) $\delta$ 10.28 (s, 1H), 9.45 (d, $J = 6.8$ Hz, 1H), 8.61 (s, 1H), 8.40 (d, $J = 8.4$ Hz, 1H), 8.24 (d, $J = 7.2$ Hz, 1H), 7.95-7.91 (m, 1H), 7.79 (d, $J = 8.8$ Hz, 1H), 7.53 (t, $J = 6.8$ Hz, 1H), 7.42 (t, $J = 8.8$ Hz, 1H), 7.28-7.16 (m, 5H),

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| F6       | 5.47-5.43 (m, 1H), 5.15-5.13 (m, 1H), 4.54-4.52 (m, 1H), 3.11 (dd, J = 16.0, 4.8 Hz, 1H), 2.91-2.86 (m, 1H). MS m/z 430.4 (M+1)^+. 
| F7       | 
| F8       | 
| F7       | 5.47-5.43 (m, 1H), 5.15-5.13 (m, 1H), 4.54-4.52 (m, 1H), 3.11 (dd, J = 16.0, 4.8 Hz, 1H), 2.91-2.86 (m, 1H). MS m/z 430.4 (M+1)^+. 
| F8       | 5.47-5.43 (m, 1H), 5.15-5.13 (m, 1H), 4.54-4.52 (m, 1H), 3.11 (dd, J = 16.0, 4.8 Hz, 1H), 2.91-2.86 (m, 1H). MS m/z 430.4 (M+1)^+. 

\[ ^1H \text{ NMR (400MHz, } d_{6}\text{-DMSO)} \delta 10.27 (s, 1H), 9.44 (d, J = 7.2 Hz, 1H), 8.60 (s, 1H), 8.39 (d, J = 8.4 Hz, 1H), 8.23 (dd, J = 7.6 Hz, 2.4, 1H), 7.95-7.91 (m, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.56-7.51 (m, 1H), 7.42 (dd, J = 10.0, 8.8 Hz, 1H), 7.27-7.17 (m, 5H), 5.45 (dd, J = 8.4, 5.2 Hz, 1H), 5.13 (d, J = 4.8 Hz, 1H), 4.55-4.50 (m, 1H), 3.10 (dd, J = 16.4, 5.2 Hz, 1H), 2.91-2.86 (m, 1H). MS m/z 430.4 (M+1)^+. 

\[ ^1H \text{ NMR (400MHz, } d_{6}\text{-DMSO)} \delta 10.29 (s, 1H), 9.46-9.43 (m, 1H), 8.84 (d, J = 8.4 Hz, 1H), 8.61 (s, 1H), 8.22 (dd, J = 7.6, 2.4 Hz, 1H), 7.91-7.86 (m, 1H), 7.81-7.77 (m, 1H), 7.56-7.51 (m, 1H), 7.45 (dd, J = 10.4, 8.8 Hz, 1H), 7.22-7.16 (m, 4H), 7.12-7.10 (m, 1H), 5.38 (d, J = 5.6 Hz, 1H), 5.30 (t, J = 7.6 Hz, 1H), 4.46-4.39 (m, 1H), 3.17 (dd, J = 15.6, 7.2 Hz, 1H), 2.75 (dd, J = 15.6, 7.6 Hz, 1H). MS m/z 430.4 (M+1)^+. 

\[ ^1H \text{ NMR (400MHz, } d_{6}\text{-DMSO)} \delta 10.29 (s, 1H), 9.46-9.43 (m, 1H), 8.84 (d, J = 8.4 Hz, 1H), 8.61 (s, 1H), 8.22 (dd, J = 7.2, 2.0 Hz, 1H), 7.91-7.86 (m, 1H), 7.80-7.77 (m, 1H), 7.56-7.51 (m, 1H), 7.45 (dd, J = 10.0, 8.8 Hz, 1H), 7.22-7.16 (m, 4H), 7.12-
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<td>(^{1}H) NMR (400MHz, (d_6)-DMSO) (\delta) 10.27 (s, 1H), 9.46-9.43 (m, 1H), 8.60 (s, 1H), 8.19 (d, (J = 8.4) Hz, 1H), 8.11 (dd, (J = 7.6, 2.4) Hz, 1H), 7.84-7.77 (m, 2H), 7.56-7.51 (m, 1H), 7.42 (dd, (J = 10.0, 8.4) Hz, 1H), 7.19 (td, (J = 6.8, 1.2) Hz, 1H), 4.63 (d, (J = 5.2) Hz, 1H), 3.66-3.58 (m, 1H), 3.44-3.37 (m, 1H), 1.91-1.82 (m, 2H), 1.66-1.62 (m, 2H), 1.28-1.20 (m, 4H). MS (m/z) 396.4 (M+1)^+.</td>
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<td>F16</td>
<td>$^1$H NMR (400 MHz, $d_6$-CD$_2$OD) $\delta$ 9.5 (1H, d), 8.6 (1H, s), 8.4 (1H, m), 7.9 (1H, s), 7.8 (1H, m), 7.6 (1H, s), 7.5 (1H, d), 7.4-7.25 (5H, m), 6.65 (1H, s), 5.2 (1H, d), 4.2 (1H, m), 4.0 (3H, s), 3.35 (1H, s), 3.3-3.1 (2H, m).</td>
<td>MS $m/z$ 511 (M+H)$^+$</td>
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**F17**

$^1$H NMR (400MHz, $d_6$-MeOH) $\delta$ 9.55 (s, 1H), 8.72 (s, 1H), 8.41 (dd, $J = 7.2$, 2.4 Hz, 1H), 7.86 (m, 3H), 7.21-7.39 (m, 5H), 5.55 (d, $J = 5.2$ Hz, 1H), 4.68 (td, $J = 8.4$, 2.0 Hz, 1H), 3.22 (dd, $J = 16$, 5.2 Hz, 1H), 3.0 (dd, $J = 16.4$, 2.0 Hz, 1H), 2.52 (s, 3H)

MS $m/z$ 445.1 (M+H)$^+$. 0.06

**F18**

$^1$H NMR (400MHz, $d_6$-MeOH) $\delta$ 9.55 (t, $J = 6.4$ Hz 1H), 8.50 (s, 1H), 8.36 (dd, $J = 7.2$, 2.4 Hz, 1H), 7.80-7.85 (m, 1H), 7.45 (d, $J = 6.4$ Hz, 1H) 7.21-7.37 (m, 5H), 7.14 (td, $J = 7.6$, 2.0 Hz, 1H) 5.57 (d, $J = 5.2$ Hz, 1H), 4.69 (dt, $J = 8.4$, 2.0 Hz, 1H), 3.22 (dd, $J = 16$, 5.2 Hz, 1H), 3.0 (dd, $J = 16.4$, 2.0 Hz, 1H).

MS $m/z$ 449.1 (M+H)$^+$. 0.086

**F19**

$^1$H NMR (400MHz, $d_6$-MeOH) $\delta$ 9.09 (d, $J = 2.4$ Hz 1H), 8.55 (s, 1H), 8.28 (dd, $J = 7.2$, 2.4 Hz, 1H), 7.73-7.77 (m, 1H), 7.56 (d, $J = 4.8$ Hz, 1H) 7.15-7.29 (m, 6H), 5.52 (d, $J = 5.2$ Hz, 1H), 4.64 (dt, $J = 8.4$, 2.0 Hz, 1H), 3.98 (s, 3H), 3.18 (dd, $J = 16$, 5.2 Hz, 1H), 2.96 (dd, $J = 16.4$, 2.0 Hz, 1H).

MS $m/z$ 461.1 (M+H)$^+$. 0.082

**F20**

$^1$H NMR (400MHz, $d_6$-DMSO) $\delta$ 10.05 (s, 1H), 9.46-9.44 (m, 1H), 8.59 (s, 1H), 8.23 (d, $J = 8.4$ Hz, 1H), 7.98 (d, $J = 1.4$ Hz, 1H), 7.81 (dd, $J = 8.0$, 2.0 Hz, 1H) 7.80-7.77 (m, 1H), 7.53-7.48 (m, 1H), 7.39 (d, $J = 8.4$ Hz, 1H), 7.27-7.14 (m, 5H), 5.45 (dd, $J = 8.4$, 5.2 Hz, 1H) 5.14 (d, $J = 4.8$ Hz, 1H) 4.54-4.50 (m, 1H), 3.10 (dd, $J = 16.4$, 5.2 Hz). 0.029
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<th>[^{1}H] NMR (400MHz, d$_6$-DMSO) δ</th>
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<td>0.095</td>
<td>10.05 (s, 1H), 9.47-9.44 (m, 1H), 8.59 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.98 (d, J = 1.6 Hz, 1H), 7.82 (dd, J = 8.0, 1.6 Hz, 1H) 7.80-7.77 (m, 1H), 7.54-7.50 (m, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.27-7.15 (m, 5H), 5.45 (dd, J = 8.4, 5.2 Hz, 1H) 5.14 (s, 1H) 4.53-4.51 (m, 1H), 3.10 (dd, J = 16.4, 5.2 Hz, 1H), 2.91-2.86 (m, 1H), 2.33 (s, 3H).</td>
<td>426.5 (M+1)^+</td>
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<td><img src="image" alt="F22" /></td>
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<td>426.5 (M+1)^+</td>
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<td><img src="image1" alt="Image" /></td>
<td>$^{1}H$ NMR (400MHz, $d_{6}$-MeOH) δ 9.47 (d, $J = 6.8$ Hz, 1H), 8.45 (s, 1H), 8.20 (dd, $J = 7.2$, 2.0 Hz, 1H), 7.65-7.70 (m, 2H), 7.53 (t, $J = 8.0$ Hz, 1H), 7.27 (t, $J = 4.8$ Hz, 1H), 7.14 (t, $J = 7.2$ Hz, 1H), 3.67-3.76 (td, $J = 10.8$, 4.0 Hz, 1H), 3.42 - 3.53 (m, 2H), 1.68-1.98 (m, 4H), 0.69-1.57 (m, 5H) (MS m/z 411.1 (M+1)$^+$.</td>
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<tr>
<td>F25</td>
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<td><img src="image2" alt="Image" /></td>
<td>$^{1}H$ NMR (400MHz, $d_{6}$-MeOH) δ 8.49 (s, 1H), 8.37 (dd, $J = 7.2$, 2.4 Hz, 1H), 7.82 (m, 1H), 7.19-7.36 (m, 5H), 5.55 (d, $J = 5.2$ Hz, 1H), 4.68 (dt, $J = 8.4$, 2.0 Hz, 1H), 3.21 (dd, $J = 16$, 5.4 Hz, 1H), 3.00 (dd, $J = 16.4$, 2.0 Hz, 1H) (MS m/z 435.1 (M+1)$^+$.</td>
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<td>F26</td>
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<td><img src="image3" alt="Image" /></td>
<td>$^{1}H$ NMR (400MHz, $d_{6}$-MeOH) δ 9.78 (s, 1H), 8.95 (s, 1H), 8.40 (dd, $J = 7.2$, 2.4 Hz, 1H), 7.85-7.90 (m, 2H), 7.48 (m, 1H), 7.20-7.40 (m, 5H), 5.56 (d, $J = 5.2$ Hz, 1H), 4.68 (td, $J = 8.4$, 2.0 Hz, 1H), 3.22 (dd, $J = 16$, 5.2 Hz, 1H), 3.00 (dd, $J = 16.4$, 2.0 Hz, 1H) (MS m/z 445.1 (M+1)$^+$.</td>
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<td>$^{1}H$ NMR (400MHz, $d_{6}$-MeOH) δ 9.57 (dd, $J = 4.8$, 2.4 Hz, 1H), 8.60 (s, 1H), 8.35 (dd, $J = 7.2$, 2.4 Hz, 1H), 7.80-7.85 (m, 2H), 7.65-7.71 (m, 1H), 7.18-7.37 (m, 5H), 5.54 (d, $J = 5.2$ Hz, 1H), 4.65 (td, $J = 8.4$, 2.0 Hz, 1H), 3.18 (dd, $J = 16$, 5.2 Hz, 1H), 2.97 (dd, $J = 16.4$, 2.0 Hz, 1H) (MS m/z 426.5 (M+1)$^+$.</td>
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<td>F28</td>
<td><img src="image" alt="Structure F28" /></td>
<td>$^1$H NMR (400MHz, d$_6$-MeOH) $\delta$ 9.53 (s, 1H), 8.71 (s, 1H), 8.36 (dd, $J = 7.2$, 2.4 Hz, 1H), 7.79-7.88 (m, 3H), 7.29-7.38 (m, 2H), 7.01 (dd, $J = 8.8$, 2.0 Hz, 1H), 6.94 (dt, $J = 8.8$, 2.4 Hz, 1H), 5.54 (d, $J = 5.2$ Hz, 1H), 4.71 (td, $J = 8.4$, 2.0 Hz, 1H), 3.20 (dd, $J = 16$, 5.2 Hz, 1H), 3.0 (dd, $J = 16.4$, 2.0 Hz, 1H), 2.53 (s, 3H). MS m/z 463.1 (M+1)$^+$.</td>
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<td>$^1$H NMR (400MHz, d$_6$-MeOH) $\delta$ 9.49 (s, 1H), 8.71 (s, 1H), 8.35 (dd, $J = 7.2$, 2.4 Hz, 1H), 7.79-7.87 (m, 3H), 7.31 (m, 1H), 7.18 (m, 1H), 6.96 (dd, $J = 8.8$, 2.0 Hz, 1H), 6.91 (td, $J = 8.8$, 2.4 Hz, 1H), 5.48 (d, $J = 5.2$ Hz, 1H), 4.64 (td, $J = 8.4$, 2.0 Hz, 1H), 3.11 (dd, $J = 16$, 5.2 Hz, 1H), 2.92 (dd, $J = 16.4$, 2.0 Hz, 1H), 2.52 (s, 3H). MS m/z 463.1 (M+1)$^+$.</td>
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| **F32** | MS m/z 609.26 (M+1)$^+$.  
$^1$H NMR (400MHz, d6-MeOH) δ 8.25 (1H, d), 7.3 (1H, s), 7.2 (1H, s), 7.05 (1H, m), 6.85 (1H, m), 6.65 (1H, s), 6.5 (1H, m), 6.25-6.15 (2H, m), 6.1-5.95 (4H, m), 5.6 (1H, d), 3.85 (1H, d), 3.4 (1H, m), 3.1 (2H, t), 2.0-1.9 (1H, m), 1.9-1.8 (1H, m), 1.3 (2H, m), 1.0 (6H, s), 0.75 (2H, m). | 0.044 |
| **F33** | MS m/z 479.12 (M+1)$^+$. | 0.163 |
| **F34** | MS m/z 447 (M+1)$^+$. | 0.195 |
| **F110** | MS m/z 385.16 (M+1)$^+$. | 0.115 |
| **F111** | $^1$H NMR (400MHz, d6-MeOH) δ 9.56 (s, 1H), 8.81 (s, 1H), 8.41 (dd, J = 7.2, 1.2 Hz, 1H), 7.91-7.98 (m, 3H), 7.35 (m, 1H), 7.18 (m, 1H), 6.85 (dd, J = 8.8, 2.0 Hz, 1H), 6.80 (dd, J = 8.8, 2.4 Hz, 1H), 5.50 (d, J = 5.2 Hz, 1H), 4.63 (dd, J = 8.4, 2.0 Hz, 1H), 3.18 (dd, J = 16, 5.2 Hz, 1H), 2.93 (dd, J = 16.4, 2.0 Hz, 1H), 2.51 (s, 3H).  
MS m/z 475.5 (M+1)$^+$. | 0.195 |
<p>| <strong>F112</strong> | $^1$H NMR (400MHz, d6-MeOH) δ 9.73 (d, J = 7.2 Hz, 1H), 8.84 (s, 1H), 8.34 (d, J = 7.2 Hz, 1H), 8.05-8.10 (m, 2H), 7.80-7.85 (m, 1H), 7.58 (t, J = 6.4 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H). | 0.076 |</p>
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<td><img src="image" alt="F113" /></td>
<td>$^1$H NMR (400MHz, d6-MeOH) $\delta$ 9.63 (dd, J = 7.2, 2.4 Hz, 1H), 8.70 (s, 1H), 8.32 (dd, J = 7.2, 1.2 Hz, 1H), 7.71-7.91 (m, 3H), 7.30 (m, 1H), 7.22 (m, 1H), 6.96 (dd, J = 8.8, 2.0 Hz, 1H), 6.90 (dd, J = 8.8, 2.4 Hz, 1H), 5.49 (d, J = 5.2 Hz, 1H), 4.65 (dd, J = 8.4, 2.0 Hz, 1H), 3.12 (dd, J = 16, 5.2 Hz, 1H), 2.92 (dd, J = 16.4, 2.0 Hz, 1H). MS m/z 419.1 (M+1)$^+$.</td>
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<td>$^1$H NMR (400MHz, d6-MeOH) $\delta$ 9.55 (s, 1H), 8.71 (s, 1H), 8.28 (dd, J = 7.2, 1.2 Hz, 1H), 7.92-7.82 (m, 3H), 7.29 (t, J = 8.8 Hz, 1H), 3.79 (m, 3H), 3.42 - 3.53 (m, 1H), 2.05 (m, 2H), 1.75 (m, 2H), 1.31-1.41 (m, 4H), 2.51 (s, 3H). MS m/z 411.4 (M+1)$^+$.</td>
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<td>$^1$H NMR (400MHz, d6-MeOH) $\delta$ 9.32 (dd, J = 7.2, 2.4 Hz, 1H), 8.41 (s, 1H), 8.26 (dd, J = 5.2, 2.4 Hz, 1H), 7.75 (m, 3H), 7.45 (s, 1H), 7.31 (t, J = 8.8 Hz, 1H), 7.06 (dd, J = 7.2, 2.0 Hz, 1H), 3.80 (m, 3H), 3.43 - 3.54 (m, 1H), 2.06 (m, 2H), 1.78 (m, 2H), 1.35-1.44 (m, 4H), 2.50 (s, 3H). MS m/z 411.4 (M+1)$^+$.</td>
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**F116**

1H NMR (400MHz, d6-MeOH) δ 9.65 (d, J = 6.8 Hz, 1H), 8.75 (s, 1H), 8.25 (dd, J = 7.6, 2.4 Hz, 1H), 7.90-7.95 (m, 2H), 7.60-7.70 (m, 4H), 7.45-7.50 (m, 1H), 7.24 (dd, J = 10.0, 8.4 Hz, 1H), 3.46 (dd, J = 13.6, 6.8 Hz, 1H), 3.39 (dd, J = 13.6, 6.8 Hz, 1H), 3.15-3.25 (m, 2H), 1.85-1.95 (m, 1H), 1.55-1.75 (m, 2H), 1.40-1.50 (m, 1H), 1.10-1.25 (m, 2H), 0.95-1.10 (m, 1H).

MS m/z 411.2 (M+1)*

**F117**

1H NMR (400MHz, d6-CD3OD) δ 9.64 (d, J = 7.2 Hz, 1H), 8.69 (s, 1H), 8.27-8.25 (m, 1H), 7.9-7.89 (m, 2H), 7.72-7.69 (m, 1H), 7.46-7.40 (m, 3H), 7.31-7.18 (m, 4H), 5.18 (d, J = 6.0 Hz, 1H), 3.95-3.92 (m, 1H), 3.58-3.47 (m, 2H), 3.24-3.23 (m, 4H) MS m/z 463.17 (M+1)*

**F118**

1H NMR (400MHz, d6-DMSO) δ 10.3 (s, 1H), 9.45 (d, J = 9.0 Hz, 1H), 8.60 (s, 1H), 8.10 (d, J = 8.8 Hz, 1H), 8.06 (dd, J = 7.6, 2.0 Hz, 1H), 7.81-7.77 (m, 1H), 7.75-7.71 (m, 1H), 7.56-7.51 (m, 1H), 7.42-7.37 (m, 1H), 7.35-7.27 (m, 4H), 7.23-7.18 (m, 2H), 5.86 (d, J = 5.2 Hz, 1H), 4.84 (t, J = 4.8 Hz, 1H), 4.38-4.31 (m, 1H), 3.56-3.52 (m, 1H), 3.28 (dd, J = 9.6, 7.2 Hz, 1H), 3.23 (s, 3H) MS m/z 463.17 (M+1)*
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<td>0.013</td>
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<td>437.13 (M+1)^+</td>
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**F123**

\[^1\text{H} \text{NMR} (400\text{MHz}, d-
\text{CD}_3\text{OD}) \delta 9.41 \text{ (m, 1H), 8.39 \text{ (s, 1H), 8.14-8.11 \text{ (dd, J = 7.2, 2.4 Hz 1H), 7.64-7.61 \text{ (m, 1H), 7.57-7.53 \text{ (m, 1H), 7.49-7.44 \text{ (m, 1H), 7.35 \text{ (d, J = 7.2 Hz, 2H), 7.24-7.04 \text{ (m, 5H), 4.97 \text{ (d, J = 4.8 Hz, 1H), 4.29-4.24 \text{ (m, 1H), 3.74-3.69 \text{ (m, 1H), 3.55-3.50 \text{ (m, 1H), 3.25-3.23 \text{ (m, 1H), 3.23-3.11 \text{ (m, 1H)}}. MS m/z 449.15 (M+1)^+.**

**F124**

\[^1\text{H} \text{NMR} (400\text{MHz}, d-
\text{CD}_3\text{OD}) \delta 9.41 \text{ (m, 1H), 8.39 \text{ (s, 1H), 8.14-8.11 \text{ (dd, J = 7.2, 2.4 Hz 1H), 7.64-7.61 \text{ (m, 1H), 7.57-7.53 \text{ (m, 1H), 7.49-7.44 \text{ (m, 1H), 7.35 \text{ (d, J = 7.2 Hz, 2H), 7.24-7.04 \text{ (m, 5H), 4.97 \text{ (d, J = 4.8 Hz, 1H), 4.29-4.24 \text{ (m, 1H), 3.74-3.69 \text{ (m, 1H), 3.55-3.50 \text{ (m, 1H), 3.25-3.23 \text{ (m, 1H), 3.23-3.11 \text{ (m, 1H)}}. MS m/z 411.18 (M+1)^+.**


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<td>¹H NMR (400MHz, d6-DMSO) δ 10.19 (s, 1H), 9.36 (d, J = 5.2 Hz, 1H), 8.49 (s, 1H), 8.09-8.05 (m, 2H), 7.67 (brs, 1H), 7.56 (s, 1H), 7.38-7.27 (m, 5H), 7.23-7.17 (m, 1H), 7.03 (dd, J = 6.8, 1.2 Hz, 1H), 5.60 (brs, 1H), 4.83 (d, J = 4.4 Hz, 1H), 4.37-4.30 (m, 1H), 3.56-3.51 (m, 1H), 3.29-3.24 (m, 1H), 3.23 (s, 3H), 2.43 (s, 3H) MS m/z 477.19 (M+1)^+.</td>
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<td><img src="image3" alt="Chemical Structure" /></td>
<td>¹H NMR (400MHz, d6-DMSO) δ 10.19 (s, 1H), 9.36 (d, J = 6.4 Hz, 1H), 8.50 (s, 1H), 8.09-8.07 (m, 1H), 7.86 (d, J = 8.4 Hz, 1H), 7.67 (brs, 1H), 7.56 (s, 1H), 7.37 (m, 3H), 7.29 (t, J = 7.6 Hz, 2H), 7.22-7.17 (m, 1H), 7.04 (dd, J = 7.2, 1.6 Hz, 1H), 5.53 (brs, 1H), 4.92 (brs, 1H), 4.79 (brs, 1H), 4.21-4.14 (m, 1H), 3.63-3.57 (m, 1H), 3.40-3.34 (m, 1H), 2.43 (s, 3H) MS m/z 463.17 (M+1)^+.</td>
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<tr>
<td>F128</td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>¹H NMR (400MHz, d6-DMSO) δ 10.5 (1H, s), 9.5 (1H, s) 8.8 (1H, s), 8.1 (2H, m), 7.9 (1H, d), 7.75 (1H, m) 7.6 (2H, s), 7.4-7.3 (5H, m) 7.2 (1H, s), 6 (2H, bs), 4.9 (1H, d), 4.2 (1H, m), 4 (3H, s), 3.6 (1H,</td>
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Representative compounds of Formula (I) with PDGFR inhibition IC$_{50}$ values greater than 200 nM and prepared following the procedures described above, are set forth in Table 2.

<table>
<thead>
<tr>
<th>Cmpd No.</th>
<th>Structure</th>
<th>Physical Data</th>
<th>PDGFR (Rat A10) µM</th>
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<td>MS m/z 461.15 (M+1)$^+$</td>
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<tr>
<td>F37</td>
<td><img src="image1" alt="F37" /></td>
<td>431.14 (M+1)$^+$</td>
<td>MS m/z 431.14 (M+1)$^+$</td>
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<tr>
<td>F38</td>
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<td>MS m/z 431.14 (M+1)$^+$</td>
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<tr>
<td>F39</td>
<td><img src="image3" alt="F39" /></td>
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<td>MS m/z 609.26 (M+1)$^+$</td>
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<td>MS m/z 499.2 (M+1)$^+$</td>
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<tr>
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<td>MS m/z 411.21 (M+1)$^+$</td>
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<td>MS m/z 401.16 (M+1)$^+$</td>
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<td><strong>MS m/z 431.15 (M+1)^+</strong></td>
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</table>
Assays

Compounds of Formula (I) 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 µL of CellTiter Glo (Promega) to the cells and the luminescence was measured by a CLARIOCCD camera (Molecular Devices).

**Rat A10 cell proliferation assay**

Rat A10 cells (ATCC) were resuspended in DMEM supplemented with 1% 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 CLARIOCCD 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 CLARIOCCD camera (Molecular Devices).

**Certain Assay Results**
Various compounds of Formula (I) 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) having specific IC$_{50}$ for PDGFR inhibition values of less than or equal to 200 nM are listed in Table 1, while certain compounds of Formula (I) having specific IC$_{50}$ for PDGFR inhibition values greater than 200 nM are listed in Table 2.

In other embodiments, compounds of Formula (I) have IC$_{50}$ values for PDGFR inhibition in the range from 1 nM to 1 µM. In other embodiments, compounds of Formula (I) have IC$_{50}$ values for PDGF inhibition in the range from 1 nM to 500 nM. In other embodiments, compounds of Formula (I) have IC$_{50}$ values for PDGF inhibition in the range from 1 nM to 200 nM. In other embodiments, compounds of Formula (I) have IC$_{50}$ values for PDGF inhibition in the range from 1 nM to 100 nM. In other embodiments, compounds of Formula (I) have IC$_{50}$ values for PDGF inhibition in the range from 1 nM to 50 nM. In other embodiments, compounds of Formula (I) have IC$_{50}$ values for PDGF inhibition in the range from 1 nM to 25 nM. In other embodiments, compounds of Formula (I) have IC$_{50}$ values for PDGF inhibition in the range from 1 nM to 10 nM. In other embodiments, compounds of Formula (I) have IC$_{50}$ values for PDGF inhibition in the range from 1 nM to 5 nM. In other embodiments, compounds of Formula (I) have IC$_{50}$ values for PDGF 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.
WE CLAIM:

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

   - m is 1 and R²₀ is selected from H, halo, d-Cₖ alkyl, R⁶, R¹⁰, -OR⁴, d-Cₖ haloalkyl and -(CR₃)₂nOR¹⁻;
   - or m is 4 and R²₀ is deuterium;
   - R¹ is selected from H, d-Cₖ alkyl and halo;
   - each R² is independently selected from H, halo, and d-Cₖ alkyl;
   - R³ is selected from -(R⁵R⁶)(CR²)nOH, -C(R⁵R⁶)C(R⁶R⁷)(CR³)₂nOH, -(CR³)₂nC(R⁶R⁷R¹⁻), -(CR³)₂nR¹⁰, C₅-C₆ cycloalkyl substituted with 1-3 R⁶, -(CR³)₂nC(R⁶R⁷R¹²), -(CR³R⁶)(CR³)₂nS⁻R⁴, -(CR³R⁶)C(R⁶R⁷R¹⁻), -(CR³R⁶)C(R⁴R⁷R¹²), benzyl substituted with R¹⁰,
   - and C₅-C₆ cycloalkyl substituted with 1-3 substituents independently selected from R⁶, halo and d-Cₖ alkyl;
   - each R⁴ is independently selected from H and d-Cₖ alkyl;
   - R⁵ is d-Cₖ alkyl, -(CR²)₂nR¹⁰, phenyl or benzyl;
each $R^6$ is independently selected from -OH or -(CR$_2^9$)$_n$OH;
each $R^7$ is independently selected from H, -OR$_4$, and halo;
$R^8$ is selected from 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, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S and a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N,
wherein the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, and the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N of $R^8$ are substituted with 1-3 substituents independently selected from Cl-C$_6$alkyl and -0(C(R$_9$)$_2$)$_n$NR$_4$;
each $R^9$ is independently selected from H and C$_1$-C$_6$alkyl;
$R^{10}$ is selected from an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted C$_3$-C$_g$cycloalkyl, an unsubstituted adamantane, a substituted adamantane, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted C$_3$-C$_g$cycloalkyl,
wherein the substituted C$_3$-C$_g$cycloalkyl, substituted adamantane and substituted 4-6 membered heterocycloalkyl of $R^{10}$ are substituted with 1-3 $R^8$ or substituted with 1-3 substituents independently selected from $R^8$ and d-dalkyl;
$R^{11}$ is d-C$_6$haloalkyl;
$R^{12}$ is an unsubstituted phenyl or phenyl substituted with 1-3 substituents independently selected from halo and -SR$_4$;
$R^{13}$ is -(CR$_9^9$)$_2$nOR$_4$,
and
each n is independently selected from 1, 2, 3 and 4.

2. The compound of Formula (I), or pharmaceutically acceptable salt thereof:
Formula (I)

wherein:

m is 1 and R⁰ is selected from H, halo, Ci-C₆alkyl, R⁸, R¹⁰, -OR⁴, C₈haloalkyl and -(CR₂)ₙOR¹¹;

or m is 4 and R⁰ is deuterium;

R¹ is selected from H, d-Cealkyl and halo;

each R² is independently selected from H, halo, and Ci-C₆alkyl;

R³ is selected from -C(R⁵R⁹)(CR³)ₙOH, -(CR³)ₙC(R⁹R¹⁰R¹¹), -(CR³)ₙR¹⁰,

C₅-C₈cycloalkyl substituted with 1-3 R⁶, benzyl substituted with R¹⁰,

each R⁴ is independently selected from H and Ci-C₆alkyl;

R⁵ is Ci-C₆alkyl, -(CR³)ₙR¹⁰, phenyl or benzyl;

each R⁶ is independently selected from -OH or -(CR³)ₙOH;

each R⁷ is independently selected from H, -OR⁴, and halo;

R⁸ is selected from 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, a substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S and a substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N,

wherein the substituted 5-6 membered heteroaryl with 1-2 heteroatoms independently selected from N, O or S, and the substituted 5 membered heteroaryl with 1-4 heteroatoms selected from N of R⁸ are substituted with 1-3 substituents independently selected from Ci-C₆alkyl and -0(C(R⁵)₂)ₙN⁹R⁴₂;

each R⁹ is independently selected from H and Ci-C₆alkyl;
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$R^0$ is selected from an unsubstituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, an unsubstituted $C_3$-$C_8$cycloalkyl, an unsubstituted adamantane, a substituted adamantane, a substituted 4-6 membered heterocycloalkyl with 1-2 heteroatoms independently selected from N, O or S, and a substituted $C_3$-$C_8$cycloalkyl, wherein the substituted $C_3$-$C_8$cycloalkyl, substituted adamantane and substituted 4-6 membered heterocycloalkyl of $R^0$ are substituted with 1-3 $R^8$;

$R^{11}$ is $C_1$-$C_6$haloalkyl; and each $n$ is independently selected from 1, 2, 3 and 4.

3. The compound of claim 1 or claim 2, wherein each $R^9$ is independently selected from H and methyl.

4. The compound of any one of claims 1-3, wherein $R^3$ is $-CH(R^5)CH_2OH$ or benzyl substituted with $R^{10}$.

5. The compound of any one of claims 1-3, wherein $R^3$ is $-(CR^9R^6)C(R^8R^6R^{12})$.

6. The compound of claim 1 or claim 2 wherein the compound is a compound of Formula (la), Formula (lb), Formula (lc) or Formula (ld):

$$\text{Formula (la)}$$

$$\text{Formula (lb)}$$

$$\text{Formula (lc)}$$

$$\text{Formula (ld)}$$

7. The compound of any one of claims 1-6, wherein $R^1$ is selected from H, $-CH_3$ and F.
8. The compound of any one of claims 1-7, wherein \( R^1 \) is -CH\(_3\).

9. The compound of any one of claims 1-8, wherein each \( R^2 \) is H.

10. The compound of any one of claims 1-9, wherein each \( R^8 \) is independently selected from -OH and -CH\(_2\)OH.

11. The compound of any one of claims 1-10, wherein each \( R^7 \) is independently selected from H, -F and -Cl;

12. The compound of any one of claims 1-11, wherein each \( R^5 \) is independently selected from benzyl, phenyl, methyl, ethyl, propyl, and i-propyl.

13. The compound of any one of claims 1-12, wherein \( m \) is 1 and \( R^{30} \) is selected from H, halo, Cl-C\(_2\)alkyl, R\(^8\), -OR\(^4\).

14. The compound of any one of claims 1-13, wherein \( m \) is 1 and \( R^{30} \) is selected from H, -F, -Br, -CH\(_3\), -OCH\(_3\) and R\(^8\).

15. The compound of any one of claims 1-14, wherein:
   \( R^8 \) is selected from pyridyl and pyrazolyl, each of which is unsubstituted or each of which is substituted with 1-2 substituents independently selected from d-C\(_2\)alkyl and -O(CH\(_2\))\(_n\)NR\(^4\)\(_2\).

16. The compound of any one of claims 1-15, wherein:
   \( R^8 \) is selected from pyridyl and pyrazolyl, each of which is unsubstituted or each of which is substituted with 1-2 substituents independently selected from -CH\(_3\), -and -O(CH\(_2\))\(_2\)CH\(_2\)N(CH\(_3\))\(_2\).

17. The compound of any one of claims 1-16, wherein \( m \) is 1 and \( R^{30} \) is -CH\(_3\).

18. The compound of any one of claims 1-17, wherein \( m \) is 1 and \( R^{30} \) is H.

19. The compound of any one of claims 1-18, wherein each \( R^4 \) is H or methyl.

20. The compound of any one of claims 1-13, wherein \( m \) is 4 and \( R^{30} \) is deuterium.

21. The compound of claim 1 selected from:

- N-[5-[(1-hydroxy-3-phenylpropan-2-yl)carbamoyl]-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- N-[5-[(2-hydroxy-1-phenylethyl)carbamoyl]-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- N-[5-[(1-hydroxy-3-methylbutan-2-yl)carbamoyl]-2-methylphenyl]imidazo[1,2-a]pyridine-3-carboxamide;
- N-[2-fluoro-5-[(2-hydroxy-1-phenylethyl)carbamoyl]phenyl]imidazo[1,2-a]pyridine-3-carboxamide;
N-(5-[(1S,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)-2-methylphenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2R)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-[(1R,2S)-2-hydroxy-2,3-dihydro-1H-inden-1-yl]carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-\{[(1S,2S)-2-hydroxycyclohexyl]carbamoyl\}phenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-\{[(1S,2R)-2-hydroxycyclohexyl]methyl\}carbamoyl)phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-\{[(1S,2S)-1-hydroxy-3-methoxy-1-phenylpropan-2-yl]carbamoyl\}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-\{[(1S,2S)-1-hydroxy-3-methoxy-1-phenylpropan-2-yl]carbamoyl\}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-\{[(1S,2R)-1-hydroxy-1-phenylpropan-2-yl]carbamoyl\}phenyl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(5-\{[(2S)-2-(2-chlorophenyl)-2-hydroxyethyl]carbamoyl\}-2-fluorophenyl)imidazo[1,2-a]pyridine-3-carboxamide;
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N-(2-fluoro-5-\{[(1S,2S)-1-hydroxy-3-methoxy-1-phenylpropan-2-yl]carbamoyl\}phenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide;
N-(5-\{[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]carbamoyl\}-2-fluorophenyl)-7-methylimidazo[1,2-a]pyridine-3-carboxamide;
N-(5-\{[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]carbamoyl\}-2-fluorophenyl)-7-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-a]pyridine-3-carboxamide;
N-(2-fluoro-5-\{[(1S,2S)-1-hydroxy-3-methoxy-1-phenylpropan-2-yl]carbamoyl\}phenyl)-7-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-a]pyridine-3-carboxamide;
and
N-(5-\{[(1S,2S)-1,3-dihydroxy-1-phenylpropan-2-yl]carbamoyl\}-2-fluorophenyl)-7-(1-methyl-1H-pyrazol-5-yl)imidazo[1,2-a]pyridine-3-carboxamide.
22. A pharmaceutical composition comprising a therapeutically effective amount a
compound of any one of claims 1-21 and a pharmaceutically acceptable carrier.

23. A medicament for treating a disease associated with PDGFR kinase activity, or c-kit and PDGFR kinase activity, wherein the medicament comprises a
therapeutically effective amount of a compound of any one of claims 1-21, and the
disease is age-related macular degeneration (AMD), 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).

24. The medicament of claim 23, wherein the disease is age-related macular
degeneration (AMD), asthma, allergic rhinitis, pulmonary arterial hypertension
(PAH), pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable
bowel syndrome (IBS), inflammatory bowel disease (IBD), urticaria, dermatosis,
type I diabetes or type II diabetes.

25. Use of a compound of any one of claims 1-21 in the manufacture of a medicament
for treating a disease or disorder in a patient where PDGFR kinase activity, or c-kit
and PDGFR kinase activity is implicated, wherein the disease is age-related
macular degeneration (AMD), 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).

26. A method for treating a disease or disorder where PDGFR kinase activity, or c-kit
and PDGFR kinase activity is implicated, wherein the method comprises
administering to a system or subject in need of such treatment an effective amount
of a compound of any one of claims 1-21.

27. The method of claim 26, wherein the disease is age-related macular degeneration
(AMD), 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).

28. The method of claim 27, wherein the disease is age-related macular degeneration
(AMD), asthma, allergic rhinitis, pulmonary arterial hypertension (PAH), pulmonary
fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), urticaria, dermatosis, type I diabetes or type II diabetes.

29. A compound any one of claims 1-21 for use in treating a disease mediated by PDGFR kinase activity, or PDGFR and c-kit kinase activity, wherein the disease is selected from age-related macular degeneration (AMD), 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).

30. The compound of claim 29, wherein the disease is age-related macular degeneration (AMD), asthma, allergic rhinitis, pulmonary arterial hypertension (PAH), pulmonary fibrosis, hepatic fibrosis, cardiac fibrosis, scleroderma, irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), urticaria, dermatosis, type I diabetes or type II diabetes.
INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/053498

A. CLASSIFICATION OF SUBJECT MATTER
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Fax: (+31-70) 340-3016

B. FIELDS SEARCHED

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal , WPI Data, CHEM ABS Data, BEI LSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>EP 2 210 891 AI (DOMAIN THERAPEUTICS [FR]) 28 July 2010 (2010-07-28) pages 1-2; exampl e s 127-128</td>
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Further documents are listed in the continuation of Box C. X See patent family annex.

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Date of the actual completion of the international search
5 November 2012

Date of mailing of the international search report
12/11/2012

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Authorized officer
Lauro, Paol a
## INTERNATIONAL SEARCH REPORT

Information on patent family members

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