

PYRROLO[2,1-F][1,2,4]TRIAZINE COMPOUNDS ACTING AGAINST CANCERS,
INFLAMMATORY DISEASES, AND FIBROTIC DISEASE VIA INTERACTION WITH RAS
SUPERFAMILY PROTEINS

CROSS-REFERENCE TO RELATED APPLICATIONS

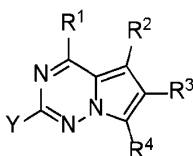
[0001] This application claims the benefit of U.S. Provisional Application No. 63/589,174 filed October 10, 2023, the content of which is incorporated herein by reference in its entirety.

1. FIELD

[0002] Provided herein are compounds of Formula I, or a pharmaceutically acceptable form thereof, and pharmaceutical compositions comprising the same. Also provided herein methods of modulating the activity of cellular targets by administering to a subject a compound of Formula I, or a pharmaceutically acceptable form thereof. Further provided herein are methods of treating cancer, fibrotic diseases, and inflammatory diseases by administering to a subject a compound of Formula I, or a pharmaceutically acceptable form thereof.

2. SUMMARY

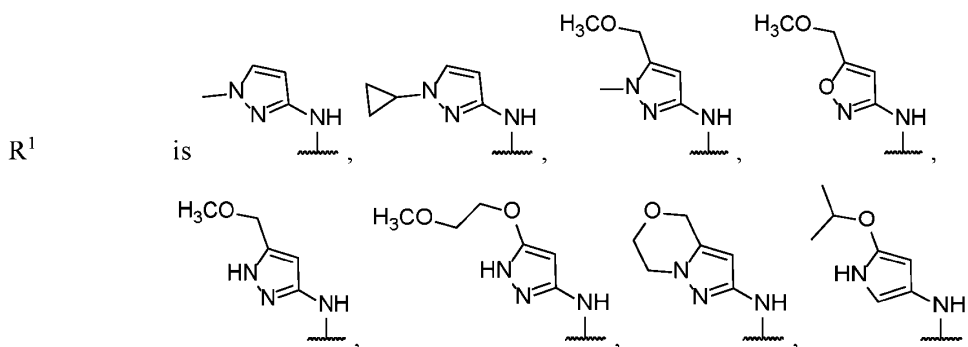
[0003] Provided herein is a compound of Formula I:

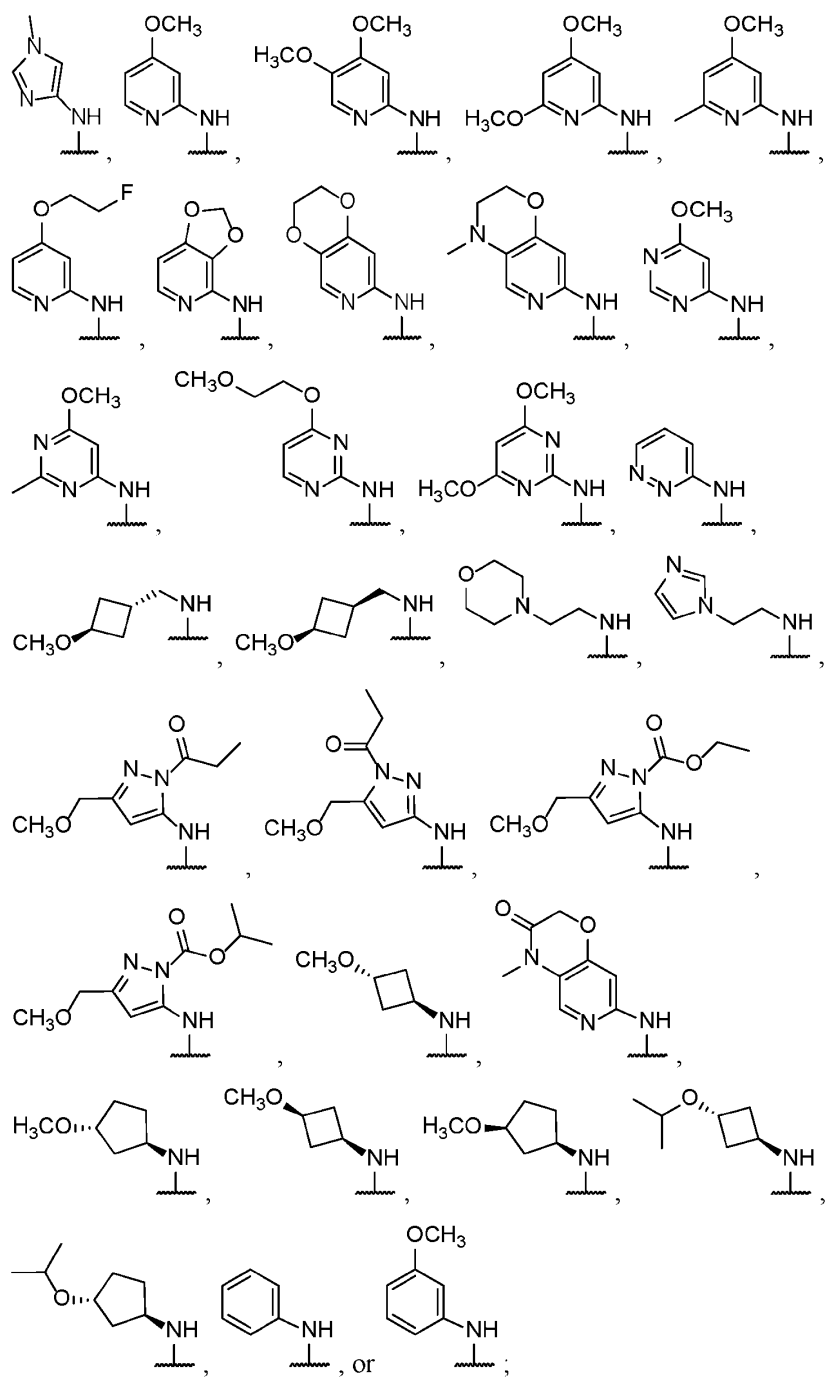


Formula I

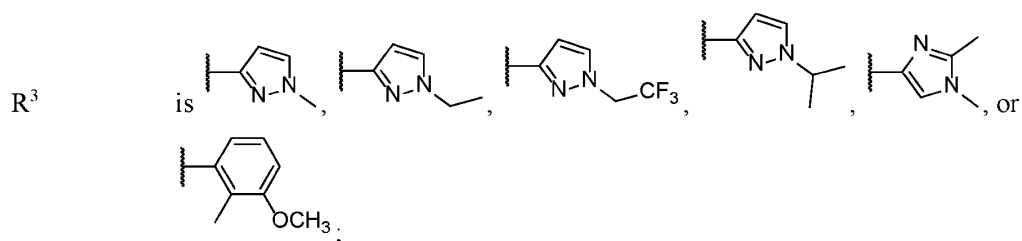
or a pharmaceutically acceptable form thereof, wherein:

Y is an imidazolyl; wherein the imidazolyl is optionally substituted with 1 R⁵ substituent and optionally substituted with 1-2 R⁶ substituents;



 $\mathbb{R}^2$

is C₁₋₂ alkyl or C₁₋₂ haloalkyl;



R⁴ is hydrogen or C₁₋₆ alkyl;

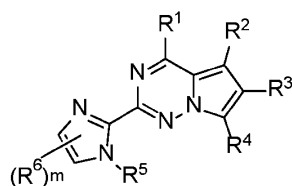
R⁵ and R⁶ are each independently C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, aryl, C₅₋₁₀ heteroaryl, C₃₋₇ heterocycloalkyl, C₁₋₆ heteroalkyl, halo, -NR⁹R¹⁰, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -C(O)NR⁹R¹⁰, -(CO)R⁸, -(CO)OH, -(CO)OR⁸, or CN, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, aryl, C₅₋₁₀ heteroaryl, C₃₋₇ heterocycloalkyl, and C₁₋₆ heteroalkyl are each independently optionally substituted with 1-3 R⁷ substituents;

R⁷ is independently selected from the group consisting of halo, CN, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, 3-6 membered heterocycloalkyl, -NR⁹R¹⁰, -(CO)R⁸, -(CO)OH, -(CO)OR⁸, -C(O)NR⁹R¹⁰, oxo, -OH, C₁₋₆ alkoxy, C₃₋₆ cycloalkoxy, C₁₋₆ haloalkoxy, or 5-6 membered heteroaryl;

R⁸ is C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or C₁₋₆ heteroalkyl, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₁₋₆ heteroalkyl, are each independently optionally substituted with 1-3 R⁷ substituents; and

R⁹ and R¹⁰ are each independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, -OH, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ heterocycloalkyl, aryl, or 5-10 membered heteroaryl, wherein the C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ heterocycloalkyl, aryl, and 5-10 membered heteroaryl are optionally substituted with 1-3 R⁷ substituents, or R⁹ and R¹⁰ are combined to form a 3-7 membered heterocycloalkyl including the nitrogen atom to which they are both attached.

[0004] Also provided herein is a compound of Formula IA:

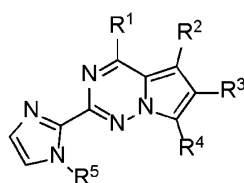


Formula IA

or a pharmaceutically acceptable form thereof;

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , and m , are as defined herein.

[0005] Also provided herein is a compound of Formula IA(1):

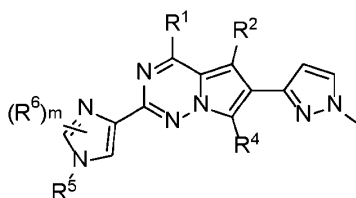


Formula IA(1)

wherein R^1 , R^2 , R^3 , R^4 , and R^5 , are as defined herein;

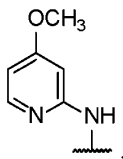
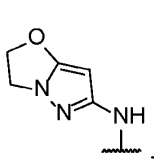
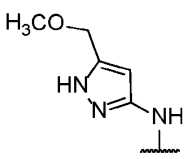
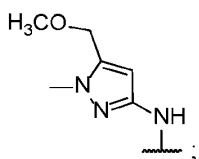
or a pharmaceutically acceptable form thereof.

[0006] Also provided herein is a compound of Formula IB:



Formula IB

or a pharmaceutically acceptable form thereof, wherein:

- R^1 is , , , or ;
- R^2 is C_{1-2} alkyl or C_{1-2} haloalkyl;
- R^4 is hydrogen or C_{1-6} alkyl;
- R^5 and R^6 are each independently C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, C_{1-6} heteroalkyl, halo, $-NR^9R^{10}$, C_{1-6} alkoxy,

C₁₋₆ haloalkoxy, -C(O)NR⁹R¹⁰, -(CO)R⁸, -(CO)OH, -(CO)OR⁸, or CN, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, aryl, C₅₋₁₀ heteroaryl, C₃₋₇ heterocycloalkyl, and C₁₋₆ heteroalkyl are each independently optionally substituted with 1-3 R⁷ substituents;

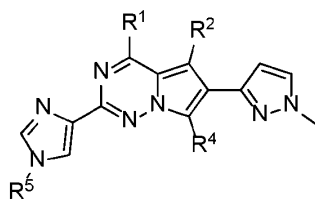
R⁷ is independently selected from the group consisting of halo, CN, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, 3-6 membered heterocycloalkyl, -NR⁹R¹⁰, -(CO)R⁸, -(CO)OH, -(CO)OR⁸, -C(O)NR⁹R¹⁰, oxo, -OH, C₁₋₆ alkoxy, C₃₋₆ cycloalkoxy, C₁₋₆ haloalkoxy, or 5-6 membered heteroaryl;

R⁸ is C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or C₁₋₆ heteroalkyl, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₁₋₆ heteroalkyl, are each independently optionally substituted with 1-3 R⁷ substituents;

R⁹ and R¹⁰ are each independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, -OH, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ heterocycloalkyl, aryl, or 5-10 membered heteroaryl, wherein the C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ heterocycloalkyl, aryl, and 5-10 membered heteroaryl are optionally substituted with 1-3 R⁷ substituents, or R⁹ and R¹⁰ are combined to form a 3-7 membered heterocycloalkyl including the nitrogen atom to which they are both attached; and

m is 0, 1 or 2.

[0007] Also provided herein is a compound of Formula IB(1):

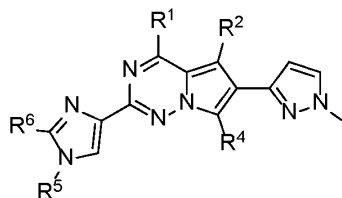


Formula IB(1)

wherein R¹, R², R³, R⁴, and R⁵, are as defined herein;

or a pharmaceutically acceptable form thereof.

[0008] Also provided herein is a compound of Formula IB(2):

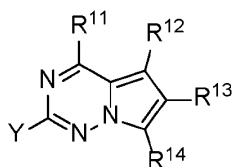


Formula IB(2)

wherein R¹, R², R³, R⁴, R⁵, and R⁶, are as defined herein;

or a pharmaceutically acceptable form thereof.

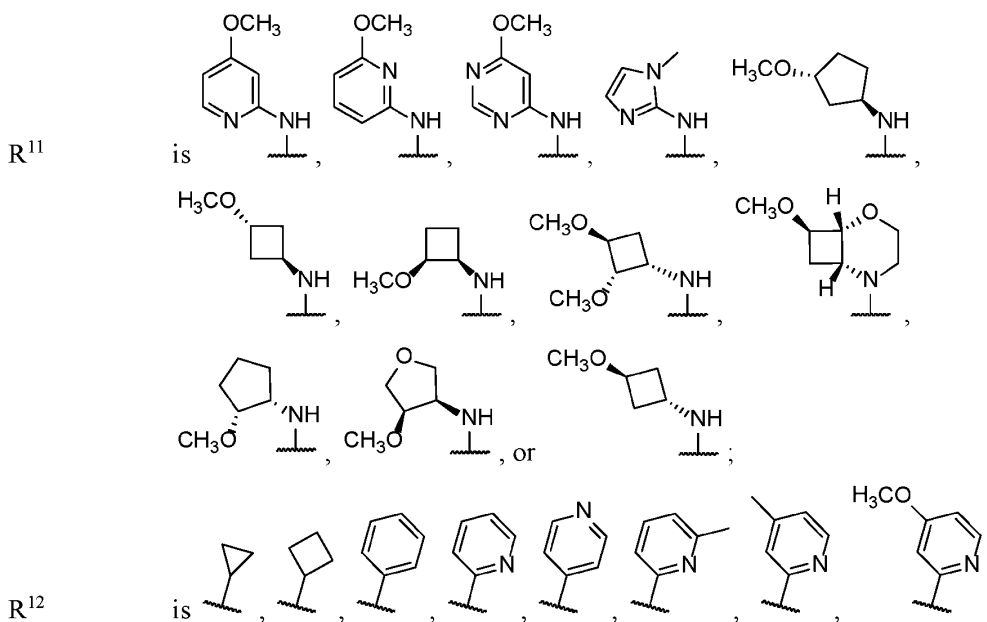
[0009] Also provided herein is a compound of Formula II:

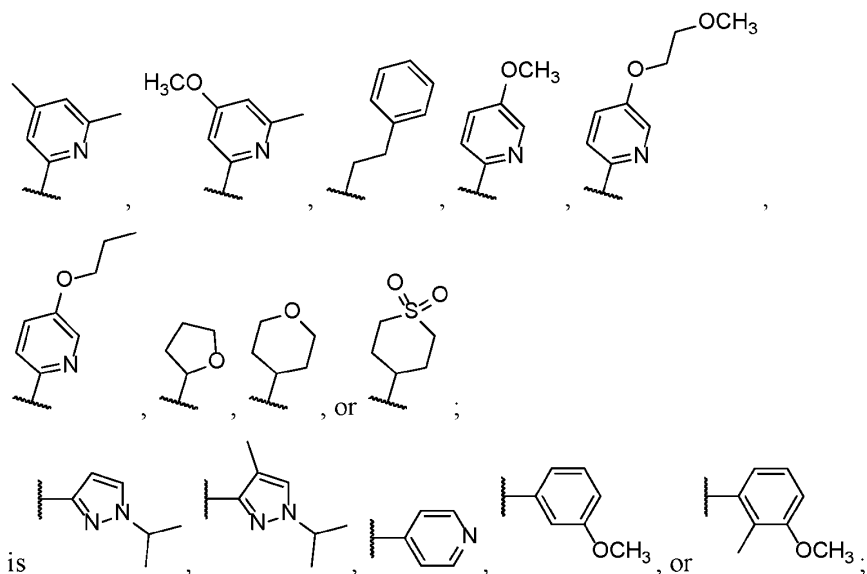


Formula II

or a pharmaceutically acceptable form thereof, wherein:

Y is an imidazolyl; wherein the imidazolyl is optionally substituted with 1 R¹⁵ substituent and optionally substituted with 1-2 R¹⁶ substituents;

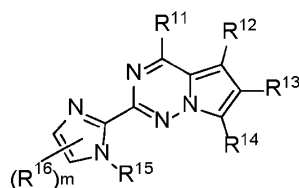




- R¹³ is
- R¹⁴ is hydrogen or C₁₋₆ alkyl;
- R¹⁵ and R¹⁶ are each independently C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, aryl, C₅₋₁₀ heteroaryl, C₃₋₇ heterocycloalkyl, C₁₋₆ heteroalkyl, halo, -NR¹⁹R²⁰, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -C(O)NR¹⁹R²⁰, -(CO)R¹⁸, -(CO)OH, -(CO)OR¹⁸, or CN, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, aryl, C₅₋₁₀ heteroaryl, C₃₋₇ heterocycloalkyl, and C₁₋₆ heteroalkyl are each independently optionally substituted with 1-3 R¹⁷ substituents;
- R¹⁷ is independently selected from the group consisting of halo, CN, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, 3-6 membered heterocycloalkyl, -NR¹⁹R²⁰, -(CO)R¹⁸, -(CO)OH, -(CO)OR¹⁸, -C(O)NR¹⁹R²⁰, oxo, -OH, C₁₋₆ alkoxy, C₃₋₆ cycloalkoxy, C₁₋₆ haloalkoxy, or 5-6 membered heteroaryl;
- R¹⁸ is C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or C₁₋₆ heteroalkyl, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₁₋₆ heteroalkyl, are each independently optionally substituted with 1-3 R¹⁷ substituents; and
- R¹⁹ and R²⁰ are each independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, -OH, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ heterocycloalkyl, aryl, or 5-10 membered heteroaryl, wherein the C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆

hydroxyalkyl, C₁₋₆ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ heterocycloalkyl, aryl, and 5-10 membered heteroaryl are optionally substituted with 1-3 R¹⁷ substituents, or R¹⁹ and R²⁰ are combined to form a 3-7 membered heterocycloalkyl including the nitrogen atom to which they are both attached.

[0010] Also provided herein is a compound of Formula IIA:



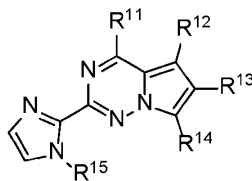
Formula IIA

wherein R¹¹, R¹², R¹³, R¹⁴, R¹⁵, and R¹⁶, are as defined herein; and

wherein m is 0, 1 or 2;

or a pharmaceutically acceptable form thereof.

[0011] Also provided herein is a compound of Formula IIA(1):

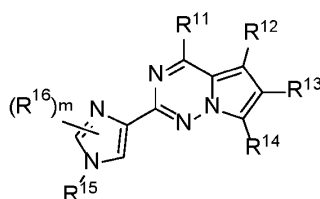


Formula IIA(1)

wherein R¹¹, R¹², R¹³, R¹⁴, and R¹⁵, are as defined herein; and

or a pharmaceutically acceptable form thereof.

[0012] Also provided herein is a compound of Formula IIB:



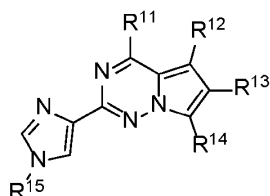
Formula IIB

wherein R¹¹, R¹², R¹³, R¹⁴, R¹⁵, and R¹⁶, are as defined herein; and

wherein m is 0, 1 or 2;

or a pharmaceutically acceptable form thereof.

[0013] Also provided herein is a compound of Formula IIB(1):

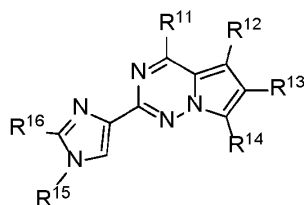


Formula IIB(1)

wherein R¹¹, R¹², R¹³, R¹⁴, and R¹⁵, are as defined herein; and

or a pharmaceutically acceptable form thereof.

[0014] Also provided herein is a compound of Formula IIB(2):



Formula IIB(2)

wherein R¹¹, R¹², R¹³, R¹⁴, R¹⁵, and R¹⁶, are as defined herein; and

or a pharmaceutically acceptable form thereof.

[0015] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[0016] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, wherein the compound is a modulator of Ras superfamily activity according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments,

the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 20 μ M according to a Ras Superfamily Activity Assay.

[0017] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, wherein the compound inhibits phosphorylation of Erk1/2 according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 10 μ M according to Erk1/2 Phosphorylation Assay.

[0018] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, wherein the compound activates phosphorylation of Erk1/2 according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, about 90% to about 100%, or 100% or more at 10 μ M according to Erk1/2 Phosphorylation Assay.

[0019] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, wherein the compound inhibits phosphorylation of Akt according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M

according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 10 μ M according to Akt Phosphorylation Assay.

[0020] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, wherein the compound activates phosphorylation of Akt according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, about 90% to about 100%, or 100% or more at 10 μ M according to Akt Phosphorylation Assay.

[0021] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, wherein the compound inhibits phosphorylation of Smad2/3 according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay.

[0022] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater

than 100% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, about 90% to about 100%, or 100% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay.

[0023] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, wherein the compound inhibits JNK according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 10 μ M according to JNK Activation Assay.

[0024] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, wherein the compound activates JNK according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, about 90% to about 100%, or 100% or more at 10 μ M according to JNK Activation Assay.

[0025] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, wherein the compound inhibits MAPK p38 according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof

inhibits MAPK p38 by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 10 μ M according to MAPK p38 Activation Assay.

[0026] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, wherein the compound activates MAPK p38 according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, about 90% to about 100%, or 100% or more at 10 μ M according to MAPK p38 Activation Assay.

[0027] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, wherein the compound inhibits proliferation in MiaPaca2 according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 1 μ M or less, 0.9 μ M or less, 0.8 μ M or less, 0.75 μ M or less, 0.7 μ M or less, 0.6 μ M or less, 0.5 μ M or less, 0.4 μ M or less, 0.3 μ M or less, 0.25 μ M or less, 0.2 μ M or less, 0.15 μ M or less, 0.1 μ M or less, 0.09 μ M or less, 0.05 μ M or less, or 0.03 μ M or less, according to Proliferation Assay.

[0028] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, wherein the compound inhibits IL-6 according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 10 μ M according to IL-6 Quantification Assay.

[0029] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA,

IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof inhibits TNF-alpha according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 10 μ M according to TNF-alpha Quantification Assay.

[0030] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof that has a half-life of 10 minutes or more, 20 minutes or more, 30 minutes or more, 40 minutes or more, or 50 minutes or more in mouse liver microsomes according to Mouse Liver Microsome Metabolic Stability Assay.

[0031] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof that has a kinetic solubility of 10 μ M or more, 20 μ M or more, 30 μ M or more, 40 μ M or more, 50 μ M or more, 60 μ M or more, 70 μ M or more, 80 μ M or more, 90 μ M or more, 100 μ M or more, 150 μ M or more, or 200 μ M or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay.

[0032] Also provided herein is a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof that inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, with an IC₅₀ value of 50 nM or less, 40 nM or less, 30 nM or less, 20 nM or less, 10 nM or less, 1 nM or less, 0.1 nM or less, or 0.01 nM or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MM.1R with an IC₅₀ value of 1 nM or less, 0.1 nM or less, or 0.01 nM or less according to Proliferation Assay.

[0033] Also provided herein are methods of modulating a Ras superfamily protein,

comprising contacting the Ras superfamily protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0034] Also provided herein are methods of modulating a Ras superfamily protein, comprising contacting the Ras superfamily protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0035] Also provided herein are methods of modulating caspase activity, comprising contacting the caspase with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0036] Also provided herein are methods of modulating caspase activity, comprising contacting the caspase with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0037] Also provided herein are methods of modulating Erk1/2 activity, comprising contacting an Erk1/2 protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0038] Also provided herein are methods of modulating Erk1/2 activity, comprising contacting an Erk1/2 protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0039] Also provided herein are methods of modulating Akt activity, comprising contacting an Akt protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0040] Also provided herein are methods of modulating Akt activity, comprising contacting an AKT protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0041] Also provided herein are methods of modulating Smad2/3 activity, comprising contacting a Smad2/3 protein with an effective amount of a compound of Formula I, IA, IA(1),

IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0042] Also provided herein are methods of modulating Smad2/3 activity, comprising contacting a Smad2/3 protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0043] Also provided herein are methods of modulating JNK activity, comprising contacting a JNK protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0044] Also provided herein are methods of modulating JNK activity, comprising contacting a JNK protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0045] Also provided herein are methods of modulating MAPK p38 activity, comprising contacting a MAPK p38 protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0046] Also provided herein are methods of modulating MAPK p38 activity, comprising contacting a MAPK p38 protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0047] Also provided herein are methods of modulating IL-6 activity, comprising contacting a IL-6 protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0048] Also provided herein are methods of modulating IL-6 activity, comprising contacting a IL-6 protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0049] Also provided herein are methods of modulating TNF-alpha activity, comprising contacting a TNF-alpha protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form

thereof.

[0050] Also provided herein are methods of modulating TNF-alpha activity, comprising contacting a TNF-alpha protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof.

[0051] Also provided herein are methods of treating cancer in a subject, comprising administering a therapeutically effective amount of the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, to the subject having cancer. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[0052] Also provided herein are methods of treating cancer in a subject, comprising administering a therapeutically effective amount of a pharmaceutical comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, to the subject having cancer.

[0053] Also provided herein are methods of treating a fibrotic disease in a subject, comprising administering a therapeutically effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, to the subject.

[0054] Also provided herein are methods treating a fibrotic disease in a subject, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, to the subject.

[0055] Also provided herein are methods treating an inflammatory disease in a subject, comprising administering a therapeutically effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, to the subject.

[0056] Also provided herein are methods of treating an inflammatory disease in a subject,

comprising administering a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, to the subject.

[0057] Also provided herein are pharmaceutical compositions provided herein comprising therapeutically effective amounts of one or more of compounds provided herein (e.g. compounds of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2)) and a pharmaceutically acceptable carrier, diluent or excipient.

3. DETAILED DESCRIPTION

3.1. DEFINITIONS

[0058] To facilitate understanding of the disclosure set forth herein, a number of terms are defined below.

[0059] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of ordinary skill in the art. All patents, applications, published applications and other publications are incorporated by reference in their entirety. In the event that there is a plurality of definitions for a term herein, those in this section prevail unless stated otherwise.

[0060] The singular forms “a,” “an,” and “the” include plural references, unless the context clearly dictates otherwise.

[0061] As used herein “subject” is an animal, such as a mammal, including human, such as a patient.

[0062] As used herein, biological activity refers to the *in vivo* activities of a compound or physiological responses that result upon *in vivo* administration of a compound, composition or other mixture. Biological activity, thus, encompasses therapeutic effects and pharmacokinetic behavior of such compounds, compositions and mixtures. Biological activities can be observed in *in vitro* systems designed to test for such activities.

[0063] As used herein, pharmaceutically acceptable derivatives of a compound include, but are not limited to, salts, esters, enol ethers, enol esters, acetals, ketals, orthoesters, hemiacetals, hemiketals, acids, bases, clathrates, solvates or hydrates thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects

and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethylbenzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxymethyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and inorganic salts, such as but not limited to, sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates, mesylates, and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, aralkyl, and cycloalkyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula $C=C(OR)$ where R is alkyl, alkenyl, alkynyl, aryl, aralkyl and cycloalkyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula $C=C(OC(O)R)$ where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, aralkyl and cycloalkyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecules, or 1 to about 100, or 1 to about 10, or one to about 2, 3 or 4, solvent or water molecules.

[0064] As used herein, treatment means any manner in which one or more of the symptoms of a disease or disorder are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical use of the compositions herein, such as use for treating a fibrotic disease, for example DMD.

[0065] As used herein, amelioration of the symptoms of a particular disorder by administration of a particular compound or pharmaceutical composition refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the composition.

[0066] As used herein, and unless otherwise indicated, the terms “manage,” “managing” and

“management” encompass preventing the recurrence of the specified disease or disorder in a subject who has already suffered from the disease or disorder, and/or lengthening the time that a subject who has suffered from the disease or disorder remains in remission. The terms encompass modulating the threshold, development and/or duration of the disease or disorder, or changing the way that a subject responds to the disease or disorder.

[0067] As used herein, the terms “fibrosis” or “fibrotic disease” may be used interchangeably and refer to any pathological wound healing process in which connective tissue replaces normal parenchymal tissue, leading to considerable tissue re-modeling and the formation of permanent scar tissue. For example, in some embodiments, the fibrotic disease may be fibrosis of the kidney, such as progressive kidney disease. In some embodiments, the fibrotic disease may be fibrosis of the cardiovascular system, such as atherosclerosis or restenosis. In some embodiments, the fibrotic disease may be pulmonary fibrosis. In some embodiments, the fibrotic disease may be cystic fibrosis. In some embodiments, the fibrotic disease may be idiopathic fibrosis, such as idiopathic pulmonary fibrosis. In some embodiments, the fibrotic disease may be fibrosis of the lung, such as progressive massive fibrosis or radiation-induced lung injury. In some embodiments, the fibrotic disease may be bridging fibrosis. In some embodiments, the fibrotic disease may be fibrosis of the liver, such as cirrhosis. In some embodiments, the fibrotic disease may be fibrosis of the intestine, such as Crohn’s disease. In some embodiments, the fibrotic disease may be fibrosis of the muscular system, such as Duchenne muscular dystrophy (DMD). In some embodiments, the fibrotic disease may be fibrosis of the brain, such as glial scar. In some embodiments, the fibrotic disease may be fibrosis of the joints, such as arterial stiffness, fibrosis of the knee or fibrosis of the shoulder. In some embodiments, the fibrotic disease may be fibrosis of the skin, such as Keloid. In some embodiments, the fibrotic disease may be fibrosis of the bone marrow, such as myelofibrosis. In some embodiments, the fibrotic disease may be fibrosis of the heart, such as myocardial fibrosis. In some embodiments, the fibrotic disease may be fibrosis of the soft tissue. In some embodiments, the fibrotic disease may be fibrosis of the tendons. In some embodiments, the fibrotic disease may be fibrosis of the lymph nodes. In some embodiments, the fibrotic disease may be fibrosis of the eyes. In some embodiments, the fibrotic disease may be retroperitoneum. In some embodiments, the fibrotic disease may be scleroderma. In some embodiments, the fibrotic disease may be surgical scarring.

[0068] As used herein, “Duchenne muscular dystrophy” (“DMD”) refers to muscular

dystrophy and all forms of Duchenne muscular dystrophy (DMD). For example, in some embodiments, the DMD may be Becker Muscular Dystrophy (BMD), an intermediate clinical presentation between DMD and BMD, or DMD-associated dilated cardiomyopathy (heart-disease) with little or no clinical skeletal, or voluntary, muscle disease.

[0069] As used herein, the IC_{50} refers to an amount, concentration or dosage of a particular test compound that achieves a 50% inhibition of a maximal response in an assay that measures such response.

[0070] As used herein, the K_d refers to the measured equilibrium dissociation constant between a compound (or ligand) and a protein (or binding domain of a protein).

[0071] As used herein, “Smad 2/3” means the members of the receptor-regulated Smad (R-Smads) family of transcription factors, Smad2 and Smad3, collectively.

[0072] As used herein, “MAPK” means mitogen-activated protein kinase, which includes the stress-activated MAPK protein, MAPK p38, or simply p38.

[0073] As used herein, “JNK” means the stress-activated MAPK protein c-Jun NH_2 -terminal kinase.

[0074] As used herein, “Ras superfamily” means the protein superfamily of small guanosine triphosphatases (GTPases) which consists of the five main families Ras, Rho, Rab, Ran and Arf, or mutants thereof. Subfamilies of the five main families are also included, *e.g.*, the Rac subfamily of the Rho main family.

[0075] Without being bound by theory, the Ras superfamily of proteins are small GTPases with substantial amino acid sequence homology that act as signal transducers between cell surface receptors and several intracellular signaling cascades. These proteins are involved in the regulation of essential cellular functions such as cell survival, proliferation, motility and cytoskeletal organization (see Karnoub et al., *Nat. Rev. Mol. Cell Biol.*, 9: 517-531 (2008)). These proteins play essential roles in regulating many biological processes including, without limitation, cell growth, cell differentiation, cell migration, lipid vesicle trafficking, fibrosis, inflammation and apoptosis.

[0076] Research has defined a number of subfamilies of the Ras superfamily, based largely on amino acid sequence homologies. These subfamilies are often referred to in an abbreviated manner based on the most commonly studied member of the class.

[0077] The GTP binding domains of one subfamily of the Ras superfamily having substantial

sequence homology is commonly referred to as the Ras family or Ras.

[0078] There are four isoforms of Ras proteins, expressed from three different genes: H-Ras (Harvey sarcoma viral oncogene), N-Ras (neuroblastoma oncogene), and the splice variants K-Ras4A and K-Ras4B (Kirsten sarcoma viral oncogene) (see Karnoub et al., *supra*).

[0079] The GTP binding domains of another subfamily of the Ras superfamily having substantial sequence homology is commonly referred to as the Rho family and includes proteins and groups of proteins referred to as Rho, Rac and Cdc42.

[0080] Without being bound by theory, all Ras isoforms share sequence identity in all of the regions that are responsible for GDP/GTP binding, GTPase activity, and effector interactions, suggesting a functional redundancy. However, studies clearly demonstrate that each Ras isoform can function in a unique, different way from the other Ras proteins in normal physiological processes as well as in pathogenesis (Quinlan et al., *Future Oncol.*, 5: 105-116 (2009)).

[0081] Without being bound by theory, several cell surface receptors activate Ras, such as Receptor Tyrosine Kinases (RTKs), growth factor receptors, cytokine receptors and integrins.

[0082] Without being bound by theory, Ras proteins cycle between 'on' and 'off' conformations that are conferred by the binding of GTP and GDP, respectively. Under physiological conditions, the transition between these two states is regulated by guanine nucleotide exchange factors (GEFs), such as Son of sevenless (Sos) (Bar-Sagi D, *Trends Endocrin. Metab.* 5, 165-169 (1994)), which promote the activation of Ras proteins by stimulating the exchange of GDP for GTP exchange, and by GTPase-activating proteins (GAPs), which accelerate Ras-mediated GTP hydrolysis to GDP.

[0083] Without being bound by theory, the region of Sos functional for nucleotide exchange on Ras spans about 500 residues, and contains blocks of sequence that are conserved in Sos and other Ras-specific GEF's such as Cdc25, Sdc25 and Ras guanine-nucleotide-release factor (GRF) (Boguske et al, *Nature* 366, 643-654 (1993)).

[0084] Without being bound by theory, once activated, Ras initiates signaling of the "MAPK pathway" (also referred to as the Ras-RAF-MEK-MAPK/ERK1/2 pathway) that affects cell growth, differentiation, proliferation, apoptosis and migration. The MAPK pathway operates through a sequence of interactions among kinases. Activated by Ras in the "on", GTP bound, state, a MAPK kinase kinase (MAPK3), such as Raf, MLK, or TAK, phosphorylates and activates a MAPK kinase, such as MEK, which then phosphorylates and increases the activity of

one or more MAPKs, such as ERK1/2.

[0085] Without being bound by theory, Ras activation also initiates signaling of the “Akt pathway” that affects cellular survival, proliferation, migration, anti-apoptotic and cell cycle regulation. Ras in the “on”, GTP bound, state, activates phosphoinositide 3-kinase (PI3K) which, in turn, induces the production of phosphatidylinositol (3,4,5) trisphosphates (PIP3). These lipids serve as plasma membrane docking sites for proteins that harbor pleckstrin-homology (PH) domains, including Akt (also known as protein kinase B or PKB) and its upstream activator PDK1. There are three highly related isoforms of Akt (Akt1, Akt2 and Akt3) that phosphorylate shared substrates, but isoform-specific Akt substrates have also been identified. At the membrane, Akt is phosphorylated and activated by PDK1, PDK2 and mTORC2. The Akt pathway can also be activated by receptor tyrosine kinases, integrins, B and T cell receptors, cytokine receptors and G-protein-coupled receptors that directly interact and activate PI3K.

[0086] Without being bound by theory, Ras activation is also associated with signaling through other molecular pathways other than phosphoinositide 3-kinases (PI3Ks), such as Rac1 GEF and the Ral-guanine nucleotide dissociation stimulator (GDS). Regarding PI3K, that is part of the PI3K/AKT/mTOR pathway regulating intracellular signaling important for several cellular functions such as survival, anti-apoptotic and cell cycle regulation.

[0087] Without being bound by theory, Ras and its downstream pathways, including ERK1/2 and Akt, have been studied extensively. They are causally associated with a range of diseases, including certain cancers, inflammatory disorders, Ras-associated autoimmune leukoproliferative disorder, type II diabetes, and certain Rasopathies.

[0088] Without being bound by theory, activation of MAPKs, in particular ERK1/2, is a component of the inflammatory response. Thus, the compounds provided herein, which are ERK1/2 inhibitors via inhibition of Ras and/or a Ras superfamily member, are useful in the treatment of inflammatory diseases.

[0089] Without being bound by theory, activation of Akt is a component of the inflammatory response. Thus, the compounds provided herein, which are Akt inhibitors via inhibition of Ras and/or a Ras superfamily member, are useful in the treatment of inflammatory diseases.

[0090] Without being bound by theory, there is more than one distinct route to aberrant Ras activation including mutational activation of Ras itself, excessive activation of the wild-type protein through upstream signaling, and loss of a GAP function that is required to terminate

activity of the protein.

[0091] One million deaths per year are attributed in the literature to mutations in K-Ras alone. (Frank McCormick. “K-Ras protein as a drug target.” *Journal of Molecular Medicine* (Berlin) 2016: 94: 253-258)

[0092] Without being bound by theory, Ras is causally associated with inflammatory diseases including the following: rheumatoid arthritis (Abreu JR, de Launay D, Sanders ME, Grabiec AM, Sande van de MG, Tak PP, Reedquist KA: The Ras guanine nucleotide exchange factor RasGRF1 promotes matrix metalloproteinase-3 production in rheumatoid arthritis synovial tissue (*Arthritis Res Ther.* 2009, 11: R121-10.1186/ar2785), which is the most common cause of disability (Hootman JM, Brault MW, Helmick CG, Theis KA, Armour BS. Prevalence and most common causes of disability among adults—United States 2005, *MMWR*, 2009, 58(16):421-6); atherosclerosis (Fonarow G (2003), *Cleve. Clin. J. Med.* 70: 431–434); inflammatory bowel disease (IBD), such as Crohn’s disease (Ignacio CS, Sandvik AK, Bruland T, Andreu-Ballester JC, *J. Crohns Colitis*, 2017 Mar 16. doi: 10); ulcerative colitis; spondyloarthropathies; idiopathic pulmonary fibrosis; juvenile arthritis; psoriasis; psoriatic arthritis; and others.

[0093] Without being bound by theory, Ras has been causally associated with Ras-associated autoimmune leukoproliferative disorder, a nonmalignant clinical syndrome initially identified in a subset of putative autoimmune lymphoproliferative syndrome (ALPS) patients. (Katherin Calvo, et al. “JMML and RALD (Ras-associated autoimmune leukoproliferative disorder): common genetic etiology yet clinically distinct entities” *Blood*, 2015 Apr 30; 125(18): 2753–2758)

[0094] Without being bound by theory, Ras signaling is causally implicated in rasopathies. Thus, the compounds provided herein, which inhibit the function of one or more members of the Ras superfamily, are useful in the treatment of rasopathies including neurofibromatosis type 1, Noonan’s syndrome, and Costello syndrome.

[0095] As used herein, “Ras” or “Ras family” or “Ras subfamily” or “Ras group” means DIRAS1; DIRAS2; DIRAS3; ERAS; GEM; HRAS; KRAS; MRAS; NKIRAS1; NKIRAS2; NRAS; RALA; RALB; RAP1A; RAP1B; RAP2A; RAP2B; RAP2C; RASD1; RASD2; RASL10A; RASL10B; RASL11A; RASL11B; RASL12; REM1; REM2; RERG; RERGL; RRAD; RRAS; RRAS2, or mutants thereof.

[0096] As used herein, “Rho” or “Rho family” or “Rho subfamily” or “Rho group” means

RHOA; RHOB; RHOBTB1; RHOBTB2; RHOBTB3; RHOC; RHOD; RHOF; RHOG; RHOH; RHOJ; RHOQ; RHOU; RHOV; RND1; RND2; RND3; RAC1; RAC2; RAC3; CDC42, or mutants thereof.

[0097] As used herein, “Rac” or “Rac family” or “Rac subfamily” or “Rac group” means RAC1; RAC2; RAC3; RHOG, or mutants thereof.

[0098] Without being bound by theory, the Rho subfamily of the Ras superfamily currently includes approximately 22 proteins most of which scientists commonly divide into subgroups including those referred to as Cdc42, Rac, and Rho. (Boureux A, Vignal E, Faure S, Fort P (2007). "Evolution of the Rho family of ras-like GTPases in eukaryotes". *Mol Biol Evol* 24 (1): 203–16).

[0099] Without being bound by theory, the three most commonly studied members of the Rho subfamily have been Cdc42, Rac1, and RhoA.

[00100] Without being bound by theory, the Cdc42 group includes Cdc42, TC10, TCL, Chip, and Wrch-1.

[00101] Without being bound by theory, the Rac group includes Rac1, Rac2, Rac3, and RhoG.

[00102] Without being bound by theory, the RhoA group includes RhoA, RhoB, and RhoC.

[00103] Without being bound by theory, other Rho subfamily GTPases not included in the Cdc42, Rac, or Rho groups include RhoE/Rnd3, RhoH/TTF, Rif, RhoBTB1, RhoBTB2, Miro-1, Miro-2, RhoD, Rnd1, and Rnd2.

[00104] Without being bound by theory, like other Ras superfamily proteins, the Rho subfamily GTPases cycle between 'on' and 'off' conformations that are conferred by the binding of GTP and GDP, respectively. Under physiological conditions, the transition between these two states is regulated by guanine nucleotide exchange factors (GEFs), which promote the activation of Rho subfamily proteins by stimulating the release of GDP and the binding of GTP, and by GTPase-activating proteins (GAPs), which accelerate Rho subfamily member-mediated GTP hydrolysis to GDP. Guanine nucleotide dissociation inhibitors (GDIs) proteins form a large complex with the Rho protein, helping to prevent diffusion within the membrane and into the cytosol and thus acting as an anchor and allowing tight spatial control of Rho activation.

[00105] Without being bound by theory, the Rho subfamily members are intracellular proteins that affect a large number of downstream pathways broadly involving cytoskeleton organization, cell polarity, migration, transcription and proliferation, and, more particularly, membrane and

vesicular trafficking, cell cycling, microtubule stability, actin membrane linkages, actin polymerization, myosin phosphorylation, API dependent gene expression, cell adhesion, cell contractility, cell adhesion, and MTOC orientation. (Martin Schwartz. "Rho Signalling at a Glance." *Journal of Cell Science*. 2004: (117:pp. 5457-5458).and (Bustelo XR, Sauzeau V, Berenjeno IM (2007). "GTP-binding proteins of the Rho/Rac family: regulation, effectors and functions in vivo" *BioEssays*. 29 (4): 356–370).

[00106] Without being bound by theory, Rho subfamily associated kinases (ROCK1 and ROCK2) are implicated as mediators of multiple profibrotic processes including those associated with idiopathic pulmonary fibrosis. (Knipe RS, Tager EM, and Liao JK. "The Rho kinases: critical mediators of multiple profibrotic processes and rational targets for new therapies for pulmonary fibrosis." *Pharmacol Rev*. 2015 67(1):103-17.)

[00107] Without being bound by theory, given their roles in disease processes, Rho subfamily members have been identified as potential Therapeutic Molecular Targets.

[00108] Without being bound by theory, Rho subfamily members have been identified as potential Therapeutic Molecular Targets in cancer.

[00109] Without being bound by theory, Rho subfamily members have been identified as potential Therapeutic Molecular Targets in fibrotic disease.

[00110] As used herein, "GTP binding site" or "GTP binding domain" both mean the region of a protein which binds GTP, and the surrounding region of said protein in which another compound may bind, wherein such binding blocks the ability of GTP to bind to said protein.

[00111] As used herein, "GDP binding site" or "GDP binding domain" both mean the region of a protein which binds GDP, and the surrounding region of said protein in which another compound may bind, wherein such binding blocks the ability of GDP to bind to said protein.

[00112] As used herein, "guanosine binding region" means a region of a protein which is part of the GDP binding domain or GTP binding domain, that mediates interaction with the guanosine portion of GDP or GTP.

[00113] As used herein, "metal region" means a region of a protein which is part of the GDP binding domain or GTP binding domain, that is proximal to a magnesium (Mg²⁺) binding site.

[00114] As used herein, "alternative Tyr32 conformation" means the conformation of the GTP or GDP binding domain in the region of Tyr 32 in KRas crystal structure PDB code:3gft in comparsion to the KRas crystal structure PDB code:4epr.

[00115] Without being bound by theory, as used herein “apoptosis” refers to a process of programmed cell death which plays important roles in physiology and pathology. It is activated during embryonic development and beyond to eliminate unwanted or damaged cells. Apoptosis also plays important roles in preventing cancer. Loss of apoptotic control allows tumor cells to survive longer and provides them time to accumulate mutations which can increase invasiveness during cancer progression, stimulate angiogenesis, deregulate cell proliferation, and interfere with differentiation.

[00116] Without being bound by theory, in regard to apoptosis, it has been demonstrated that several members of the Ras superfamily of small GTPases have pro- and anti-apoptosis functions. Members of the Rho family of GTPases such as Rho, Rac and cdc42 can activate apoptosis via the JNK or p38 pathways. On the other hand, members of the Ras and Rab families of GTPases have anti-apoptotic activity mediated by activating the PI3K/Akt/mTOR survival pathway which prevent apoptosis and leads to increased cellular proliferation. In addition, it has been demonstrated that GTPase Activating Proteins (GAPs) can promote apoptosis in tumor cells by regulating apoptosis-related proteins and pathways. It should be noted that some GAPs also exert apoptosis-inhibiting effects and thus promote tumor progression

[00117] Without being bound by theory, the c-Jun N-terminal kinase (JNK) pathway is one of the major signaling cascades of the mitogen-activated protein kinase (MAPK) signaling pathway. It functions in the control of a number of cellular processes, including proliferation, embryonic development and apoptosis. The JNK pathway is activated by environmental stresses (ionizing radiation, heat, oxidative stress such as reactive oxygen species (ROS) and DNA damage), inflammatory cytokines, as well as growth factors. JNK activation often involves the Rho family of GTPases such as Rho, Cdc42 and Rac.

[00118] Without being bound by theory, JNK activates apoptotic signaling by the upregulation of pro-apoptotic genes through transactivation of c-Jun/AP1-dependent or p53/73 protein-dependent mechanisms. In these pathways directed at mitochondrial apoptotic proteins, activated JNK directly modulates the activities of mitochondrial pro-apoptotic proteins through distinct phosphorylation events.

[00119] Without being bound by theory, another member of the MAPK signaling pathway is p38 MAPK (also referred to herein as MAPK p38) which allows cells to interpret a wide range of external signals and respond by activating downstream pathways mediating several biological

effects. This pathway also functions in the control of apoptosis and the release of cytokines by macrophages and neutrophils.

[00120] Without being bound by theory, apoptosis can be activated by both extrinsic (death ligand) and intrinsic (mitochondrial) pathways. Members of the Bcl-2 family of proteins, like Bax and Bak, regulate and mediate the intrinsic apoptosis process by which mitochondria contributes to cell death. Upon apoptotic stimuli, these proteins are activated and oligomerize at the mitochondrial outer membrane to mediate its permeabilization. Permeabilization enables the release of cytochrome c from mitochondria which, in turn, induces a series of biochemical reactions resulting in caspase activation and subsequent cell death.

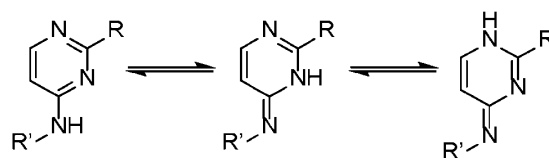
[00121] Without being bound by theory, induction of apoptosis, such as in mammalian cells, can be mediated by several mechanisms, including inhibition of the ubiquitin proteasome system (UPS). The UPS system is a major proteolytic pathway for the removal of cytosolic, nuclear, and membrane associated proteins and has essential functions in homeostasis, which include preventing the accumulation of misfolded or deleterious proteins. The proteins targeted for degradation are selected by tagging them covalently with ubiquitin, typically with lysine48-linked tetraubiquitin chains, followed by proteolysis within the 26S proteasome. The 26S proteasome holoenzyme consists of a 19S regulatory particle (RP) which is responsible for recognizing the ubiquitin signal and unfolding the target protein, and a 20S core particle (CP), which hydrolyzes the unfolded polypeptide into short peptides of varying lengths. Accordingly, impairment of the UPS has been associated with several pathological conditions including cancers. Tumor cells can be characterized by the loss of cell cycle checkpoint control and can often be subjected to elevated levels of stress because of hyperactivation of oncogenic signaling and/or adverse microenvironmental conditions. Therefore, transformed cells can rely to a great extent on the correct function of UPS for survival and proliferation. Inhibition of the UPS, such as with proteasome inhibitors, can induce cell death and apoptosis. To date, three proteasome inhibitors have gained FDA approval to treat multiple myeloma cancer patients. The three proteasome inhibitors, Velcade (bortezomib), Kyprolis (carfilzomib), and Ninlaro (ixazomib), are reported as targeting the proteolytic sites within the 20S CP.

[00122] Without being bound by theory, as used herein “caspase(s)” refers to one or more of a family of cysteine proteases that cleave proteins following aspartic acid residues. All caspases are synthesized in cells as catalytically inactive zymogens and must undergo a cleavage

activation process to yield large and small subunits which dimerize to create active enzymes. Caspases exist in a hierarchy including so-called upstream caspases 2, 8, 9, and 10 and downstream caspases 3, 6, and 7. Active caspase-9 initiates caspase cleavage which activate downstream executioner caspases 3, 6 and 7 which cleave other cellular targets and initiate apoptosis. In some embodiments, the anti-proliferative inhibitory activity of the compounds disclosed herein is mediated by the induction of apoptosis, as determined by an Annexin V apoptosis assay kit.

[00123] It is to be understood that the compounds provided herein may contain chiral centers. Such chiral centers may be of either the (R) or (S) configuration, or may be a mixture thereof. Thus, the compounds provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. As such, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization *in vivo*, to administration of the compound in its (S) form.

[00124] As used herein, substantially pure means sufficiently homogeneous to appear free of readily detectable impurities as determined by standard methods of analysis, such as thin layer chromatography (TLC), gel electrophoresis, high performance liquid chromatography (HPLC) and mass spectrometry (MS), used by those of skill in the art to assess such purity, or sufficiently pure such that further purification would not detectably alter enzymatic and biological activities of the substance. Methods for purification of the compounds to produce substantially chemically pure compounds are known to those of skill in the art. A substantially chemically pure compound may, however, be a mixture of stereoisomers. In such instances, further purification might increase the specific activity of the compound. The instant disclosure is meant to include all such possible isomers, as well as, their racemic and optically pure forms. Optically active (+) and (-), (R)- and (S)-, or (D)- and (L)-isomers may be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques, such as chiral reverse phase HPLC. When the compounds described herein contain olefinic double bonds or other centers of geometric asymmetry, and unless specified otherwise, it is intended that the compounds include both E and Z geometric isomers. Likewise, all tautomeric forms are also intended to be included. For example, Formula A includes, but is not limited to, the three tautomeric structures below.



Formula A

[00125] As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) Biochem. 11:942-944), or the IUPAC Nomenclature of Organic Chemistry (see, Favre HA and Powell WH, Nomenclature of Organic Chemistry: IUPAC Recommendations and Preferred Names 2013, Cambridge, UK: The Royal Society of Chemistry, 2013: Print ISBN 978-0-85404-182-4, PDF eISBN 978-1-84973-306-9, DOI 10.1039/9781849733069; Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H, Pergamon Press, Oxford, 1979. Copyright 1979 IUPAC; and A Guide to IUPAC Nomenclature of Organic Compounds (Recommendations 1993), 1993, Blackwell Scientific publications, Copyright 1993 IUPAC).

[00126] As used herein, alkyl, alkenyl and alkynyl carbon chains, if not specified, contain from 1 to 20 carbons, or 1 to 16 carbons, and are straight or branched. Alkenyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 double bonds, and the alkenyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 double bonds. Alkynyl carbon chains of from 2 to 20 carbons, in certain embodiments, contain 1 to 8 triple bonds, and the alkynyl carbon chains of 2 to 16 carbons, in certain embodiments, contain 1 to 5 triple bonds. Exemplary alkyl, alkenyl and alkynyl groups herein include, but are not limited to, methyl, ethyl, propyl, isopropyl, isobutyl, n-butyl, sec-butyl, tert-butyl, isopentyl, neopentyl, tert-pentyl, isohexyl, ethenyl, propenyl, butenyl, pentenyl, acetylenyl and hexynyl. As used herein, lower alkyl, lower alkenyl, and lower alkynyl refer to carbon chains having from about 1 or about 2 carbons up to about 6 carbons. As used herein, "alk(en)(yn)yl" refers to an alkyl group containing at least one double bond and at least one triple bond.

[00127] As used herein, "heteroalkyl" refers to a straight or branched aliphatic hydrocarbon group having, inserted in the hydrocarbon chain one or more oxygen, sulfur, including S(=O) and S(=O)₂ groups, or substituted or unsubstituted nitrogen atoms, including -NR- and -N⁺RR- groups, where the nitrogen substituent(s) is(are) alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, S(=O)₂R' or COR', where R' is alkyl, aryl, aralkyl, heteroaryl, heteroaralkyl, -OY or -NYY',

where Y and Y' are each independently hydrogen, alkyl, aryl, heteroaryl, cycloalkyl or heterocyclyl, in some embodiments having from 1 to about 20 atoms, in another embodiment having from 1 to 12 atoms in the chain.

[00128] As used herein, "cycloalkyl" refers to a saturated mono- or multicyclic ring system, in certain embodiments of 3 to 10 carbon atoms, in other embodiments of 3 to 6 carbon atoms; cycloalkenyl and cycloalkynyl refer to mono- or multicyclic ring systems that respectively include at least one double bond and at least one triple bond. Cycloalkenyl and cycloalkynyl groups may, in certain embodiments, contain 3 to 10 carbon atoms, with cycloalkenyl groups, in further embodiments, containing 4 to 7 carbon atoms and cycloalkynyl groups, in further embodiments, containing 8 to 10 carbon atoms. The ring systems of the cycloalkyl, cycloalkenyl and cycloalkynyl groups may be composed of one ring or two or more rings which may be joined together in a fused, bridged or spiro-connected fashion. "Cycloalk(en)(yn)yl" refers to a cycloalkyl group containing at least one double bond and at least one triple bond. In some embodiments, the cycloalkyl ring is unsaturated or partially saturated.

[00129] As used herein, "carbocyclic" refers to a mono- or multicyclic ring system, in which all of the atoms composing the ring are carbon atoms, such as benzene or cyclopropane. In some embodiments, the carbocyclic ring is unsaturated or partially saturated.

[00130] As used herein, "substituted alkyl," "substituted alkenyl," "substituted alkynyl," "substituted cycloalkyl," "substituted cycloalkenyl," and "substituted cycloalkynyl" refer to alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl and cycloalkynyl groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three or four substituents, where the substituents are as defined herein.

[00131] As used herein, "aryl" refers to aromatic monocyclic or multicyclic groups containing from 6 to 19 carbon atoms. Aryl groups include, but are not limited to groups such as fluorenyl, substituted fluorenyl, phenyl, substituted phenyl, naphthyl and substituted naphthyl.

[00132] As used herein, "heteroaryl" refers to a monocyclic or multicyclic aromatic ring system, in certain embodiments, of about 5 to about 15 members where one or more, in some embodiments 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. The heteroaryl group may be optionally fused to a benzene ring. Heteroaryl groups include, but are not limited to, furyl, imidazolyl, pyrimidinyl, tetrazolyl, thienyl, pyridyl, pyrrolyl, N-methylpyrrolyl, quinoliny and

isoquinolinyl. In certain embodiments, the heteroaryl may be optionally fused to a heterocycloalkyl ring. In certain embodiments, the heteroaryl may be a partially saturated heteroaryl, such as a phenyl ring fused to a heterocycloalkyl ring, for example a phenyl ring fused to a tetrahydrofuryl ring.

[00133] As used herein, “heterocycloalkyl,” “heterocyclyl” or “heterocyclic” refers to a monocyclic or polycyclic non-aromatic ring system, in some embodiments of 3 to 10 members, in another embodiment of 4 to 7 members, in a further embodiment of 5 to 6 members, where one or more, in certain embodiments, 1 to 3, of the atoms in the ring system is a heteroatom, that is, an element other than carbon, including but not limited to, nitrogen, oxygen or sulfur. In embodiments where the heteroatom(s) is(are) nitrogen, the nitrogen is optionally substituted with hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl, heterocyclyl, cycloalkylalkyl, heterocyclalkyl, acyl, guanidino, amidino, sulfonyl or the nitrogen may be quaternized to form an ammonium group where the substituents are selected as above. In some embodiments, the heterocyclalkyl ring is saturated. In some embodiments, the heterocyclalkyl ring is unsaturated or partially saturated.

[00134] As used herein, “substituted aryl,” “substituted heteroaryl” and “substituted heterocyclalkyl” refer to aryl, heteroaryl and heterocyclalkyl groups, respectively, that are substituted with one or more substituents, in certain embodiments one to three or four substituents, where the substituents are as defined herein.

[00135] As used herein, “aralkyl” or “arylalkyl” refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by an aryl group.

[00136] As used herein, “heteroaralkyl” refers to an alkyl group in which one of the hydrogen atoms of the alkyl is replaced by a heteroaryl group.

[00137] As used herein, “halo”, “halogen” or “halide” refers to F, Cl, Br or I.

[00138] As used herein, “haloalkyl” refers to an alkyl group in which one or more of the hydrogen atoms are replaced by halogen. Such groups include, but are not limited to, chloromethyl, trifluoromethyl and 1-chloro-2-fluoroethyl.

[00139] As used herein, “haloalkoxy” refers to RO in which R is a haloalkyl group.

[00140] As used herein, “hydroxalkyl” refers to an alkyl group in which one or more of the hydrogen atoms are replaced by a hydroxyl group (-OH).

[00141] As used herein, “cycloalkoxy” refers to an -OR group, in which R is a cycloalkyl

group.

[00142] As used herein, "carboxy" refers to a divalent radical, $-\text{C}(\text{O})\text{O}-$.

[00143] As used herein, "aminocarbonyl" refers to $-\text{C}(\text{O})\text{NH}_2$.

[00144] As used herein, "alkylaminocarbonyl" refers to $-\text{C}(\text{O})\text{NHR}$ in which R is alkyl, including lower alkyl. As used herein, "dialkylaminocarbonyl" refers to $-\text{C}(\text{O})\text{NR}'\text{R}$ in which R' and R are independently alkyl, including lower alkyl; "carboxamide" refers to groups of formula $-\text{NR}'\text{COR}$ in which R' and R are independently alkyl, including lower alkyl.

[00145] As used herein, "arylalkylaminocarbonyl" refers to $-\text{C}(\text{O})\text{NRR}'$ in which one of R and R' is aryl, including lower aryl, such as phenyl, and the other of R and R' is alkyl, including lower alkyl.

[00146] As used herein, "arylamino carbonyl" refers to $-\text{C}(\text{O})\text{NHR}$ in which R is aryl, including lower aryl, such as phenyl.

[00147] As used herein, "hydroxycarbonyl" refers to $-\text{COOH}$.

[00148] As used herein, "alkoxycarbonyl" refers to $-\text{C}(\text{O})\text{OR}$ in which R is alkyl, including lower alkyl.

[00149] As used herein, "aryloxycarbonyl" refers to $-\text{C}(\text{O})\text{OR}$ in which R is aryl, including lower aryl, such as phenyl.

[00150] As used herein, "alkoxy" and "alkylthio" refer to $\text{RO}-$ and $\text{RS}-$, in which R is alkyl, including lower alkyl.

[00151] As used herein, "aryloxy" and "arylthio" refer to $\text{RO}-$ and $\text{RS}-$, in which R is aryl, including lower aryl, such as phenyl.

[00152] Where the number of any given substituent is not specified (e.g., "haloalkyl"), there may be one or more substituents present. For example, "haloalkyl" may include one or more of the same or different halogens.

[00153] As used herein, "cyclic structure" may be a cycloalkyl, carbocyclic, heterocyclic, aryl or heteroaryl group.

[00154] As used herein, the abbreviations for any protective groups, amino acids and other compounds, are, unless indicated otherwise, in accord with their common usage, recognized abbreviations, the IUPAC-IUB Commission on Biochemical Nomenclature (see, (1972) Biochem. 11:942-944), or the IUPAC Nomenclature of Organic Chemistry (see, Favre HA and Powell WH, Nomenclature of Organic Chemistry: IUPAC Recommendations and Preferred

Names 2013, Cambridge, UK: The Royal Society of Chemistry, 2013: Print ISBN 978-0-85404-182-4, PDF eISBN 978-1-84973-306-9, DOI 10.1039/9781849733069; Nomenclature of Organic Chemistry, Sections A, B, C, D, E, F, and H, Pergamon Press, Oxford, 1979. Copyright 1979 IUPAC; and A Guide to IUPAC Nomenclature of Organic Compounds (Recommendations 1993), 1993, Blackwell Scientific publications, Copyright 1993 IUPAC).

[00155] The term “subject” refers to an animal, including, but not limited to, a primate (*e.g.*, human), cow, pig, sheep, goat, horse, dog, cat, rabbit, rat, or mouse. The terms “subject” and “patient” are used interchangeably herein in reference, for example, to a mammalian subject, such as a human subject, in some embodiments, a human.

[00156] The terms “treat,” “treating,” and “treatment” are meant to include alleviating or abrogating a disorder, disease, or condition, or one or more of the symptoms associated with the disorder, disease, or condition; or alleviating or eradicating the cause(s) of the disorder, disease, or condition itself.

[00157] The terms “prevent,” “preventing,” and “prevention” are meant to include a method of delaying and/or precluding the onset of a disorder, disease, or condition, and/or its attendant symptoms; barring a subject from acquiring a disorder, disease, or condition; or reducing a subject’s risk of acquiring a disorder, disease, or condition.

[00158] The term “therapeutically effective amount” are meant to include the amount of a compound that, when administered, is sufficient to prevent development of, or alleviate to some extent, one or more of the symptoms of the disorder, disease, or condition being treated. The term “therapeutically effective amount” also refers to the amount of a compound that is sufficient to elicit the biological or medical response of a biological molecule (*e.g.*, a protein, enzyme, RNA, or DNA), cell, tissue, system, animal, or human, which is being sought by a researcher, veterinarian, medical doctor, or clinician. A therapeutically effective amount of a compound provided herein can be administered in one dose (*i.e.*, a single dose administration) or divided and administered over time (*i.e.*, continuous administration or multiple sub-dose administration). Single dose administration, continuous administration, or multiple sub-dose administration can be repeated, for example, to maintain the level of the compound in a biological molecule (*e.g.*, a protein, enzyme, RNA, or DNA), cell, tissue, system, animal, or human.

[00159] The term “pharmaceutically acceptable carrier,” “pharmaceutically acceptable excipient,” “physiologically acceptable carrier,” or “physiologically acceptable excipient” refers

to a pharmaceutically-acceptable material, composition, or vehicle, such as a liquid or solid filler, diluent, solvent, or encapsulating material. In some embodiments, each component is “pharmaceutically acceptable” in the sense of being compatible with the other ingredients of a pharmaceutical formulation, and suitable for use in contact with the tissue or organ of humans and animals without excessive toxicity, irritation, allergic response, immunogenicity, or other problems or complications, commensurate with a reasonable benefit/risk ratio. *See, Remington: The Science and Practice of Pharmacy*, 22nd ed.; Loyd *et al.*, Eds.; The Pharmaceutical Press, 2012; *Handbook of Pharmaceutical Excipients*, 7th ed.; Rowe *et al.*, Eds.; The Pharmaceutical Press, 2012; *Handbook of Pharmaceutical Additives*, 3rd ed.; Ash and Ash Eds.; Synapse Information Resources, Inc., 2007; *Pharmaceutical Preformulation and Formulation*, 2nd ed.; Gibson Ed.; CRC Press LLC, 2009.

[00160] As used herein, a “pharmaceutically acceptable form” of compounds disclosed herein includes, but is not limited to, a pharmaceutically acceptable salt, solvate, isomer, and isotopologue (i.e., isotopically labeled derivative) of compounds disclosed herein. In some embodiments, a “pharmaceutically acceptable form” includes, but is not limited to, a pharmaceutically acceptable salt, solvate, isomer, and isotopologue (i.e., isotopically labeled derivative) of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), as disclosed herein.

[00161] The term “about” or “approximately” means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term “about” or “approximately” means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term “about” or “approximately” means within 50%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range.

[00162] The term “percent by weight” or “% by weight” refers to the weight of a specified component (*e.g.*, an active compound or excipient) in a composition (*e.g.*, a pharmaceutical composition) as a percentage of the total weight of the composition. Thus, the sum of the weight percentages of all the components in a composition is 100%.

[00163] The terms “active ingredient” and “active substance” refer to a compound, which is administered, alone or in combination with one or more pharmaceutically acceptable excipients, to a subject for treating, preventing, or ameliorating one or more symptoms of a condition,

disorder, or disease. As used herein, “active ingredient” and “active substance” may be an optically active isomer or an isotopic variant of a compound described herein.

[00164] The terms “drug,” “therapeutic agent,” and “chemotherapeutic agent” refer to a compound, or a pharmaceutical composition thereof, which is administered to a subject for treating, preventing, or ameliorating one or more symptoms of a condition, disorder, or disease.

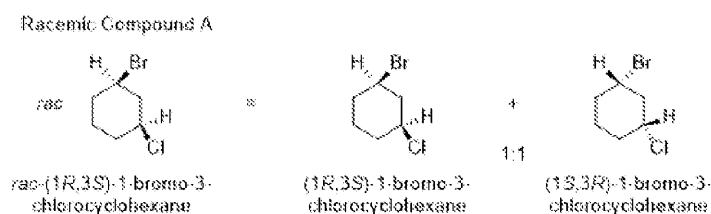
[00165] In certain embodiments, “optically active” and “enantiomerically active” and “diastereomerically active” refer to a collection of molecules which has an enantiomeric excess or a diastereomeric excess. For example, in some embodiments the collection of enantiomerically active molecules may have an enantiomeric excess of no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, no less than about 91%, no less than about 92%, no less than about 93%, no less than about 94%, no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%. In certain embodiments, the compound comprises about 95% or more of one enantiomer and about 5% or less of the other enantiomer based on the total weight of the racemate in question. For example, in some embodiments the collection of diastereomerically active molecules may have a diastereomeric excess of no less than about 50%, no less than about 70%, no less than about 80%, no less than about 90%, no less than about 91%, no less than about 92%, no less than about 93%, no less than about 94%, no less than about 95%, no less than about 96%, no less than about 97%, no less than about 98%, no less than about 99%, no less than about 99.5%, or no less than about 99.8%. In certain embodiments, the compound comprises about 95% or more of one diastereomer and about 5% or less of the other diastereomers based on the total weight of the diastereomeric mixture in question.

[00166] In describing an optically active compound, the prefixes *R* and *S* are used to denote the absolute configuration of the molecule about its chiral center(s). The (+) and (-) are used to denote the optical rotation of the compound, that is, the direction in which a plane of polarized light is rotated by the optically active compound. The (-) prefix indicates that the compound is levorotatory, that is, the compound rotates the plane of polarized light to the left or counterclockwise. The (+) prefix indicates that the compound is dextrorotatory, that is, the compound rotates the plane of polarized light to the right or clockwise. However, the sign of optical rotation, (+) and (-), is not related to the absolute configuration of the molecule, *R* and *S*.

[00167] The term “racemate” is understood to refer to an equimolar mixture of a pair of

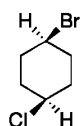
enantiomers. It does not exhibit *optical activity*. The chemical name or formula of a racemate is distinguished from those of the enantiomers by the prefix ($\pm$)-, or *rac*- (or *rac.* or *racem*-) or by the symbols *RS* and *SR*. See IUPAC Recommendations 1996, Basic Terminology of Stereochemistry, *Pure & Appl. Chem.*, Vol. 68, No. 12, pp. 2193-2222, 1996.

[00168] Racemic compounds disclosed herein that contain two asymmetric centers with known relative configuration are named using the configurational descriptors *R,S* or *R,R*, preceded by the prefix *rac*-. For example, Racemic Compound A below is named *rac*-(1*R*,3*S*)-1-bromo-3-chlorocyclohexane and is a 1:1 mixture of enantiomers (1*R*,3*S*)-1-bromo-3-chlorocyclohexane and (1*S*,3*R*)-1-bromo-3-chlorocyclohexane.



[00169] Lower case *r/s* stereo descriptors are used to describe pseudo-asymmetric centers, according to Cahn-Ingold-Prelog Rules (see R.S. Cahn, C.K. Ingold and V. Prelog, *Angew. Chem. Internat. Ed. Eng.* 5, 385-415, 511 (1966); and V. Prelog and G. Helmchen, *Angew. Chem. Internat. Ed. Eng.* 21, 567-583 (1982)). For example, Compound B below is named (1*s*,4*s*)-1-bromo-4-chlorocyclohexane.

Compound B



(1*s*,4*s*)-1-bromo-4-chlorocyclohexane

[00170] Compound names included herein were generated from the corresponding chemical structures using ChemDraw® version 22.2.0.3348. If there is a discrepancy between the chemical structure and the name disclosed herein, the structure shall control.

[00171] The term “isotopic variant” refers to a compound that contains an unnatural proportion of an isotope at one or more of the atoms that constitute such compounds. In certain embodiments, an “isotopic variant” of a compound contains unnatural proportions of one or more isotopes, including, but not limited to, hydrogen (^1H), deuterium (^2H), tritium (^3H), carbon-

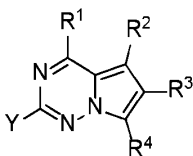
11 (^{11}C), carbon-12 (^{12}C), carbon-13 (^{13}C), carbon-14 (^{14}C), nitrogen-13 (^{13}N), nitrogen-14 (^{14}N), nitrogen-15 (^{15}N), oxygen-14 (^{14}O), oxygen-15 (^{15}O), oxygen-16 (^{16}O), oxygen-17 (^{17}O), oxygen-18 (^{18}O), fluorine-17 (^{17}F), fluorine-18 (^{18}F), sulfur-32 (^{32}S), sulfur-33 (^{33}S), sulfur-34 (^{34}S), sulfur-35 (^{35}S), sulfur-36 (^{36}S), chlorine-35 (^{35}Cl), chlorine-36 (^{36}Cl), and chlorine-37 (^{37}Cl). In certain embodiments, an “isotopic variant” of a compound is in a stable form, that is, non-radioactive. It will be understood that, in a compound as provided herein, any hydrogen can be ^2H , for example, or any carbon can be ^{13}C , as example, or any nitrogen can be ^{15}N , as example, and any oxygen can be ^{18}O , where feasible according to the judgment of one of skill. In certain embodiments, an “isotopic variant” of a compound contains unnatural proportions of deuterium. In some embodiments, a pharmaceutically acceptable derivative of a compound is an isotopic variant.

[00172] The term “solvate” refers to a complex or aggregate formed by one or more molecules of a solute, *e.g.*, a compound provided herein, and one or more molecules of a solvent, which present in stoichiometric or non-stoichiometric amount. Suitable solvents include, but are not limited to, water, methanol, ethanol, *n*-propanol, isopropanol, and acetic acid. In certain embodiments, the solvent is pharmaceutically acceptable. In some embodiments, the complex or aggregate is in a crystalline form. In another embodiment, the complex or aggregate is in a noncrystalline form. Where the solvent is water, the solvate is a hydrate. Examples of hydrates include, but are not limited to, a hemihydrate, monohydrate, dihydrate, trihydrate, tetrahydrate, and pentahydrate.

[00173] The phrase “an isotopic variant thereof; or a pharmaceutically acceptable salt thereof; or a pharmaceutically acceptable solvate thereof” has the same meaning as the phrase “an isotopic variant of the compound referenced therein; or a pharmaceutically acceptable salt of the compound referenced therein; or a pharmaceutically acceptable salt of an isotopic variant of the compound referenced therein; or a pharmaceutically acceptable solvate of the compound referenced therein; or a pharmaceutically acceptable solvate of an isotopic variant of the compound referenced therein; or a pharmaceutically acceptable solvate of a pharmaceutically acceptable salt of the compound referenced therein; or a pharmaceutically acceptable solvate of a pharmaceutically acceptable salt of an isotopic variant of the compound referenced therein or its variant or its variant.”

3.2. COMPOUNDS

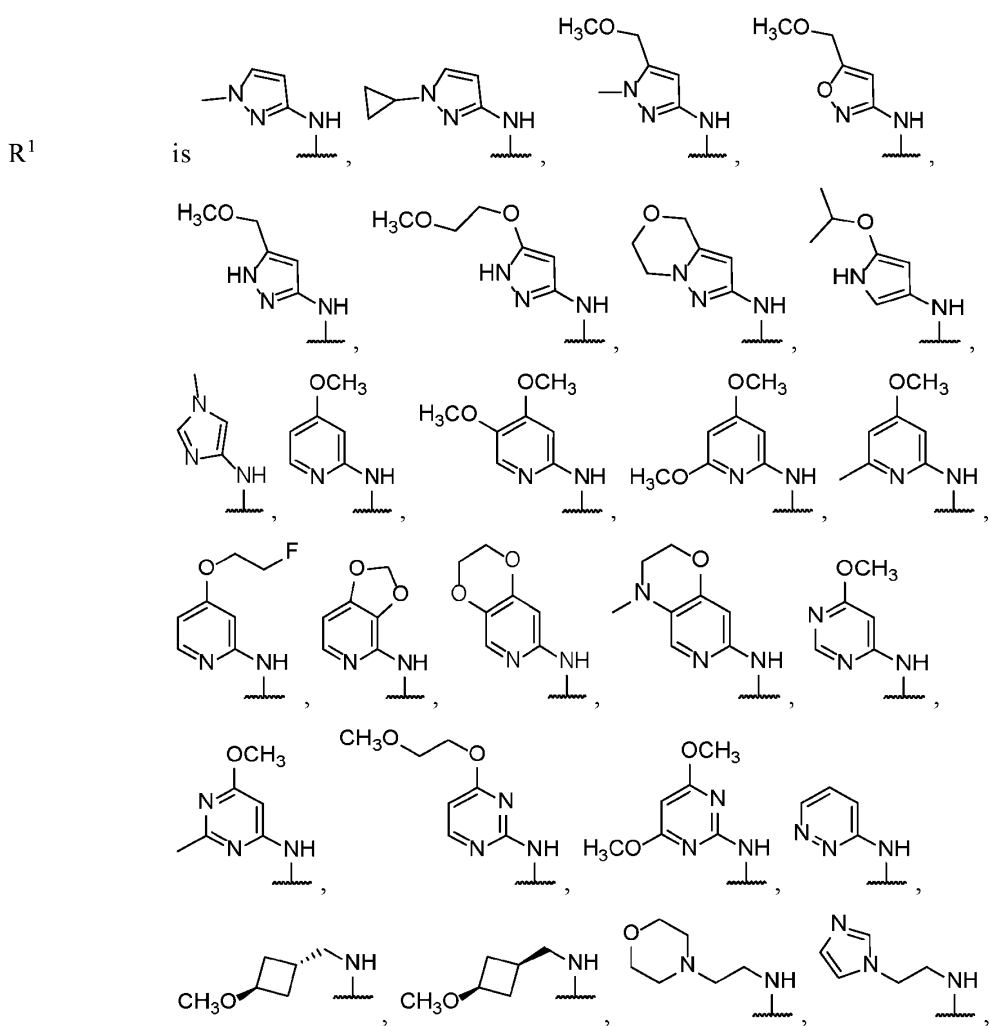
[00174] Provided herein is a compound of Formula I:

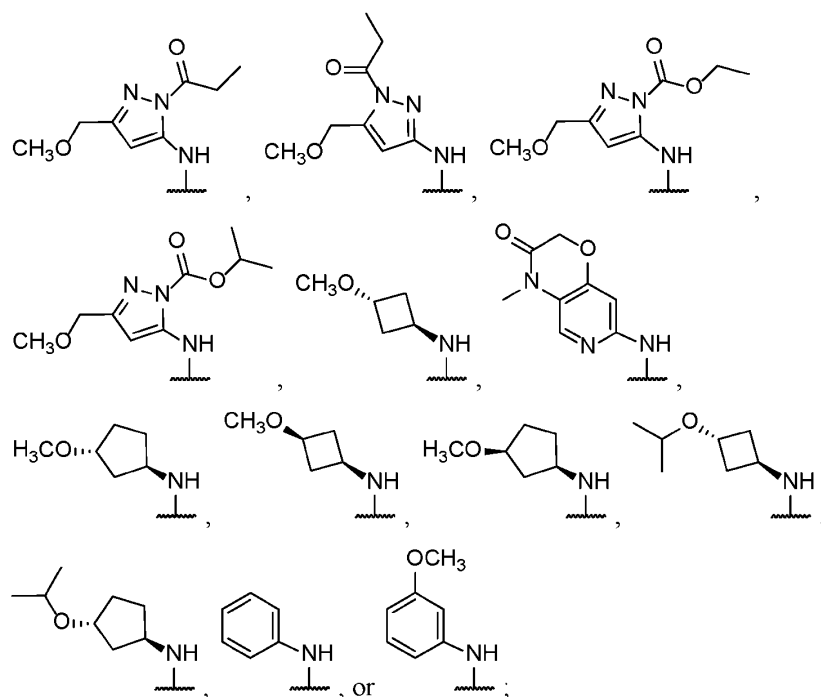


Formula I

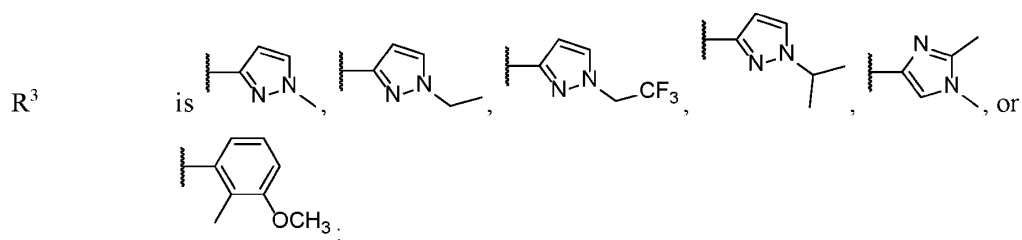
or a pharmaceutically acceptable form thereof, wherein:

Y is an imidazolyl; wherein the imidazolyl is optionally substituted with 1 R⁵ substituent and optionally substituted with 1-2 R⁶ substituents;





R² is C₁₋₂ alkyl or C₁₋₂ haloalkyl;



R⁴ is hydrogen or C₁₋₆ alkyl;

R⁵ and R⁶ are each independently C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, aryl, C₅₋₁₀ heteroaryl, C₃₋₇ heterocycloalkyl, C₁₋₆ heteroalkyl, halo, -NR⁹R¹⁰, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -C(O)NR⁹R¹⁰, -(CO)R⁸, -(CO)OH, -(CO)OR⁸, or CN, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, aryl, C₅₋₁₀ heteroaryl, C₃₋₇ heterocycloalkyl, and C₁₋₆ heteroalkyl are each independently optionally substituted with 1-3 R⁷ substituents;

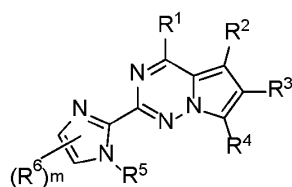
R⁷ is independently selected from the group consisting of halo, CN, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, 3-6 membered heterocycloalkyl, -NR⁹R¹⁰, -(CO)R⁸, -(CO)OH, -(CO)OR⁸,

–C(O)NR⁹R¹⁰, oxo, –OH, C₁₋₆ alkoxy, C₃₋₆ cycloalkoxy, C₁₋₆ haloalkoxy, or 5-6 membered heteroaryl;

R⁸ is C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or C₁₋₆ heteroalkyl, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₁₋₆ heteroalkyl, are each independently optionally substituted with 1-3 R⁷ substituents; and

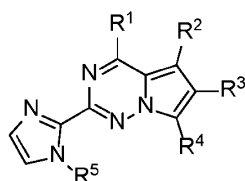
R⁹ and R¹⁰ are each independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, –OH, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ heterocycloalkyl, aryl, or 5-10 membered heteroaryl, wherein the C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ heterocycloalkyl, aryl, and 5-10 membered heteroaryl are optionally substituted with 1-3 R⁷ substituents, or R⁹ and R¹⁰ are combined to form a 3-7 membered heterocycloalkyl including the nitrogen atom to which they are both attached.

[00175] In some embodiments, the compound of Formula I is such that Y is an imidazolyl optionally substituted with 1 R⁵ substituent and optionally substituted with 1-2 R⁶ substituents. In some embodiments, the compound of Formula I is such that Y is a C-linked imidazolyl that is substituted with 1 R⁵ substituent at a nitrogen of the imidazolyl ring and optionally substituted with 1-2 R⁶ substituents at carbons of the imidazolyl ring. In some embodiments, the compound of Formula I is a compound of Formula IA:



Formula IA

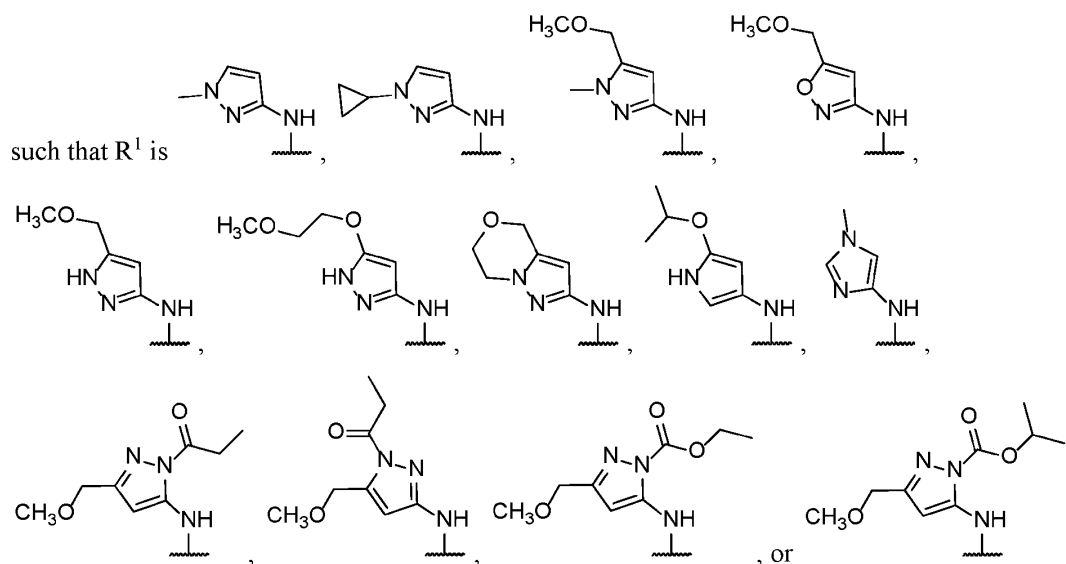
or a pharmaceutically acceptable form thereof; wherein m is 0, 1 or 2. In some embodiments, the compound is a compound of Formula I, wherein m is 0, and the compound is a compound of Formula IA(1):



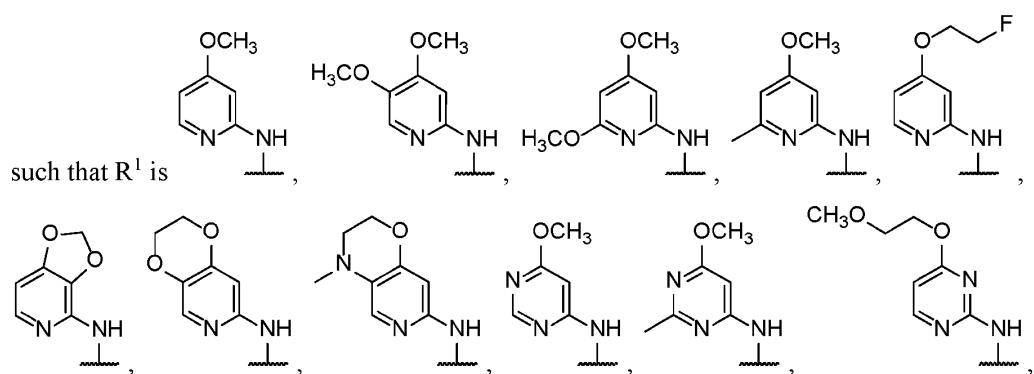
Formula IA(1)

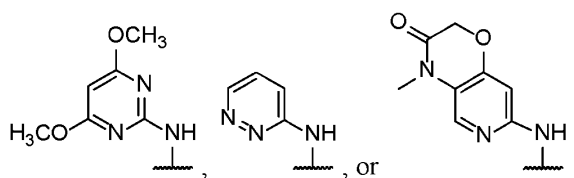
or a pharmaceutically acceptable form thereof. In some embodiments, the compound is a compound of Formula I, wherein m is 1. In some embodiments, the compound is a compound of Formula I, wherein m is 2.

[00176] In some embodiments, the compound of Formula I, Formula IA, or Formula IA(1), is

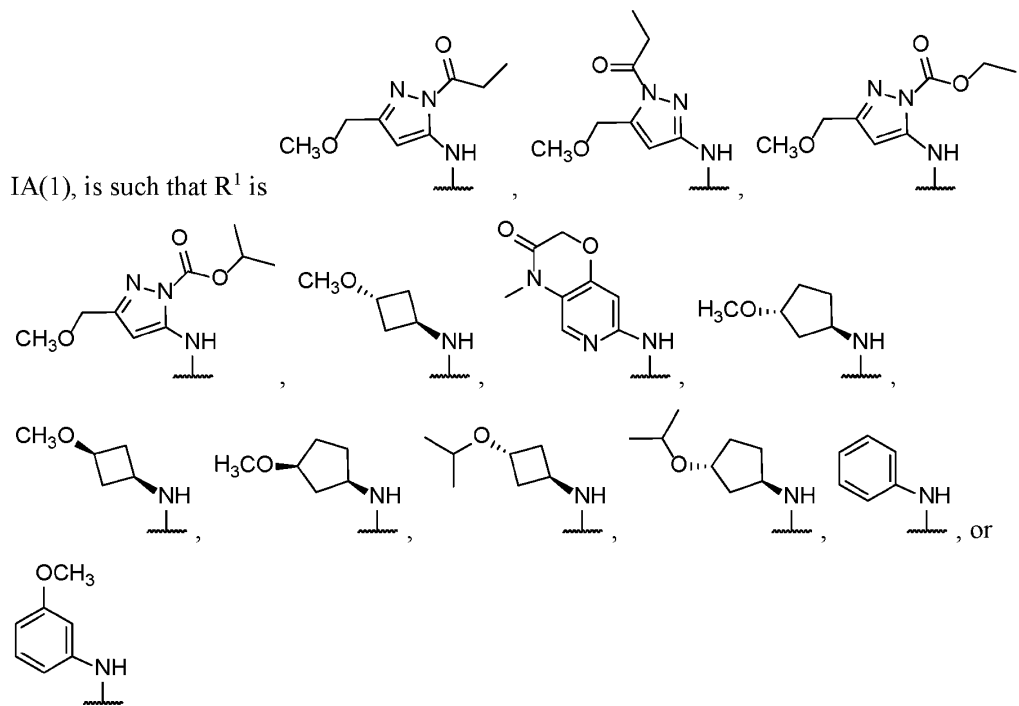


[00177] In some embodiments, the compound of Formula I, Formula IA, or Formula IA(1), is

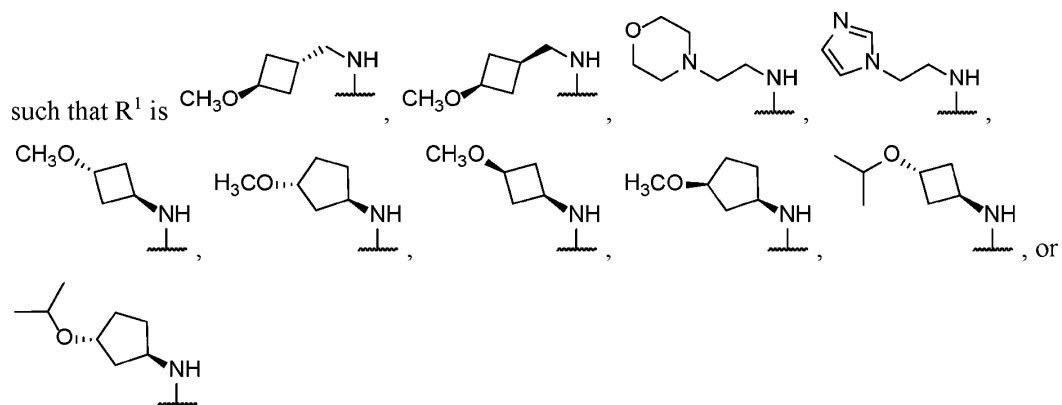




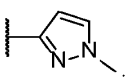
[00178] In some embodiments, the the compound of Formula I, Formula IA, or Formula



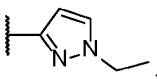
[00179] In some embodiments, the compound of Formula I, Formula IA, or Formula IA(1), is



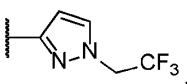
[00180] In some embodiments, the compound of Formula I, Formula IA, or Formula IA(1), is

such that R³ is 

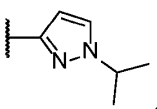
[00181] In some embodiments, the compound of Formula I, Formula IA, or Formula IA(1), is

such that R³ is 

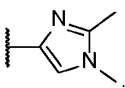
[00182] In some embodiments, the compound of Formula I, Formula IA, or Formula IA(1), is

such that R³ is 

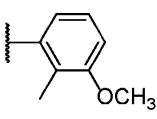
[00183] In some embodiments, the compound of Formula I, Formula IA, or Formula IA(1), is

such that R³ is 

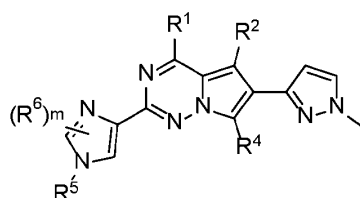
[00184] In some embodiments, the compound of Formula I, Formula IA, or Formula IA(1), is

such that R³ is 

[00185] In some embodiments, the compound of Formula I, Formula IA, or Formula IA(1), is

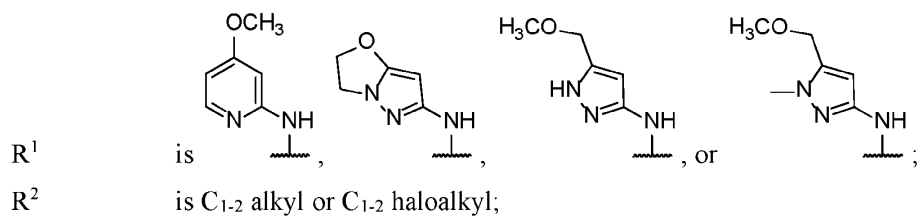
such that R³ is 

[00186] Provided herein is a compound of Formula IB:



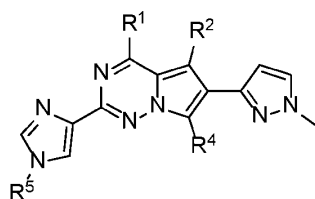
Formula IB

or a pharmaceutically acceptable form thereof, wherein:



- R^4 is hydrogen or C_{1-6} alkyl;
- R^5 and R^6 are each independently C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, C_{1-6} heteroalkyl, halo, $-NR^9R^{10}$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-C(O)NR^9R^{10}$, $-(CO)R^8$, $-(CO)OH$, $-(CO)OR^8$, or CN, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, and C_{1-6} heteroalkyl are each independently optionally substituted with 1-3 R^7 substituents;
- R^7 is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, $-NR^9R^{10}$, $-(CO)R^8$, $-(CO)OH$, $-(CO)OR^8$, $-C(O)NR^9R^{10}$, oxo, $-OH$, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, C_{1-6} haloalkoxy, or 5-6 membered heteroaryl;
- R^8 is C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^7 substituents;
- R^9 and R^{10} are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, $-OH$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-7} heterocycloalkyl, aryl, or 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-7} heterocycloalkyl, aryl, and 5-10 membered heteroaryl are optionally substituted with 1-3 R^7 substituents, or R^9 and R^{10} are combined to form a 3-7 membered heterocycloalkyl including the nitrogen atom to which they are both attached; and
- m is 0, 1 or 2.

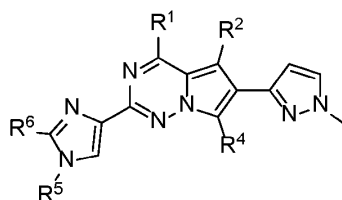
[00187] In some embodiments, the compound is a compound of Formula IB, wherein m is 0, and the compound is a compound of Formula IB(1):



Formula IB(1)

or a pharmaceutically acceptable form thereof.

[00188] In some embodiments, the compound is a compound of Formula IB, wherein m is 1, and, for example, the compound is a compound of Formula IB(2):

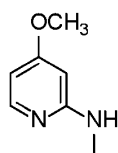


Formula IB(2)

or a pharmaceutically acceptable form thereof.

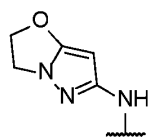
[00189] In some embodiments, the compound is a compound of Formula IB, wherein m is 2, or a pharmaceutically acceptable form thereof.

[00190] In some embodiments, the compound of Formula IB, Formula IB(1), or Formula



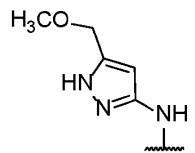
IB(2), is such that R¹ is

[00191] In some embodiments, the compound of Formula IB, Formula IB(1), or Formula



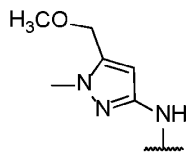
IB(2), is such that R¹ is

[00192] In some embodiments, the compound of Formula IB, Formula IB(1), or Formula



IB(2), is such that R¹ is

[00193] In some embodiments, the compound of Formula IB, Formula IB(1), or Formula



IB(2), is such that R^1 is

[00194] In some embodiments, the compound of Formula I, Formula IA, Formula IA(1), Formula IB, Formula IB(1), or Formula IB(2), is such that R^2 is methyl, ethyl, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CF}_2\text{CH}_3$, or $-\text{CF}_2\text{CF}_3$. In some embodiments, R^2 is methyl.

[00195] In some embodiments, the compound of Formula I, Formula IA, Formula IA(1), Formula IB, Formula IB(1), or Formula IB(2), is such that R^4 is hydrogen or C_{1-6} alkyl. In some embodiments, R^4 is hydrogen, methyl, ethyl, or isopropyl. In some embodiments, R^4 is hydrogen.

[00196] In some embodiments, the compound of Formula I, Formula IA, Formula IA(1), Formula IB, Formula IB(1), or Formula IB(2), is such that R^5 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, C_{1-6} heteroalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-\text{C}(\text{O})\text{NR}^9\text{R}^{10}$, $-(\text{CO})\text{R}^8$, or $-\text{C}(\text{O})\text{OR}^8$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, and C_{1-6} heteroalkyl are each independently optionally substituted with 1-3 R^7 substituents. In some embodiments, R^5 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^7 substituents. In some embodiments, R^5 is methyl, ethyl, or isopropyl, wherein the methyl, ethyl, and isopropyl are each independently optionally substituted with 1-3 R^7 , wherein R^7 is $-\text{OH}$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy. In some embodiments, R^5 is methyl, ethyl, or isopropyl. In some embodiments, R^5 is methyl.

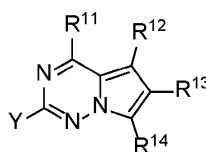
[00197] In some embodiments, the compound of Formula I, Formula IA, Formula IA(1), Formula IB, Formula IB(1), or Formula IB(2), is such that R^6 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^7 substituents. In some embodiments, R^6 is methyl, ethyl, or isopropyl, wherein the methyl, ethyl, and isopropyl are each independently optionally substituted with 1-3 R^7 , wherein R^7 is $-\text{OH}$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy. In some embodiments, R^6 is methyl, ethyl, or isopropyl. In some embodiments, R^6 is methyl.

[00198] In some embodiments, the compound of Formula I, Formula IA, Formula IA(1), Formula IB, Formula IB(1), or Formula IB(2), is such that R^7 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, $-NR^9R^{10}$, $-(CO)R^8$, oxo, C_{1-6} alkoxy, or C_{3-6} cycloalkoxy. In some embodiments, R^7 is independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-5} cycloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} heteroalkyl, 3-5 membered heterocycloalkyl, $-NR^9R^{10}$, $-(CO)R^8$, oxo, C_{1-4} alkoxy, or C_{3-5} cycloalkoxy. In some embodiments, R^7 is independently selected from the group consisting of methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, C_{2-3} hydroxyalkyl, C_{2-4} heteroalkyl, $-NR^9R^{10}$, $-(CO)R^8$, oxo, methoxy, ethoxy, isopropoxy, cyclopropoxy, or cyclobutoxy.

[00199] In some embodiments, the compound of Formula I, Formula IA, Formula IA(1), Formula IB, Formula IB(1), or Formula IB(2), is such that R^8 is methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or C_{2-4} heteroalkyl.

[00200] In some embodiments, the compound of Formula I, Formula IA, Formula IA(1), Formula IB, Formula IB(1), or Formula IB(2), is such that R^9 and R^{10} are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} heteroalkyl, $-OH$, or C_{1-4} alkoxy. In some embodiments, R^9 and R^{10} are each independently selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, methoxy, or ethoxy. In some embodiments, R^9 and R^{10} are each independently selected from the group consisting of hydrogen or methyl. In some embodiments, R^9 and R^{10} are each hydrogen.

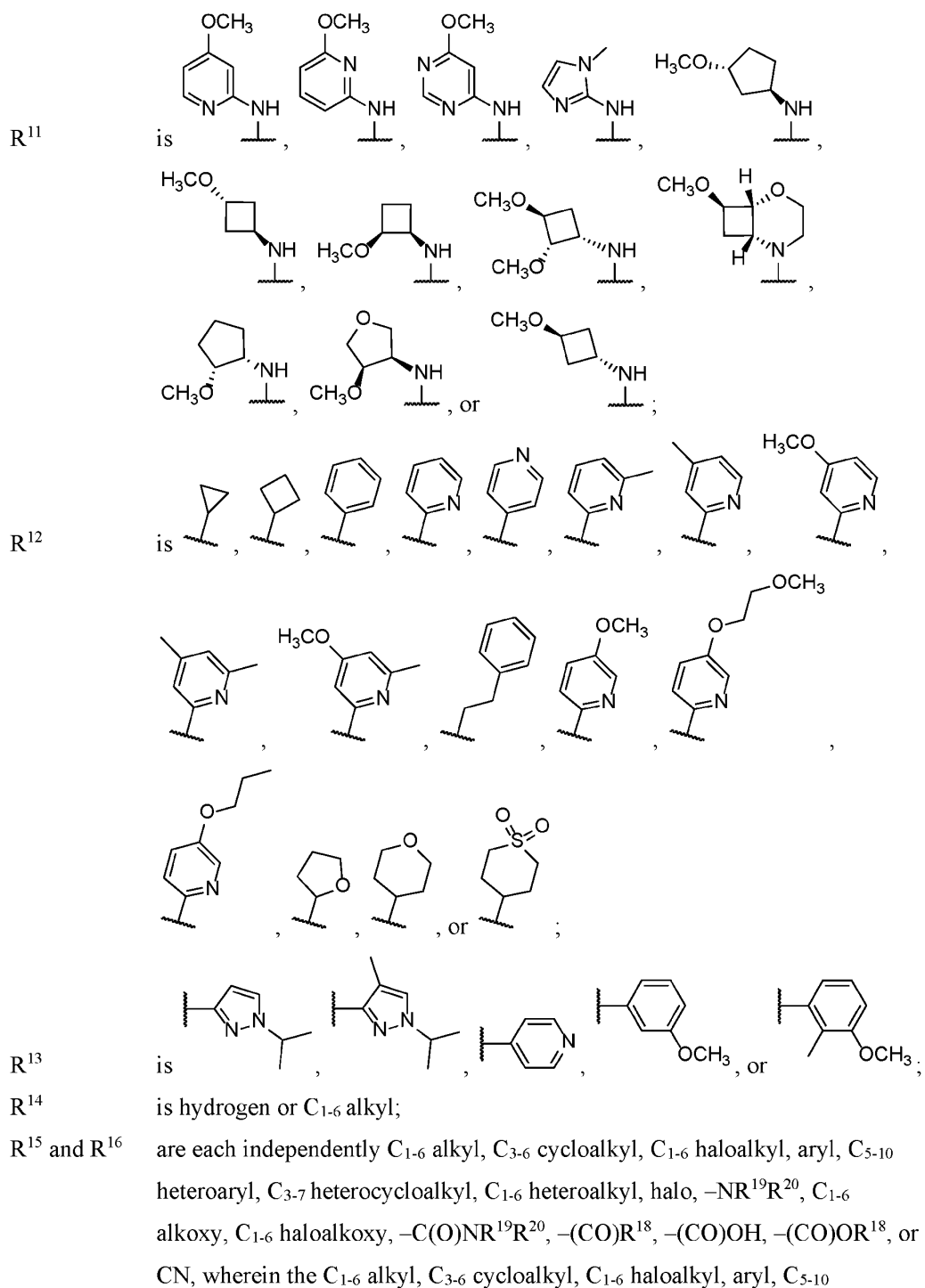
[00201] Provided herein is a compound of Formula II:



Formula II

or a pharmaceutically acceptable form thereof, wherein:

Y is an imidazolyl; wherein the imidazolyl is optionally substituted with 1 R^{15} substituent and optionally substituted with 1-2 R^{16} substituents;

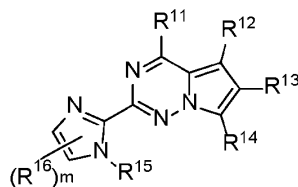


heteroaryl, C₃₋₇ heterocycloalkyl, and C₁₋₆ heteroalkyl are each independently optionally substituted with 1-3 R¹⁷ substituents;

- R¹⁷ is independently selected from the group consisting of halo, CN, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, 3-6 membered heterocycloalkyl, -NR¹⁹R²⁰, -(CO)R¹⁸, -(CO)OH, -(CO)OR¹⁸, -C(O)NR¹⁹R²⁰, oxo, -OH, C₁₋₆ alkoxy, C₃₋₆ cycloalkoxy, C₁₋₆ haloalkoxy, or 5-6 membered heteroaryl;
- R¹⁸ is C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or C₁₋₆ heteroalkyl, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₁₋₆ heteroalkyl, are each independently optionally substituted with 1-3 R¹⁷ substituents; and
- R¹⁹ and R²⁰ are each independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, -OH, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ heterocycloalkyl, aryl, or 5-10 membered heteroaryl, wherein the C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ heterocycloalkyl, aryl, and 5-10 membered heteroaryl are optionally substituted with 1-3 R¹⁷ substituents, or R¹⁹ and R²⁰ are combined to form a 3-7 membered heterocycloalkyl including the nitrogen atom to which they are both attached.

[00202] In some embodiments, the compound of Formula II is such that Y is an imidazolyl optionally substituted with 1 R¹⁵ substituent and optionally substituted with 1-2 R¹⁶ substituents. In some embodiments, the compound of Formula I is such that Y is a C-linked imidazolyl that is substituted with 1 R¹⁵ substituent at a nitrogen of the imidazolyl ring and optionally substituted with 1-2 R¹⁶ substituents at carbons of the imidazolyl ring.

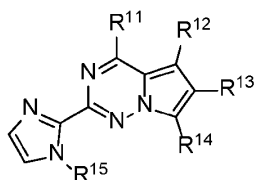
[00203] In some embodiments, the compound of Formula II is a compound of Formula IIA:



Formula IIA

or a pharmaceutically acceptable form thereof; wherein m is 0, 1 or 2. In some embodiments, the

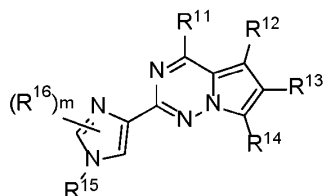
compound is a compound of Formula II, wherein m is 0, and the compound is a compound of Formula IIA(1):



Formula IIA(1)

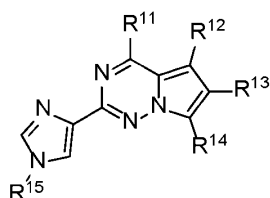
or a pharmaceutically acceptable form thereof. In some embodiments, the compound is a compound of Formula I, wherein m is 1. In some embodiments, the compound is a compound of Formula I, wherein m is 2.

[00204] In some embodiments, the compound of Formula II is a compound of Formula IIB:



Formula IIB

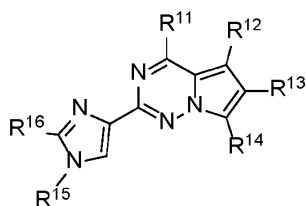
or a pharmaceutically acceptable form thereof; wherein m is 0, 1 or 2. In some embodiments, the compound is a compound of Formula IIB, wherein m is 0, and the compound is a compound of Formula IIB(1):



Formula IIB(1)

or a pharmaceutically acceptable form thereof.

[00205] In some embodiments, the compound is a compound of Formula IIB, wherein m is 1, and, for example, the compound is a compound of Formula IIB(2):

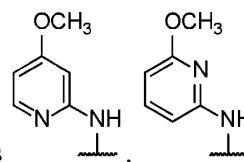


Formula IIB(2)

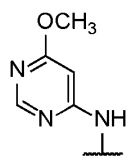
or a pharmaceutically acceptable form thereof.

[00206] In some embodiments, the compound is a compound of Formula IIB, wherein m is 2, or a pharmaceutically acceptable form thereof.

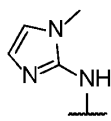
[00207] In some embodiments, the compound of Formula II, Formula IIA, Formula IIA(1),



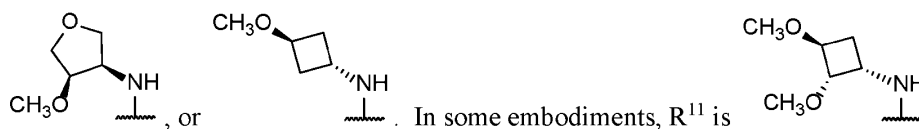
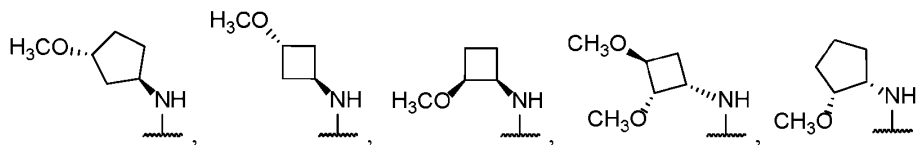
Formula IIB, Formula IIB(1), or Formula IIB(2), is such that R^{11} is



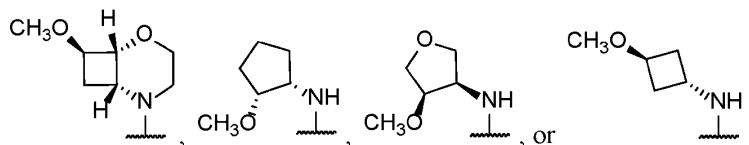
. In some embodiments, R^{11} is



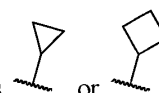
. In some embodiments, R^{11} is



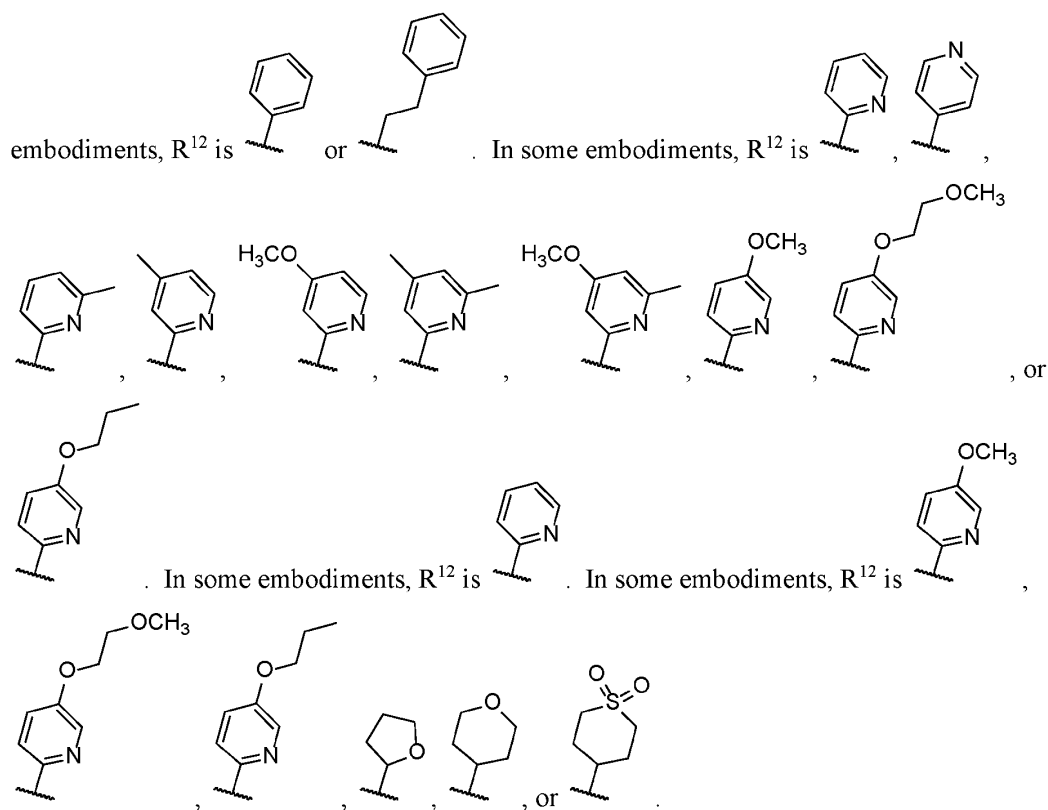
. In some embodiments, R^{11} is

 $\text{CH}_3\text{O} \quad \begin{array}{c} | \\ \sim \end{array}, \text{ or}$

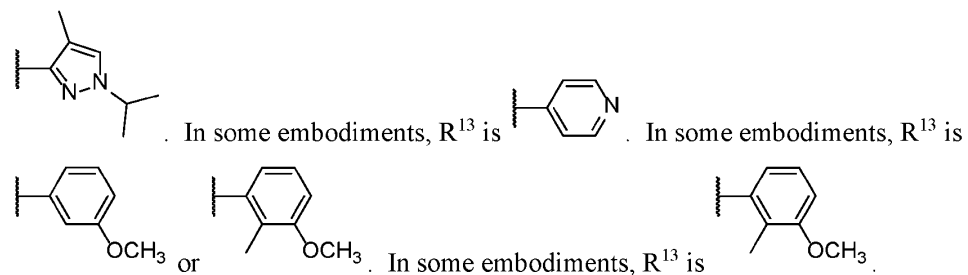
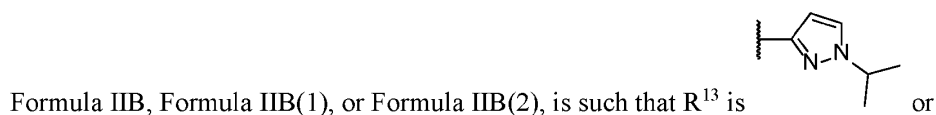
[00208] In some embodiments, the compound of Formula II, Formula IIA, Formula IIA(1),



Formula IIB, Formula IIB(1), or Formula IIB(2), is such that R^{12} is or . In some



[00209] In some embodiments, the compound of Formula II, Formula IIA, Formula IIA(1),



[00210] In some embodiments, the compound of Formula II, Formula IIA, Formula IIA(1), Formula IIB, Formula IIB(1), or Formula IIB(2), is such that R^{14} is hydrogen or C_{1-6} alkyl. In some embodiments, R^{14} is hydrogen, methyl, ethyl, or isopropyl. In some embodiments, R^{14} is hydrogen.

[00211] In some embodiments, the compound of Formula II, Formula IIA, Formula IIA(1), Formula IIB, Formula IIB(1), or Formula IIB(2), is such that R^{15} is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, C_{1-6} heteroalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-C(O)NR^{19}R^{20}$, $-(CO)R^{18}$, or $-C(O)OR^{18}$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, and C_{1-6} heteroalkyl are each independently optionally substituted with 1-3 R^{17} substituents. In some embodiments, R^{15} is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^{17} substituents. In some embodiments, R^{15} is methyl, ethyl, or isopropyl, wherein the methyl, ethyl, and isopropyl are each independently optionally substituted with 1-3 R^{17} , wherein R^{17} is $-OH$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy. In some embodiments, R^{15} is methyl, ethyl, or isopropyl. In some embodiments, R^{15} is methyl.

[00212] In some embodiments, the compound of Formula II, Formula IIA, Formula IIA(1), Formula IIB, Formula IIB(1), or Formula IIB(2), is such that R^{16} is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^{17} substituents. In some embodiments, R^{16} is methyl, ethyl, or isopropyl, wherein the methyl, ethyl, and isopropyl are each independently optionally substituted with 1-3 R^{17} , wherein R^{17} is $-OH$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy. In some embodiments, R^{16} is methyl, ethyl, or isopropyl. In some embodiments, R^{16} is methyl.

[00213] In some embodiments, the compound of Formula II, Formula IIA, Formula IIA(1), Formula IIB, Formula IIB(1), or Formula IIB(2), is such that R^{17} is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, $-NR^{19}R^{20}$, $-(CO)R^{18}$, oxo, C_{1-6} alkoxy, or C_{3-6} cycloalkoxy. In some embodiments, R^{17} is independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-5} cycloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} heteroalkyl, 3-5 membered heterocycloalkyl, $-NR^{19}R^{20}$, $-(CO)R^{18}$, oxo, C_{1-4} alkoxy, or C_{3-5} cycloalkoxy. In some embodiments, R^{17} is independently selected from the group consisting of methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, C_{2-3} hydroxyalkyl, C_{2-4} heteroalkyl, $-NR^{19}R^{20}$, $-(CO)R^{18}$, oxo, methoxy, ethoxy, isopropoxy, cyclopropoxy, or cyclobutoxy.

[00214] In some embodiments, the compound of Formula II, Formula IIA, Formula IIA(1),

Formula IIB, Formula IIB(1), or Formula IIB(2), is such that R¹⁸ is methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or C₂₋₄ heteroalkyl.

[00215] In some embodiments, the compound of Formula II, Formula IIA, Formula IIA(1), Formula IIB, Formula IIB(1), or Formula IIB(2), is such that R¹⁹ and R²⁰ are each independently selected from the group consisting of hydrogen, C₁₋₄ alkyl, C₃₋₅ cycloalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ heteroalkyl, -OH, or C₁₋₄ alkoxy. In some embodiments, R¹⁹ and R²⁰ are each independently selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, methoxy, or ethoxy. In some embodiments, R¹⁹ and R²⁰ are each independently selected from the group consisting of hydrogen or methyl. In some embodiments, R¹⁹ and R²⁰ are each hydrogen.

[00216] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), has a molecular weight (MW) of no more than 1000 g/mol. In some embodiments, the compound has a MW of no more than 900 g/mol, no more than 800 g/mol, no more than 700 g/mol, no more than 600 g/mol, or no more than 500 g/mol. In some embodiments, the compound has a MW of no more than 900 g/mol. In some embodiments, the compound has a MW of no more than 800 g/mol. In some embodiments, the compound has a MW of no more than 700 g/mol. In some embodiments, the compound has a MW of no more than 600 g/mol. In some embodiments, the compound has a MW of no more than 500 g/mol. In some embodiments, the compound has a MW of no more than 450 g/mol.

[00217] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof. In some embodiments, the compound is selected from the group consisting of Compounds 9, 10, 11, 13, 14, 15, 16, 18, 19, 22, and 23, or a pharmaceutically acceptable form thereof. In some embodiments, the compound is selected from the group consisting of Compounds 9, 11, 19, 22, and 23, or a pharmaceutically acceptable form thereof. In some embodiments, the compound is selected from the group consisting of Compounds 9 and 11, or a pharmaceutically acceptable form thereof. In some embodiments, the compound is selected from the group consisting of

Compounds 36, 37, 38, 39, 40, and 62, or a pharmaceutically acceptable form thereof.

[00218] In some embodiments, the compound of Formula I is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 22, 23, 24, 25, 26, 27, 28, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 69, 70, 71, 72, 73, 74, 75, 76, 84, 85, 86, 87, 88, 89, 90, and 91, or a pharmaceutically acceptable form thereof.

[00219] In some embodiments, the compound of Formula IA or IA(1) is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 25, 26, 27, 28, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 70, 71, 72, 73, 74, 75, 76, 84, 85, 86, 87, 88, 89, 90, and 91, or a pharmaceutically acceptable form thereof.

[00220] In some embodiments, the compound of Formula IB(1) is selected from the group consisting of Compounds 22, 23, 24, and 30, or a pharmaceutically acceptable form thereof.

[00221] In some embodiments, the compound of Formula IB(2) is selected from the group consisting of Compounds 31, 32, 33, and 69, or a pharmaceutically acceptable form thereof.

[00222] In some embodiments, the compound of Formula II is selected from the group consisting of Compounds 16, 17, 18, 19, 20, 21, 29, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 77, 78, 79, 80, 81, 82, 83, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00223] In some embodiments, the compound of Formula IIA or IIA(1) is selected from the group consisting of Compounds 16, 17, 18, 19, 20, 21, 29, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 77, 78, 79, 80, 81, 82, 83, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00224] In some embodiments, the compound of Formula IIB(1) is selected from the group consisting of Compounds 63, 64, and 65, or a pharmaceutically acceptable form thereof.

[00225] In some embodiments, the compound of Formula IIB(2) is selected from the group consisting of Compounds 66, 67, and 68, or a pharmaceutically acceptable form thereof.

[00226] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof is a modulator of Ras superfamily activity according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 20 μ M

according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by 50% or more at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by 75% or more at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by 90% or more at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by 95% or more at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by about 50% to about 60% at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by about 60% to about 70% at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by about 70% to about 80% at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by about 80% to about 90% at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by about 90% to about 100% at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 9, 10, 11, 12, 13, 16, 18, 22, 23, 24, 27, 28, 32, 33, 36, 37, 38, 39, 40, 57, 62, 75, 84, 86, and 92, or a pharmaceutically acceptable form thereof.

[00227] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof inhibits

phosphorylation of Erk1/2 according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by 50% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by 75% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by 80% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by 85% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by 90% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by 95% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by about 50% to about 60% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by about 60% to about 70% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by about 70% to about 80% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by about 80% to about 90% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by about 90% to about 100% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound is

selected from the group consisting of Compounds 19, 20, 21, 49, 51, 53, 56, 67, 68, 79, 80, 81, 82, 89, and 94, or a pharmaceutically acceptable form thereof.

[00228] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, about 90% to about 100%, or about 100% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by 50% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by 75% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by 85% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by 90% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by 95% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by equal or greater than 100% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by about 50% to about 60% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by about 60% to about 70% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by about 70% to about 80% at 10 μ M according to Erk1/2

Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by about 80% to about 90% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by about 90% to about 100% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by about 100% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 16, 18, 23, 27, 28, 36, 37, 38, 40, 54, 55, 57, 60, 61, 62, 75, and 83, or a pharmaceutically acceptable form thereof.

[00229] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by 50% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by 75% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by 85% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by 90% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by 95% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by about 50% to about 60% at 10 μ M according to

Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by about 60% to about 70% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by about 70% to about 80% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by about 80% to about 90% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by about 90% to about 100% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 19, 20, 49, 51, 53, 56, 79, 80, 81, and 94, or a pharmaceutically acceptable form thereof. In some embodiments, the compound **[00230]** In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof activates phosphorylation of Akt according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, about 90% to about 100%, or about 100% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by 50% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by 75% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by 85% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by 90% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by 95% or more at 10 μ M according to Akt Phosphorylation Assay. In

some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by equal or greater than 100% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by about 50% to about 60% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by about 60% to about 70% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by about 70% to about 80% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by about 80% to about 90% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by about 90% to about 100% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by about 100% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 18, 22, 27, 28, 32, 36, 37, 38, 39, 40, 47, 54, 55, 57, 59, 60, 61, 62, 66, 67, 74, 75, 76, 83, 84, 86, 87, 88, and 91, or a pharmaceutically acceptable form thereof.

[00231] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by 50% or more at 10 μ M according to Phospho-Smad2/3

Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by 75% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by 80% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by 85% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by 90% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by 95% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by about 50% to about 60% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by about 60% to about 70% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by about 70% to about 80% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by about 80% to about 90% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by about 90% to about 100% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound is selected from the group consisting of Compounds 19, 20, 21, 29, 49, 51, 56, 58, 61, 63, 64, 65, 68, 77, 79, 80, 81, 87, 88, 89, and 94, or a pharmaceutically acceptable form thereof.

[00232] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater

than 100% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, about 90% to about 100%, or about 100% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by 50% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by 75% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by 85% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by 90% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by 95% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by equal or greater than 100% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by about 50% to about 60% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by about 60% to about 70% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by about 70% to about 80% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by about 80% to about 90% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by about 90% to about 100% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by about 100% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In

some embodiments, the compound is Compound 12, 14, 25, 26, 31, 32, 33, 37, 78, 90 or a pharmaceutically acceptable form thereof.

[00233] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof inhibits JNK according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by 50% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by 75% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by 85% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by 90% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by 95% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by about 50% to about 60% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by about 60% to about 70% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by about 70% to about 80% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by about 80% to about 90% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by about 90% to about 100% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 29, 30, 32, 33, and 34, or a pharmaceutically acceptable form thereof. In some embodiments, the compound is Compound 8, or a pharmaceutically acceptable form thereof. In some

embodiments, the compound is selected from the group consisting of Compounds 29, 32, and 34, or a pharmaceutically acceptable form thereof.

[00234] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof activates JNK according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, about 90% to about 100%, or about 100% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by 50% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by 75% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by 85% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by 90% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by 95% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by equal or greater than 100% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by about 50% to about 60% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by about 60% to about 70% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by about 70% to about 80% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by about 80% to about 90% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by about 90% to about 100% at 10 μ M according to JNK Activation Assay. In some embodiments,

the compound or pharmaceutically acceptable form thereof activates JNK by about 100% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, and 7, or a pharmaceutically acceptable form thereof.

[00235] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof inhibits MAPK p38 according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by 50% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by 75% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by 85% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by 90% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by about 50% to about 60% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by about 60% to about 70% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by about 70% to about 80% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by about 80% to about 90% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by about 90% to about 100% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or

pharmaceutically acceptable form thereof inhibits MAPK p38 by 95% or more at 10 μ M according to MAPK p38 Activation Assay.

[00236] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof activates MAPK p38 according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, about 90% to about 100%, or about 100% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by 50% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by 75% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by 85% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by 90% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by 95% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by equal or greater than 100% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by about 50% to about 60% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by about 60% to about 70% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by about 70% to about 80% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by about 80% to about 90% at 10

μM according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by about 90% to about 1000% at 10 μM according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by about 100% or more at 10 μM according to MAPK p38 Activation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 2, 3, 4, 5, 6, and 7, or a pharmaceutically acceptable form thereof.

[00237] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC_{50} value of 1.25 μM or less, 1.1 μM or less, 1 μM or less, 0.9 μM or less, 0.8 μM or less, 0.75 μM or less, 0.7 μM or less, 0.6 μM or less, 0.5 μM or less, 0.4 μM or less, 0.3 μM or less, 0.25 μM or less, 0.2 μM or less, 0.15 μM or less, 0.1 μM or less, 0.09 μM or less, 0.05 μM or less, or 0.03 μM or less, according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC_{50} value of about 1.25 μM to about 1.1 μM , about 1.1 μM to about 1 μM , about 1.0 μM to about 0.9 μM , about 0.9 μM to about 0.8 μM , about 0.8 μM to about 0.75 μM , about 0.75 μM to about 0.7 μM , about 0.7 μM to about 0.6 μM , about 0.6 μM to about 0.5 μM , about 0.5 μM to about 0.4 μM , about 0.4 μM to about 0.3 μM , about 0.3 μM to about 0.25 μM , about 0.25 μM to about 0.2 μM , about 0.2 μM to about 0.15 μM , about 0.15 μM to about 0.1 μM , about 0.1 μM to about 0.01 μM , about 0.01 μM to about 0.001 μM , about 0.001 μM to about 0.0001 μM , or less than about 0.0001 μM according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC_{50} value of 1.25 μM or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC_{50} value of 1 μM or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC_{50} value of 0.6 μM or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC_{50} value of 0.5 μM or less according to Proliferation Assay. In some embodiments, the compound or

pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.4 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.3 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.25 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.20 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.15 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.10 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.09 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.05 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.03 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of about 1.25 μ M to about 1.1 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of about 1.1 μ M to about 1 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of about 1.0 μ M to about 0.9 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of about 0.9 μ M to about 0.8 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of about 0.8 μ M to about 0.75 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of about 0.75 μ M to about 0.7 μ M according to Proliferation Assay. In some embodiments, the

compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC50 value of about 0.7 μ M to about 0.6 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC50 value of about 0.6 μ M to about 0.5 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC50 value of about 0.5 μ M to about 0.4 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC50 value of about 0.4 μ M to about 0.3 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC50 value of about 0.3 μ M to about 0.25 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC50 value of about 0.25 μ M to about 0.2 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC50 value of about 0.2 μ M to about 0.15 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC50 value of about 0.15 μ M to about 0.1 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC50 value about 0.1 μ M to about 0.01 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC50 value of about 0.01 μ M to about 0.001 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC50 value of about 0.001 μ M to about 0.0001 μ M according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC50 value of less than about 0.0001 μ M according to Proliferation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 3, 4, 9, 10, 11, 12, 13, 16, 18, 19, 22, 23, 28, 31, 32, 36, 37, 38, 39, 40, 47, 48, 49, 52, 57, 62, 65, 68, 75, 80, 81, 82, 83, 85, 87, and 94, or a pharmaceutically acceptable form thereof. In some embodiments, the compound is selected from the group consisting of Compounds 9, 10, 11, 16, 18, 19, 28, 36, 37, 38, 39, 40, 48, 57, 62, and 65, or a pharmaceutically

acceptable form thereof. In some embodiments, the compound is selected from the group consisting of Compounds 9, 10, 11, 36, 37, 38, 39, 40, 62, and 65, or a pharmaceutically acceptable form thereof. In some embodiments, the compound is selected from the group consisting of Compounds 9 and 11, or a pharmaceutically acceptable form thereof. In some embodiments, the compound is selected from the group consisting of Compounds 36, 37, 38, 39, 40, and 62, or a pharmaceutically acceptable form thereof.

[00238] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof inhibits IL-6 according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by 50% or more at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by 75% or more at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by 85% or more at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by 90% or more at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by 95% or more at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by about 50% to about 60% at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by about 60% to about 70% at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by about 70% to about 80% at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by about 80% to about 90% at 10 μ M

according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by about 90% to about 100% at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound is selected from the group consisting of Compounds 4, 9, 10, 11, 16, 17, 19, 20, 92, and 94, or a pharmaceutically acceptable form thereof.

[00239] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof inhibits TNF-alpha according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by about 50% to about 60%, about 60% to about 70%, about 70% to about 80%, about 80% to about 90%, or about 90% to about 100% at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by 50% or more at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by 75% or more at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by 85% or more at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by 90% or more at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by 95% or more at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by about 50% to about 60% at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by about 60% to about 70% at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by about 70% to about 80% at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by about 80% to about 90% at 10

μM according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by about 90% to about 100% at 10 μM according to TNF-alpha Quantification Assay. In some embodiments, the compound is Compound 20 and 94, or a pharmaceutically acceptable form thereof.

[00240] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof has a kinetic solubility of 10 μM or more, 20 μM or more, 30 μM or more, 40 μM or more, 50 μM or more, 60 μM or more, 70 μM or more, 80 μM or more, 90 μM or more, 100 μM or more, 150 μM or more, or 200 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay. In some embodiments, the compound has a kinetic solubility of 10 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay. In some embodiments, the compound has a kinetic solubility of 20 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay. In some embodiments, the compound has a kinetic solubility of 30 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay. In some embodiments, the compound has a kinetic solubility of 40 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay. In some embodiments, the compound has a kinetic solubility of 50 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay. In some embodiments, the compound has a kinetic solubility of 60 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay. In some embodiments, the compound has a kinetic solubility of 70 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay. In some embodiments, the compound has a kinetic solubility of 80 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay. In some embodiments, the compound has a kinetic solubility of 90 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay. In some embodiments, the compound has a kinetic solubility of 100 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay. In some embodiments, the compound has a kinetic solubility of 150 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay. In some embodiments, the compound has a kinetic solubility of 200 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay. In some embodiments, the compound is selected from the group consisting of

Compounds 9 and 11, or a pharmaceutically acceptable form thereof. In some embodiments, the compound is Compound 9, or a pharmaceutically acceptable form thereof.

[00241] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof has a half-life of 10 minutes or more, 20 minutes or more, 30 minutes or more, 40 minutes or more, or 50 minutes or more in mouse liver microsomes according to Mouse Liver Microsome Metabolic Stability Assay. In some embodiments, the compound has a half-life of 10 minutes or more in mouse liver microsomes according to Mouse Liver Microsome Metabolic Stability Assay. In some embodiments, the compound has a half-life of 20 minutes or more in mouse liver microsomes according to Mouse Liver Microsome Metabolic Stability Assay. In some embodiments, the compound has a half-life of 30 minutes or more in mouse liver microsomes according to Mouse Liver Microsome Metabolic Stability Assay. In some embodiments, the compound has a half-life of 40 minutes or more in mouse liver microsomes according to Mouse Liver Microsome Metabolic Stability Assay. In some embodiments, the compound has a half-life of 50 minutes or more in mouse liver microsomes according to Mouse Liver Microsome Metabolic Stability Assay. In some embodiments, the compound is Compound 11, or a pharmaceutically acceptable form thereof.

[00242] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in Kasumi-1 according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in BT-549 according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in GP2d according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in A375 according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in MM.1R according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in IM.9 according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in RPMI8226 according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in NCI-H358 according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in NCI-H727 according to Proliferation

Assay. In some embodiments, the compound inhibits proliferation in MiaPaca-2 according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in Panc1 according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, with an IC_{50} value of 50 nM or less, 40 nM or less, 30 nM or less, 20 nM or less, 10 nM or less, 1 nM or less, 0.1 nM or less, or 0.01 nM or less according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, with an IC_{50} value of 50 nM or less according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, with an IC_{50} value of 40 nM or less according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, with an IC_{50} value of 30 nM or less according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, with an IC_{50} value of 20 nM or less according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, with an IC_{50} value of 10 nM or less according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, with an IC_{50} value of 1 nM or less according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, with an IC_{50} value of 0.1 nM or less according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, with an IC_{50} value of 0.01 nM or less according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in MM.R1 with an IC_{50} value of 1 nM or less, 0.1 nM or less, or 0.01 nM or less according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in MM.R1 with an IC_{50} value of 1 nM or less according to Proliferation Assay. In some embodiments, the compound inhibits proliferation in MM.R1 with an IC_{50} value of 0.1 nM or less according to Proliferation Assay. In

some embodiments, the compound inhibits proliferation in MM.R1 with an IC_{50} value of 0.01 nM or less according to Proliferation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 9 and 11, or a pharmaceutically acceptable form thereof.

[00243] In some embodiments, the pharmaceutically acceptable form of the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2) is an isomer, isotopic variant, pharmaceutically acceptable salt, polymorph, or solvate of said compound. In some embodiments, the pharmaceutically acceptable form of the compound is exclusive of a salt form. In some embodiments, the isomer of the compound is a diastereomer or enantiomer of the compound.

[00244] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2) is a tautomer of the compound.

[00245] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2) is a racemate or a mixture of diastereomers.

[00246] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2) is a single enantiomer or a single diastereomer.

[00247] In one embodiment, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2) is a single enantiomer, such as an (R) enantiomer. In some embodiments, the compound has an enantiomeric excess of greater than 10% of the (R) enantiomer. In some embodiments, the compound has an enantiomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (R) enantiomer. In some embodiments, the compound has an enantiomeric excess of 15% or more of the (R) enantiomer. In some embodiments, the compound has an enantiomeric excess of 25% or more of the (R) enantiomer. In some embodiments, the compound has an enantiomeric excess of 50% or more of the (R) enantiomer. In some embodiments, the compound has an enantiomeric excess of 75% or more of the (R) enantiomer. In some embodiments, the compound has an enantiomeric excess of 90% or more of the (R) enantiomer. In some embodiments, the compound has an enantiomeric excess of 95% or more of the (R) enantiomer. In some embodiments, the compound has an enantiomeric excess of 98% or more of the (R) enantiomer.

In some embodiments, the compound has an enantiomeric excess of 99% or more of the (R) enantiomer. In some embodiments, the compound has an enantiomeric excess of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (R) enantiomer.

[00248] In one embodiment, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2) is a single enantiomer, such as an (S) enantiomer. In some embodiments, the compound has an enantiomeric excess of greater than 10% of the (S) enantiomer. In some embodiments, the compound has an enantiomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (S) enantiomer. In some embodiments, the compound has an enantiomeric excess of 15% or more of the (S) enantiomer. In some embodiments, the compound has an enantiomeric excess of 25% or more of the (S) enantiomer. In some embodiments, the compound has an enantiomeric excess of 50% or more of the (S) enantiomer. In some embodiments, the compound has an enantiomeric excess of 75% or more of the (S) enantiomer. In some embodiments, the compound has an enantiomeric excess of 90% or more of the (S) enantiomer. In some embodiments, the compound has an enantiomeric excess of 95% or more of the (S) enantiomer. In some embodiments, the compound has an enantiomeric excess of 98% or more of the (S) enantiomer. In some embodiments, the compound has an enantiomeric excess of 99% or more of the (S) enantiomer. In some embodiments, the compound has an enantiomeric excess of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (S) enantiomer.

[00249] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2) is a single diastereomer, such as a (R)/(R)-, (R)/(S)-, (S)/(R)-, or (S)/(S)-single diastereomer. In some embodiments, the compound is an (R)/(R)-single diastereomer. In some embodiments, the compound is an (R)/(S)-single diastereomer. In some embodiments, the compound is an (S)/(R)-single diastereomer. In some embodiments, the compound is an (S)/(S)-single diastereomer.

[00250] In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2) has a diastereomeric excess of greater than 10% of the

(R)/(R)-, (R)/(S)-, (S)/(R)-, or (S)/(S)-diastereomer. In some embodiments, the compound has a diastereomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (R)/(R)-, (R)/(S)-, (S)/(R)-, or (S)/(S)-diastereomer. In some embodiments, the compound has a diastereomeric excess of 15% or more of the (R) enantiomer. In some embodiments, the compound has a diastereomeric excess of 25% or more of the (R)/(R)-, (R)/(S)-, (S)/(R)-, or (S)/(S)-diastereomer. In some embodiments, the compound has a diastereomeric excess of 50% or more of the (R)/(R)-, (R)/(S)-, (S)/(R)-, or (S)/(S)-diastereomer. In some embodiments, the compound has a diastereomeric excess of 75% or more of the (R)/(R)-, (R)/(S)-, (S)/(R)-, or (S)/(S)-diastereomer. In some embodiments, the compound has a diastereomeric excess of 90% or more of the (R)/(R)-, (R)/(S)-, (S)/(R)-, or (S)/(S)-diastereomer. In some embodiments, the compound has a diastereomeric excess of 95% or more of the (R)/(R)-, (R)/(S)-, (S)/(R)-, or (S)/(S)-diastereomer. In some embodiments, the compound has a diastereomeric excess of 98% or more of the (R)/(R)-, (R)/(S)-, (S)/(R)-, or (S)/(S)-diastereomer. In some embodiments, the compound has a diastereomeric excess of 99% or more of the (R)/(R)-, (R)/(S)-, (S)/(R)-, or (S)/(S)-diastereomer. In some embodiments, the compound has a diastereomeric excess of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (R)/(R)-, (R)/(S)-, (S)/(R)-, or (S)/(S)-diastereomer. In some embodiments, the compound has a diastereomeric excess of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (R)/(R)-, (R)/(S)-, (S)/(R)-, or (S)/(S)-diastereomer. In some embodiments, the compound has a diastereomeric excess of the (R)/(R)-diastereomer. In some embodiments, the compound has a diastereomeric excess of the (R)/(S)-diastereomer. In some embodiments, the compound has a diastereomeric excess of the (S)/(R)-diastereomer. In some embodiments, the compound has a diastereomeric excess of the (S)/(S)-diastereomer.

[00251] In certain embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, is suitable for conjugation to an antibody or a fragment of an antibody. In certain embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, is suitable for delivery to a subject in the form of an

antibody-drug conjugate.

3.3. METHODS OF MODULATING ACTIVITY OF CELLULAR TARGETS

[00252] Provided herein are methods of modulating a Ras superfamily protein, comprising contacting the Ras superfamily protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof. Also provided herein are methods of modulating a Ras superfamily protein, comprising contacting the Ras superfamily protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, as disclosed herein below. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00253] In some embodiments of the methods provided herein, the Ras superfamily protein is present in a cell.

[00254] In some embodiments, the method comprises contacting the Ras superfamily protein with a compound or pharmaceutically acceptable form thereof that modulates the activity of one or more Ras superfamily proteins by 50% or more at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 9, 10, 11, 12, 13, 16, 18, 22, 23, 24, 27, 32, 33, 36, 37, 38, 39, 40, 57, 62, 75, 84, 86, and 92, or a pharmaceutically acceptable form thereof.

[00255] In some embodiments, the methods provided herein inhibit the Ras superfamily protein.

[00256] In some embodiments of the methods provided herein, the Ras superfamily protein is a Ras protein, or a mutant thereof. In some embodiments, the Ras protein is DIRAS I; DIRAS2; DIRAS3; ERAS; GEM; HRAS; KRAS; MRAS; NKIRASI; NKIRAS2; NRAS; RALA; RALB; RAPIA; RAPIB; RAP2A; RAP2B; RAP2C; RASDI; RASD2; RASL10A; RASL10B; RASL11A; RASL11B; RASL12; REMI; REM2; RERG; RERGL; RRAD; RRAS; or RRAS2. In some embodiments, the Ras protein is HRAS; KRAS; or NRAS, or a mutant thereof. In some embodiments, the Ras protein is a KRAS mutant. In some embodiments, the KRAS mutant is a

KRas G12D mutant, KRas G12C mutant, or KRas Q61H mutant. In some embodiments, the Ras protein is HRAS or a mutant thereof. In some embodiments, the Ras protein is NRAS or a mutant thereof.

[00257] In some embodiments of the methods provided herein, the Ras superfamily protein is a Rac protein, or a mutant thereof. In some embodiments, the Rac protein is RAC1; RAC2; RAC3; RHOG, or a mutant thereof. In some embodiments, the Rac protein is wild-type RAC1.

[00258] In some embodiments of the methods provided herein, the Ras superfamily protein is a Rho protein, or a mutant thereof. In some embodiments, the Rho protein is RHOA; RHOB; RHOBTB1; RHOBTB2; RHOBTB3; RHOC; RHOD; RHOF; RHOH; RHOJ; RHOQ; RHOU; RHOV; RND1; RND2; RND3; CDC42, or a mutant thereof. In some embodiments, the Rho protein is wild-type RHOA.

[00259] In some embodiments of the methods provided herein, the Ras superfamily protein is a Cdc42 protein, or a mutant thereof.

[00260] In some embodiments of the methods provided herein, the Ras superfamily protein is a Rheb protein, or a mutant thereof.

[00261] In some embodiments of the methods provided herein, the contacting of the Ras superfamily protein takes place in a cell. In some embodiments, the cell is in a subject. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a human cell. In some embodiments, the subject suffers from a cancer. In some embodiments, the subject is a human.

[00262] In some embodiments of the methods provided herein, the modulation takes place in a subject suffering from a cancer. In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is a blood borne tumor (or a hematological cancer). In some embodiments, the cancer is hepatocellular carcinoma, prostate cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, colon cancer, small intestine cancer, biliary tract cancer, endometrium cancer, skin cancer (melanoma), cervix cancer, urinary tract cancer, glioblastoma, esophageal carcinoma, mesothelioma, or multiple myeloma. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is colon cancer. In some embodiments, the cancer is triple negative breast cancer. In some embodiments, the cancer is multiple myeloma. In some embodiments, the cancer is lung cancer. In some embodiments, the lung cancer is non-small cell lung cancer (NSCLC). In some embodiments, the lung cancer is small cell lung cancer

(SCLC). In some embodiments, the lung cancer is mesothelioma. In some embodiments, the cancer is hepatocellular carcinoma, pancreatic cancer, glioblastoma, esophageal carcinoma, mesothelioma, or small cell lung cancer (SCLC). In some embodiments, the cancer is a cancer dependent on a Ras superfamily protein.

[00263] Provided herein are methods of modulating caspase activity, comprising contacting the caspase with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof. Also provided herein are methods of modulating caspase activity, comprising contacting the caspase with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, as disclosed herein below. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00264] In some embodiments, the methods provided herein activate the caspase. In some embodiments, the caspase is caspase 3, caspase 6, or caspase 9.

[00265] In some embodiments of the methods provided herein, the contacting of the caspase takes place in a cell. In some embodiments, the modulation of caspase activity induces apoptosis of the cell. In some embodiments, the cell is in a subject. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a human cell. In some embodiments, the subject suffers from a cancer. In some embodiments, the modulation takes place in a subject suffering from a cancer. In some embodiments, the cancer is a solid tumor. In some embodiments, the cancer is a blood borne tumor (or a hematological cancer). In some embodiments, the cancer is hepatocellular carcinoma, prostate cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, colon cancer, small intestine cancer, biliary tract cancer, endometrium cancer, skin cancer (melanoma), cervix cancer, urinary tract cancer, glioblastoma, esophageal carcinoma, mesothelioma, or multiple myeloma. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is colon cancer. In some embodiments, the cancer is triple negative breast cancer. In some embodiments, the cancer is multiple myeloma.

In some embodiments, the cancer is lung cancer. In some embodiments, the lung cancer is non-small cell lung cancer (NSCLC). In some embodiments, the lung cancer is small cell lung cancer (SCLC). In some embodiments, the lung cancer is mesothelioma. In some embodiments, the cancer is hepatocellular carcinoma, pancreatic cancer, glioblastoma, esophageal carcinoma, mesothelioma, or small cell lung cancer (SCLC). In some embodiments, the subject is a human.

[00266] Provided herein are methods of inhibiting a proteasome ATPase, comprising contacting a proteasome ATPase with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof. Also provided herein are methods of inhibiting an AAA-ATPase of a 19S regulatory particle, comprising contacting an AAA-ATPase with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof. Also provided herein are methods of inhibiting one or more proteasome ATPases, comprising contacting a proteasome ATPase with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof. Also provided herein are methods of inhibiting one or more AAA-ATPases of a 19S regulatory particle, comprising contacting an AAA-ATPase with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00267] In certain embodiments of the methods of inhibiting a proteasome ATPase and/or an AAA-ATPase of a 19S regulatory particle described herein, the method inhibits ATPase activity. In some embodiments, the method comprises contacting the proteasome ATPase and/or the AAA-ATPase of a 19S regulatory particle with a compound or pharmaceutically acceptable form thereof that inhibits ATPase activity by 33% or more at 100 μ M according to ATPase Activity Inhibition Assay. In some embodiments, the compound is selected from the group consisting of Compounds A, B, 9, and 38, or a pharmaceutically acceptable form thereof. In some embodiments, the compound is a compound specifically disclosed in International Patent

Application PCT/US2023/065530, filed April 7, 2023, now published as WO 2023/196975.

[00268] Provided herein are methods of modulating Erk1/2 activity, comprising contacting an Erk1/2 protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof. Also provided herein are methods of modulating Erk1/2 activity, comprising contacting an Erk1/2 protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, as disclosed herein below. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00269] In certain embodiments of the methods of modulating Erk1/2 activity described herein, the method inhibits phosphorylation of the Erk1/2 protein. In some embodiments, the method comprises contacting the Erk1/2 protein with a compound or pharmaceutically acceptable form thereof that inhibits phosphorylation of the Erk1/2 protein by 50% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 19, 20, 21, 49, 51, 53, 56, 67, 68, 79, 80, 81, 82, 89, and 94, or a pharmaceutically acceptable form thereof.

[00270] In certain embodiments of the methods of modulating Erk1/2 activity described herein, the method activates phosphorylation of the Erk1/2 protein. In some embodiments, the method comprises contacting the Erk1/2 protein with a compound or pharmaceutically acceptable form thereof that activates phosphorylation of the Erk1/2 protein by 50% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 16, 18, 23, 27, 28, 36, 37, 38, 40, 54, 55, 57, 60, 61, 62, 75, and 83, or a pharmaceutically acceptable form thereof.

[00271] In some embodiments of the methods provided herein, the contacting of the Erk1/2 protein takes place in a cell. In some embodiments, the cell is in a subject. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a human cell.

[00272] Provided herein are methods of modulating Akt activity, comprising contacting an

Akt protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof. Also provided herein are methods of modulating Akt activity, comprising contacting an AKT protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, as disclosed herein below. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00273] In certain embodiments of the methods of modulating Akt activity described herein, the method inhibits phosphorylation of the Akt protein. In some embodiments, the method comprises contacting the Akt protein with a compound or pharmaceutically acceptable form thereof that inhibits phosphorylation of the Akt protein by 50% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 19, 20, 49, 51, 53, 56, 79, 80, 81, and 94, or a pharmaceutically acceptable form thereof.

[00274] In certain embodiments of the methods of modulating Akt activity described herein, the method activates phosphorylation of the Akt protein. In some embodiments, the method comprises contacting the Akt protein with a compound or pharmaceutically acceptable form thereof that activates phosphorylation of the Akt protein by 50% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 18, 22, 27, 28, 32, 36, 37, 38, 39, 40, 47, 54, 55, 57, 59, 60, 61, 62, 66, 67, 74, 75, 76, 83, 84, 86, 87, 88, and 91, or a pharmaceutically acceptable form thereof.

[00275] In some embodiments of the methods provided herein, the contacting of the Akt protein takes place in a cell. In some embodiments, the cell is in a subject. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a human cell.

[00276] Provided herein are methods of modulating Smad2/3 activity, comprising contacting a Smad2/3 protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1),

IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof. Also provided herein are methods of modulating Smad2/3 activity, comprising contacting a Smad2/3 protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, as disclosed herein below. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00277] In certain embodiments of the methods of modulating Smad2/3 activity described herein, the method inhibits phosphorylation of the Smad2/3 protein. In some embodiments, the method comprises contacting the Smad2/3 protein with a compound or pharmaceutically acceptable form thereof that inhibits phosphorylation of the Smad2/3 protein by 50% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the method comprises contacting the Smad2/3 protein with a compound or pharmaceutically acceptable form thereof that inhibits phosphorylation of the Smad2/3 protein by 85% or more. In some embodiments, the compound is selected from the group consisting of Compounds 19, 20, 21, 29, 49, 51, 56, 58, 61, 63, 64, 65, 68, 77, 79, 80, 81, 87, 88, 89, and 94, or a pharmaceutically acceptable form thereof.

[00278] In certain embodiments of the methods of modulating Smad2/3 activity described herein, the method activates phosphorylation of the Smad2/3 protein. In some embodiments, the method comprises contacting the Smad2/3 protein with a compound or pharmaceutically acceptable form thereof that activates phosphorylation of the Smad2/3 protein by 50% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound is Compound 12, 14, 25, 26, 31, 32, 33, 37, 78, and 90, or a pharmaceutically acceptable form thereof.

[00279] In some embodiments of the methods provided herein, the contacting of the Smad2/3 protein takes place in a cell. In some embodiments, the cell is in a subject. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a human cell.

[00280] Provided herein are methods of modulating JNK activity, comprising contacting a

JNK protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof. Also provided herein are methods of modulating JNK activity, comprising contacting a JNK protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, as disclosed herein below. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00281] In certain embodiments of the methods of modulating JNK activity described herein, the method inhibits phosphorylation of the JNK protein. In some embodiments, the method comprises contacting the JNK protein with a compound or pharmaceutically acceptable form thereof that inhibits phosphorylation of the JNK protein by 50% or more according to JNK Activation Assay. In some embodiments, the compound is Compound 8, or a pharmaceutically acceptable form thereof.

[00282] In certain embodiments of the methods of modulating JNK activity described herein, the method activates phosphorylation of the JNK protein. In some embodiments, the method comprises contacting the JNK protein with a compound or pharmaceutically acceptable form thereof that activates phosphorylation of the JNK protein by 50% or more according to JNK Activation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, and 7, or a pharmaceutically acceptable form thereof.

[00283] In some embodiments of the methods provided herein, the contacting of the JNK protein takes place in a cell. In some embodiments, the cell is in a subject. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a human cell.

[00284] Provided herein are methods of modulating MAPK p38 activity, comprising contacting a MAPK p38 protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof. Also provided herein are methods of modulating MAPK p38 activity, comprising contacting a MAPK p38 protein with an effective amount of a pharmaceutical composition

comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, as disclosed herein below. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00285] In certain embodiments of the methods of modulating MAPK p38 described herein, the method inhibits phosphorylation of the MAPK p38 protein. In some embodiments, the method comprises contacting the MAPK p38 with a compound or pharmaceutically acceptable form thereof that inhibits phosphorylation of the MAPK p38 by 50% or more at 10 μ M according to MAPK p38 Activation Assay.

[00286] In certain embodiments of the methods of modulating MAPK p38 described herein, the method activates phosphorylation of the MAPK p38 protein. In some embodiments, the method comprises contacting the MAPK p38 with a compound or pharmaceutically acceptable form thereof that activates phosphorylation of the MAPK p38 by 50% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 2, 3, 4, 5, 6, and 7, or a pharmaceutically acceptable form thereof.

[00287] In some embodiments of the methods provided herein, the contacting of the MAPK p38 protein takes place in a cell. In some embodiments, the cell is in a subject. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a human cell.

[00288] Provided herein are methods of modulating IL-6 activity, comprising contacting a IL-6 protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof. Also provided herein are methods of modulating IL-6 activity, comprising contacting a IL-6 protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, as disclosed herein below. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45,

46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00289] In certain embodiments of the methods of modulating IL-6 activity described herein, the method inhibits IL-6 activity. In some embodiments, the method comprises contacting the IL-6 protein with a compound or pharmaceutically acceptable form thereof that inhibits IL-6 activity by 50% or more at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound is selected from the group consisting of Compounds 4, 9, 10, 11, 16, 17, 19, 20, 92, and 94, or a pharmaceutically acceptable form thereof.

[00290] In some embodiments of the methods provided herein, the contacting of the IL-6 protein takes place in a cell. In some embodiments, the cell is in a subject. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a human cell.

[00291] Provided herein are methods of modulating TNF-alpha activity, comprising contacting a TNF-alpha protein with an effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof. Also provided herein are methods of modulating TNF-alpha activity, comprising contacting a TNF-alpha protein with an effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, as disclosed herein below. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00292] In certain embodiments of the methods of modulating IL-6 activity described herein, the method inhibits TNF-alpha activity. In some embodiments, the method comprises contacting the TNF-alpha protein with a compound or pharmaceutically acceptable form thereof that inhibits TNF-alpha activity by 50% or more at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound is Compound 20 and 94, or a pharmaceutically acceptable form thereof.

[00293] In some embodiments of the methods provided herein, the contacting of the TNF-

alpha protein takes place in a cell. In some embodiments, the cell is in a subject. In some embodiments, the cell is a mammalian cell. In some embodiments, the cell is a human cell.

[00294] International Patent Application No. PCT/US2023/65530, filed April 7, 2023, now published as WO 2023/196975, is incorporated herein by reference in its entirety.

3.4. METHODS OF TREATING CANCER

[00295] Without being bound by theory, cancer is characterized primarily by an increase in the number of abnormal cells derived from a given normal tissue, invasion of adjacent tissues by these abnormal cells, or lymphatic or blood-borne spread of malignant cells to regional lymph nodes and to distant sites. Clinical data and molecular biologic studies indicate that cancer is a multistep process that begins with minor preneoplastic changes, which may under certain conditions progress to neoplasia. The neoplastic lesion may evolve clonally and develop an increasing capacity for invasion, growth, metastasis, and heterogeneity, especially under conditions in which the neoplastic cells escape the host's immune surveillance. (Roitt, I., Brostoff, J. and Kale, D., Immunology, 17.1-17.12 (3rd ed., Mosby, St. Louis, Mo., 1993))

[00296] Without being bound by theory, various stages of tumor development can be described generally as follows:

[00297] a) Tumor evolution commences when a cell within a normal population sustains a genetic mutation that expands its tendency to proliferate.

[00298] b) Such genetically altered cells and their offspring continue to appear normal, but they reproduce excessively and lead to a condition termed hyperplasia. The altered cells may also secrete signaling factors or other molecules that cause changes in their local cellular and extracellular environment, including without limitation, the response of the immune system to them. Such environmental effects may in turn affect the viability, proliferation, and further mutations of the altered cells. After some time (months or years) a very small fraction of these altered cells may sustain additional mutation with subsequent loss of control of cell growth and further potential effects on their environment.

[00299] c) The offspring of these cells not only proliferate excessively but also appear abnormal in shape and in orientation. The tissue is now said to exhibit a condition termed dysplasia. After some time, one or more additional mutations may further alter cell behavior and the effect of the cells on their environment.

[00300] d) The influenced and genetically altered cells turn still more abnormal in growth and

appearance. If the tumor mass does not invade through any boundaries between tissues, it is termed an in situ tumor. This tumor may stay contained indefinitely, however, some cells may acquire still more mutations.

[00301] e) A malignant or invasive tumor results if the genetic changes allow the tumor mass to initiate invading underlying tissue and to cast off cells into the blood or lymph. The defector cells may install new tumors loci (metastases) throughout the body.

[00302] Without being bound by theory, metastases represent the end products of a multistep cell-biological process termed the invasion-metastasis cascade, which involves dissemination of cancer cells to anatomically distant organ sites and their subsequent adaptation to foreign tissue microenvironments. Each of these events is driven by the acquisition of genetic and/or epigenetic alterations within tumor cells and the co-option of non-neoplastic stromal cells, which together endow incipient metastatic cells with traits needed to generate macroscopic metastases.

(Volastyan, S., et al., Cell, 2011, vol. 147, 275-292)

[00303] Without being bound by theory, an enormous variety of cancers affect different tissues throughout the body, which are described in detail in the medical literature. Over 85% of human cancers are solid tumors, including carcinomas, sarcomas and lymphomas. Different types of solid tumors are named for the type of cells that form them. Examples include cancer of the lung, colon, rectum, pancreatic, prostate, breast, brain, and intestine. Other human tumors derive from cells involved in the formation of immune cells and other blood cells, including leukemias and myelomas.

[00304] The incidence of cancer continues to climb as the general population ages, as new cancers develop, and as susceptible populations grow. A tremendous demand therefore exists for new methods and compositions that can be used to treat subjects with cancer.

[00305] Without being bound by theory, current cancer therapy may involve surgery, chemotherapy, hormonal therapy, biological therapy, targeted therapy, immunotherapy and/or radiation treatment to eradicate neoplastic cells in a patient (see, e.g., Stockdale, 1998, Medicine, vol. 3, Rubenstein and Federman, eds., Chapter 12, Section IV; and Baudino TA “Targeted Cancer Therapy: The Next Generation of Cancer Treatment”, Curr Drug Discov Technol. 2015; 12(1):3-20).

[00306] Without being bound by theory, such therapies may be used independently or in combinations. Choices of therapy will depend on the history and nature of the cancer, the

condition of the patient, and, under the circumstances, the anticipated efficacy and adverse effects of the therapeutic agents and methods considered.

[00307] Without being bound by theory, with respect to chemotherapy, there are a variety of chemotherapeutic agents and methods of delivery of such agents available for the treatment of different cancers. Most first generation chemotherapeutic agents were not tumor specific, have broad systemic effects, are toxic, and may cause significant and often dangerous side effects, including severe nausea, bone marrow depression, and immunosuppression.

[00308] Without being bound by theory, even with administration of combinations of chemotherapeutic agents, many tumor cells are or become resistant to chemotherapeutic agents. In fact, cells resistant to the particular chemotherapeutic agents used in a treatment protocol often prove to be resistant to other drugs, even if those agents act by different mechanism from those of the drugs used in the specific treatment. This phenomenon is referred to as multidrug resistance. Because of drug resistance, many cancers prove refractory to standard chemotherapeutic treatment protocols.

[00309] Thus, there exists a significant need for alternative compounds, compositions and methods for treating, preventing and managing cancer.

[00310] Without being bound by theory, whereas surgical resection and adjuvant therapy can cure well-confined primary tumors, metastatic disease is largely incurable because of its systemic nature and the resistance of disseminated tumor cells to existing therapeutic agents. This explains why greater than 90% of mortality from cancer is attributable to metastases, not the primary tumors from which these malignant lesions arise.

[00311] Provided herein are methods of treating cancer in a subject, comprising administering a therapeutically effective amount of the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, to the subject having cancer. Also provided herein are methods of treating cancer in a subject, comprising administering a therapeutically effective amount of a pharmaceutical comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, as disclosed herein below, to the subject having cancer. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59,

60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00312] In some embodiments of the methods of treating cancer provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates the activity of one or more Ras superfamily protein. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits the activity one or more Ras superfamily protein. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates the activity of one or more Ras superfamily protein by 45% or more at 20 μ M according to a Ras Superfamily Activity. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates the activity of one or more Ras superfamily protein by 50% or more at 20 μ M according to a Ras Superfamily Activity. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 9, 10, 11, 12, 13, 16, 18, 22, 23, 24, 27, 28, 32, 33, 36, 37, 38, 39, 40, 57, 62, 75, 84, 86, and 92, or a pharmaceutically acceptable form thereof.

[00313] In some embodiments of the methods of treating cancer provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates Erk1/2 activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Erk1/2 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Erk1/2 protein by 80% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Erk1/2 protein by 85% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 19, 20, 21, 49, 51, 53, 56, 67, 68, 79, 80, 81, 82, 89, and 94, or a

pharmaceutically acceptable form thereof. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Erk1/2 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Erk1/2 protein by 45% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Erk1/2 protein by 50% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 16, 18, 23, 27, 28, 36, 37, 38, 40, 54, 55, 57, 60, 61, 62, 75, and 83, or a pharmaceutically acceptable form thereof.

[00314] In some embodiments of the methods of treating cancer provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates Akt activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Akt protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Akt protein by 85% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 19, 20, 49, 51, 53, 56, 79, 80, 81, and 94, or a pharmaceutically acceptable form thereof. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Akt protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Akt protein by 50% or more at 10 μ M according to

Akt Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 18, 22, 27, 28, 32, 36, 37, 38, 39, 40, 47, 54, 55, 57, 59, 60, 61, 62, 66, 67, 74, 75, 76, 83, 84, 86, 87, 88, and 91, or a pharmaceutically acceptable form thereof.

[00315] In some embodiments of the methods of treating cancer provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates Smad2/3 activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Smad2/3 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Smad2/3 protein by 80% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Smad2/3 protein by 85% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound is selected from the group consisting of Compounds 19, 20, 21, 29, 49, 51, 56, 58, 61, 63, 64, 65, 68, 77, 79, 80, 81, 87, 88, 89, and 94, or a pharmaceutically acceptable form thereof. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Smad2/3 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Smad2/3 protein by 50% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound is Compound 12, 14, 25, 26, 31, 32, 33, 37, 78, and 90, or a pharmaceutically acceptable form thereof.

[00316] In some embodiments of the methods of treating cancer provided herein, the method administering a compound or pharmaceutically acceptable form that modulates JNK activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by

50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the JNK protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the JNK protein by 50% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound is Compound 8, or a pharmaceutically acceptable form thereof. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the JNK protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the JNK protein by about 50% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, and 7, or a pharmaceutically acceptable form thereof.

[00317] In some embodiments of the methods of treating cancer provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates MAPK p38 activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the MAPK p38 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the MAPK p38 by about 50% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the MAPK p38 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof

activates phosphorylation of the MAPK p38 by 50% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 2, 3, 4, 5, 6, and 7, or a pharmaceutically acceptable form thereof.

[00318] In some embodiments, the compounds disclosed herein inhibit cell proliferation, such as inhibit cell proliferation in a cell viability assay. In some embodiments, the anti-proliferative activity of the compounds disclosed herein are administered according to the methods of treating disclosed herein to treat cancer, including solid, soft and blood-born tumors. In some embodiments of the methods of treating cancer provided herein, the method administering a compound or pharmaceutically acceptable form thereof that inhibits proliferation in MiaPaca2. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 1.25 μ M or less, 1.1 μ M or less, 1 μ M or less, 0.9 μ M or less, 0.8 μ M or less, 0.75 μ M or less, 0.7 μ M or less, 0.6 μ M or less, 0.5 μ M or less, 0.4 μ M or less, 0.3 μ M or less, 0.25 μ M or less, 0.2 μ M or less, 0.15 μ M or less, 0.1 μ M or less, 0.09 μ M or less, 0.05 μ M or less, or 0.03 μ M or less, according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 1.1 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 1.0 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.60 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.15 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.1 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.09 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.05 μ M or less according to Proliferation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 0.03 μ M or less according to Proliferation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 3, 4, 9, 10,

11, 12, 13, 16, 18, 19, 22, 23, 28, 31, 32, 36, 37, 38, 39, 40, 47, 48, 49, 52, 57, 62, 65, 68, 75, 80, 81, 82, 83, 85, 87, and 94, or a pharmaceutically acceptable form thereof. In some embodiments, the compound is selected from the group consisting of Compounds 9, 10, 11, 16, 18, 19, 36, 37, 38, 39, 40, 62, and 65, or a pharmaceutically acceptable form thereof. In some embodiments, the compound is selected from the group consisting of Compounds 9, 10, and 11, or a pharmaceutically acceptable form thereof. In some embodiments, the compound is selected from the group consisting of Compounds 36, 37, 38, 39, 40, and 62, or a pharmaceutically acceptable form thereof.

[00319] In some embodiments of the methods provided herein, the cancer is a solid tumor. In some embodiments, the cancer is a blood borne tumor (or a hematological cancer). In some embodiments, the cancer is hepatocellular carcinoma, prostate cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, colon cancer, small intestine cancer, biliary tract cancer, endometrium cancer, skin cancer (melanoma), cervix cancer, urinary tract cancer, glioblastoma, esophageal carcinoma, mesothelioma, or multiple myeloma. In some embodiments, the cancer is pancreatic cancer. In some embodiments, the cancer is colon cancer. In some embodiments, the cancer is triple negative breast cancer. In some embodiments, the cancer is multiple myeloma. In some embodiments, the cancer is lung cancer. In some embodiments, the lung cancer is non-small cell lung cancer (NSCLC). In some embodiments, the lung cancer is small cell lung cancer (SCLC). In some embodiments, the lung cancer is mesothelioma. In some embodiments, the cancer is hepatocellular carcinoma, pancreatic cancer, glioblastoma, esophageal carcinoma, mesothelioma, or small cell lung cancer (SCLC).

[00320] In some embodiments of the methods provided herein, the cancer is a cancer dependent on a Ras superfamily protein. In some embodiments, the Ras superfamily protein is a Ras protein, or a mutant thereof. In some embodiments, the Ras protein is DIRAS I; DIRAS2; DIRAS3; ERAS; GEM; HRAS; KRAS; MRAS; NKIRASI; NKIRAS2; NRAS; RALA; RALB; RAPIA; RAPIB; RAP2A; RAP2B; RAP2C; RASDI; RASD2; RASL10A; RASL10B; RASL11A; RASL11B; RASL12; REMI; REM2; RERG; RERGL; RRAD; RRAS; or RRAS2. In some embodiments, the Ras protein is HRAS; KRAS; or NRAS, or a mutant thereof. In some embodiments, the Ras protein is a KRAS mutant. In some embodiments, the KRAS mutant is a KRas G12D mutant, KRas G12C mutant, or KRas Q61H mutant. In some embodiments, the Ras protein is HRAS or a mutant thereof. In some embodiments, the Ras protein is NRAS or a

mutant thereof. In some embodiments, the Ras superfamily protein is a Rac protein, or a mutant thereof. In some embodiments, the Rac protein is RAC1; RAC2; RAC3; RHOG, or a mutant thereof. In some embodiments, the the Rac protein is wild-type RAC1. In some embodiments, the Ras superfamily protein is a Rho protein, or a mutant thereof. In some embodiments, the Rho protein is RHOA; RHOB; RHOBTB1; RHOBTB2; RHOBTB3; RHOC; RHOD; RHOF; RHOH; RHOJ; RHOQ; RHOU; RHOV; RND1; RND2; RND3; CDC42, or a mutant thereof. In some embodiments, the Rho protein is wild-type RHOA. In some embodiments, the Ras superfamily protein is a Cdc42 protein, or a mutant thereof. In some embodiments, the Ras superfamily protein is a Rheb protein, or a mutant thereof.

[00321] In some embodiments of the methods provided herein, the administration activates caspase activity in a cancerous cell of the subject. In some embodiments, the activation induces apoptosis of the cancerous cell. In some embodiments, the subject is a human.

[00322] Also provided herein are methods of treating subjects who have been previously treated for cancer but are non-responsive to standard therapies, as well as those who have not previously been treated. Also provided are methods of treating subjects regardless of subject's age, although some diseases or disorders are more common in certain age groups. Also provided are methods of treating subjects who have undergone surgery in an attempt to treat the disease or condition at issue, as well as those who have not. Because subjects with cancer have heterogeneous clinical manifestations and varying clinical outcomes, the treatment given to a subject may vary, depending on his/her prognosis. The skilled clinician will be able to readily determine without undue experimentation specific secondary agents, types of surgery, and types of non-drug based standard therapy that can be effectively used to treat an individual subject with cancer.

[00323] As used herein, the term "cancer" includes, but is not limited to, solid tumors and blood borne tumors. The term "cancer" refers to disease of skin tissues, organs, blood, and vessels, including, but not limited to, cancers of the bladder, bone, blood, brain, breast, cervix, chest, colon, endometrium, esophagus, eye, head, kidney, liver, lymph nodes, lung, mouth, neck, ovaries, pancreas, prostate, rectum, stomach, testis, throat, and uterus. Specific cancers include, but are not limited to, advanced malignancy, amyloidosis, neuroblastoma, meningioma, hemangiopericytoma, multiple brain metastase, glioblastoma multiforms, glioblastoma, brain stem glioma, poor prognosis malignant brain tumor, malignant glioma, recurrent malignant

glioma, anaplastic astrocytoma, anaplastic oligodendroglioma, neuroendocrine tumor, rectal adenocarcinoma, Dukes C & D colorectal cancer, unresectable colorectal carcinoma, metastatic hepatocellular carcinoma, Kaposi's sarcoma, karotype acute myeloblastic leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, cutaneous T-Cell lymphoma, cutaneous B-Cell lymphoma, diffuse large B-Cell lymphoma, low grade follicular lymphoma, malignant melanoma, malignant mesothelioma, malignant pleural effusion mesothelioma syndrome, peritoneal carcinoma, papillary serous carcinoma, gynecologic sarcoma, soft tissue sarcoma, scleroderma, cutaneous vasculitis, Langerhans cell histiocytosis, leiomyosarcoma, fibrodysplasia ossificans progressive, hormone refractory prostate cancer, resected high-risk soft tissue sarcoma, unresectable hepatocellular carcinoma, Waldenstrom's macroglobulinemia, smoldering myeloma, indolent myeloma, fallopian tube cancer, androgen independent prostate cancer, androgen dependent stage IV non-metastatic prostate cancer, hormone-insensitive prostate cancer, chemotherapy-insensitive prostate cancer, papillary thyroid carcinoma, follicular thyroid carcinoma, medullary thyroid carcinoma, and leiomyoma.

[00324] In certain embodiments, the cancer is a solid tumor. In certain embodiments, the solid tumor is metastatic. In certain embodiments, the solid tumor is drug-resistant. In certain embodiments, the solid tumor is hepatocellular carcinoma, prostate cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, colon cancer, small intestine cancer, biliary tract cancer, endometrium cancer, skin cancer (melanoma), cervix cancer, urinary tract cancer, glioblastoma, esophageal carcinoma, mesothelioma, or multiple myeloma. In some embodiments, the solid tumor is lung cancer. In some embodiments, the lung cancer is non-small cell lung cancer (NSCLC). In some embodiments, the lung cancer is small cell lung cancer (SCLC). In some embodiments, the lung cancer is mesothelioma. In some embodiments, the cancer is hepatocellular carcinoma, pancreatic cancer, glioblastoma, esophageal carcinoma, mesothelioma, or small cell lung cancer (SCLC).

[00325] In certain embodiments, the cancer is a blood borne tumor (or a hematological cancer). In certain embodiments, the blood borne tumor is metastatic. In certain embodiments, the blood borne tumor is drug resistant. In certain embodiments, the cancer is leukemia. In certain embodiments, the cancer is multiple myeloma.

[00326] In some embodiments, methods provided herein encompass treating, preventing or managing various types of leukemias such as chronic lymphocytic leukemia (CLL), chronic

myelocytic leukemia (CML), acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and acute myeloblastic leukemia (AML) by administering a therapeutically effective amount of a compound provided herein or a derivative thereof.

[00327] In some embodiments, the methods provided herein encompass treating, preventing or managing acute leukemia in a subject. In some embodiments, the acute leukemia is acute myeloid leukemia (AML), which includes, but is not limited to, undifferentiated AML (M0), myeloblastic leukemia (M1), myeloblastic leukemia (M2), promyelocytic leukemia (M3 or M3 variant (M3V)), myelomonocytic leukemia (M4 or M4 variant with eosinophilia (M4E)), monocytic leukemia (M5), erythroleukemia (M6), and megakaryoblastic leukemia (M7). In some embodiments, the acute myeloid leukemia is undifferentiated AML (M0). In some embodiments, the acute myeloid leukemia is myeloblastic leukemia (M1). In some embodiments, the acute myeloid leukemia is myeloblastic leukemia (M2). In some embodiments, the acute myeloid leukemia is promyelocytic leukemia (M3 or M3 variant (M3V)). In some embodiments, the acute myeloid leukemia is myelomonocytic leukemia (M4 or M4 variant with eosinophilia (M4E)). In some embodiments, the acute myeloid leukemia is monocytic leukemia (M5). In some embodiments, the acute myeloid leukemia is erythroleukemia (M6). In some embodiments, the acute myeloid leukemia is megakaryoblastic leukemia (M7). Thus, the methods of treating, preventing or managing acute myeloid leukemia in a subject comprise the step of administering to the subject an amount of a compound provided herein or a derivative thereof effective to treat, prevent or manage acute myeloid leukemia alone or in combination. In some embodiments, the methods comprise the step of administering to the subject a compound provided herein or a derivative thereof in combination with a second active agent in amounts effective to treat, prevent or manage acute myeloid leukemia.

[00328] In some embodiments, the methods provided herein encompass treating, preventing or managing acute lymphocytic leukemia (ALL) in a subject. In some embodiments, acute lymphocytic leukemia includes leukemia that originates in the blast cells of the bone marrow (B-cells), thymus (T-cells), and lymph nodes. The acute lymphocytic leukemia can be categorized according to the French-American-British (FAB) Morphological Classification Scheme as L1 - Mature-appearing lymphoblasts (T cells or pre-B-cells), L2 - Immature and pleomorphic (variously shaped) lymphoblasts (T-cells or pre-B-cells), and L3 - Lymphoblasts (B-cells; Burkitt's cells). In some embodiments, the acute lymphocytic leukemia originates in the blast

cells of the bone marrow (B-cells). In some embodiments, the acute lymphocytic leukemia originates in the thymus (T-cells). In some embodiments, the acute lymphocytic leukemia originates in the lymph nodes. In some embodiments, the acute lymphocytic leukemia is L1 type characterized by mature-appearing lymphoblasts (T-cells or pre-B-cells). In some embodiments, the acute lymphocytic leukemia is L2 type characterized by immature and pleomorphic (variously shaped) lymphoblasts (T-cells or pre-B-cells). In some embodiments, the acute lymphocytic leukemia is L3 type characterized by lymphoblasts (B-cells; Burkitt's cells). In certain embodiments, the acute lymphocytic leukemia is T cell leukemia. In some embodiments, the T-cell leukemia is peripheral T-cell leukemia. In another embodiment, the T-cell leukemia is T-cell lymphoblastic leukemia. In another embodiment, the T-cell leukemia is cutaneous T-cell leukemia. In another embodiment, the T-cell leukemia is adult T-cell leukemia. Thus, the methods of treating, preventing or managing acute lymphocytic leukemia in a subject comprise the step of administering to the subject an amount of a compound provided herein or a derivative thereof effective to treat, prevent or manage acute lymphocytic leukemia alone or in combination with a second active agent. In some embodiments, the methods comprise the step of administering to the subject a compound provided herein or a derivative thereof in combination with a second active agent in amounts effective to treat, prevent or manage acute lymphocytic leukemia.

[00329] In some embodiments, the methods provided herein encompass treating, preventing or managing chronic myelogenous leukemia (CML) in a subject. The methods comprise the step of administering to the subject an amount of a compound provided herein or a derivative thereof effective to treat, prevent or manage chronic myelogenous leukemia. In some embodiments, the methods comprise the step of administering to the subject a compound provided herein or a derivative thereof in combination with a second active agent in amounts effective to treat, prevent or manage chronic myelogenous leukemia.

[00330] In some embodiments, the methods provided herein encompass treating, preventing or managing chronic lymphocytic leukemia (CLL) in a subject. The methods comprise the step of administering to the subject an amount of a compound provided herein or a derivative thereof effective to treat, prevent or manage chronic lymphocytic leukemia. In some embodiments, the methods comprise the step of administering to the subject a compound provided herein or a derivative thereof in combination with a second active agent in amounts effective to treat,

prevent or manage chronic lymphocytic leukemia.

[00331] In certain embodiments, provided herein are methods of treating, preventing, and/or managing disease in subjects with impaired renal function. In certain embodiments, provided herein are method of treating, preventing, and/or managing cancer in subjects with impaired renal function. In certain embodiments, provided herein are methods of providing appropriate dose adjustments for subjects with impaired renal function due to, but not limited to, disease, aging, or other subject factors.

[00332] In certain embodiments, provided herein are methods of treating, preventing, and/or managing lymphoma, including non-Hodgkin's lymphoma. In some embodiments, provided herein are methods for the treatment or management of non-Hodgkin's lymphoma (NHL), including but not limited to, diffuse large B-cell lymphoma (DLBCL), using prognostic factors.

[00333] In certain embodiments, provided herein are methods of treating, preventing, and/or managing multiple myeloma, including relapsed/refractory multiple myeloma in subjects with impaired renal function or a symptom thereof, comprising administering a therapeutically effective amount of a compound provided herein, or a derivative thereof to a subject having relapsed/refractory multiple myeloma with impaired renal function.

[00334] In certain embodiments, the subject to be treated with one of the methods provided herein has not been treated with anticancer therapy prior to the administration of the compound provided herein, or a derivative thereof. In certain embodiments, the subject to be treated with one of the methods provided herein has been treated with anticancer therapy prior to the administration of the compound provided herein, or a derivative thereof. In certain embodiments, the subject to be treated with one of the methods provided herein has developed drug resistance to the anticancer therapy.

[00335] The methods provided herein encompass treating a patient regardless of subject's age, although some diseases or disorders are more common in certain age groups.

[00336] As discussed herein, Ras signaling is causally implicated in rasopathies. Thus, the compounds provided herein, which inhibit the function of one or more members of the Ras superfamily, are useful in the treatment of rasopathies including neurofibromatosis type 1, Noonan's syndrome, and Costello syndrome.

3.5. METHODS OF TREATING FIBROSIS

[00337] Fibrosis, or the accumulation of extracellular matrix molecules that constitute scar

tissue, is a common result of tissue injury. Fibrosis can occur in many tissues within the body, typically as a result of inflammation or damage. Pulmonary fibrosis, renal fibrosis, and hepatic cirrhosis are among the common fibrotic diseases which altogether represent a large unmet medical need. (Friedman SL, Sheppard D, Duffield JS, Violette S. *Sci Transl Med* 2013 Jan9; 5(167): 167sr1).

[00338] Without being bound by theory, fibrosis, also known as fibrotic scarring, is a pathological wound healing process in which connective tissue replaces normal parenchymal tissue, leading to considerable tissue re-modeling and the formation of permanent scar tissue. Repeated injuries, chronic inflammation and repair are susceptible to fibrosis where excessive extracellular matrix (ECM) components, such as collagen and glycosaminoglycans, accumulate and lead to the formation of a permanent fibrotic scar which can interfere with normal organ and tissue functions. Mechanisms of fibrogenesis include inflammation as well as other pathways and generally involve reorganization of the actin cytoskeleton of affected cells, including epithelial cells, fibroblasts, endothelial cells, and macrophages.

[00339] Without being bound by theory, actin filament assembly and actomyosin contraction are directed by the Rho-associated coiled-coil forming protein kinase (ROCK) family of serine/threonine kinases (ROCK1 and ROCK2) and thus Rho is associated with fibrogenesis.

[00340] Tissue fibrosis is a leading cause of morbidity and mortality. 45% of deaths in the United States are attributable to fibrotic disorders. (Wynn TA. "Fibrotic Disease and the TH1/TH2 Paradigm." *Nat Rev Immunol* 2004 Aug; 4(8): 583-594.) Treatments are generally palliative.

[00341] Without being bound by theory, idiopathic pulmonary fibrosis (IPF) is characterized by progressive lung scarring, short median survival, and limited therapeutic options, creating great need for new pharmacologic therapies. It is thought to result from repetitive environmental injury to the lung epithelium.

[00342] As noted above, fibrosis can occur in many tissues within the body, typically as a result of inflammation or damage. Examples include: fibrosis of kidney, fibrosis of cardiovascular system, pulmonary fibrosis, cystic fibrosis, idiopathic fibrosis, fibrosis of the lung, bridging fibrosis, fibrosis of the liver, fibrosis of the intestine, fibrosis of the muscular system, fibrosis of the brain, fibrosis of the joints, fibrosis of the skin, fibrosis of the bone marrow, fibrosis of the heart, fibrosis of the soft tissue, fibrosis of the tendons, fibrosis of the

lymph nodes, fibrosis of the eyes, retroperitoneum, scleroderma and surgical scarring.

[00343] Without being bound by theory, the process of tissue repair is a complex one, with tight regulation of ECM synthesis and degradation ensuring maintenance of normal tissue architecture. However, the process can lead to a progressive irreversible fibrotic response if tissue injury is severe or repetitive, or if the wound healing response itself becomes deregulated. Fibrosis is initiated when immune cells such as macrophages and damaged tissue between surfaces called interstitium release soluble factors that stimulate fibroblasts. The best characterized pro-fibrotic mediators are the transforming growth factor- β (TGF- β ligands such as TGF- β 1, - β 2 and - β 3, bone morphogenetic proteins (BMPs), and Activin.

[00344] Without being bound by theory, the pro-fibrotic TGF- β and its related ligands bind a heteromeric complex of type I and type II trans-membrane TGF- β receptors, each equipped with an intracellular kinase domain. Upon ligand binding the type II receptor kinases phosphorylate and thereby activate the type I receptors, which are also known as activin receptor-like kinases (ALKs). Downstream of this activated complex, a canonical signaling pathway is composed of the Smad family of transcription factors, among which Smad2 and Smad3 are phosphorylated and activated by type I TGF- β receptors. Activated Smad2/3 (RSmads) form a trimeric complex with Smad4 that translocates to the nucleus to regulate target gene expression.

[00345] Without being bound by theory, other soluble mediators of fibrosis include connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), and interleukin 10 (IL-10).

[00346] Without being bound by theory, inhibition of the TGF- β 1 signaling pathway and Smad2 and 3 phosphorylation and activation represent potential therapeutic approaches for treating fibrosis.

[00347] Duchenne muscular dystrophy (DMD) is a genetic disorder characterized by progressive muscle degeneration and weakness due to the alterations of a protein called *dystrophin* that helps keep muscle cells intact. DMD is one of four conditions known as dystrophinopathies. Three diseases that belong to this group are Becker Muscular Dystrophy (BMD, a mild form of DMD); an intermediate clinical presentation between DMD and BMD; and DMD-associated dilated cardiomyopathy (heart-disease) with little or no clinical skeletal, or voluntary, muscle disease.

[00348] DMD primarily affects boys, but in rare cases it can affect girls. In Europe and North

America, the prevalence of DMD is approximately 6 per 100,000 individuals.

[00349] Muscle weakness is the principal symptom of DMD. Symptom onset is in early childhood, usually between ages 2 and 3. The disease first affects the proximal muscles, and later the distal limb muscles. Usually, the lower external muscles are affected before the upper external muscles. Later on, the heart and respiratory muscles are affected. Progressive weakness and scoliosis result in impaired pulmonary function, which can eventually cause acute respiratory failure. Becker muscular dystrophy (BMD) is similar to DMD, but with onset usually in the teens or early adulthood. The disease course for BMD is slower and less predictable compared to DMD.

[00350] DMD was first described by the French neurologist Guillaume Benjamin Amand Duchenne in the 1860s, but until the 1980s little was known about the cause of any kind of muscular dystrophy. In 1986, researchers identified a particular gene on the X chromosome that, when mutated, leads to DMD. In 1987, the protein associated with this gene was identified and named *dystrophin*. Lack of wild type dystrophin protein in muscle cells causes them to be fragile and easily damaged. DMD has an X-linked recessive inheritance pattern and is passed on by the mother, who is referred to as a *carrier*.

[00351] Until relatively recently, boys with DMD usually did not survive much beyond their teen years. Thanks to advances in cardiac and respiratory care, and targeted therapeutic products, life expectancy is increasing and survival into the early 30s is becoming more common but there is still an unmet need for therapeutics to reduce morbidity and lengthen lifespans.

[00352] Without being bound by theory, when skeletal muscle is unable to regenerate due to DMD, damaged muscle is eventually replaced with fibrotic tissue. Development of this fibrosis is partially mediated by the TGF- β 1 signaling pathway, which, therefore may be a therapeutic target for DMD.

[00353] Without being bound by theory, a growing number of published studies also suggest that pharmacological activation of the stress-activated MAPK proteins p-38 MAPK and c-Jun NH₂-terminal kinase (JNK) may also represent a therapeutic approach for the treatment of DMD related fibrosis.

[00354] Without being bound by theory, targeted therapies are a cornerstone of what is also referred to as precision medicine, a form of medicine that uses information about a person's genes and proteins to prevent, diagnose, and treat disease. Such therapeutics are sometimes

called "molecularly targeted drugs," "molecularly targeted therapies," or similar names. The process of discovering them is often referred to as "rational drug design." This concept can also be referred to as "personalized medicine."

[00355] Without being bound by theory, a series of actions among molecules in a cell that leads to a certain end point or cell function is referred to as a molecular pathway.

[00356] Without being bound by theory, molecularly targeted drugs interact with a particular target molecule, or structurally related set of target molecules, in a pathway; thus modulating the endpoint effect of that pathway, such as a disease-related process; and, thus, yielding a therapeutic benefit.

[00357] Without being bound by theory, molecularly targeted drugs may be small molecules or biologics, usually antibodies. They may be useful alone or in combinations with other therapeutic agents and methods.

[00358] Without being bound by theory, because they target a particular molecule, or related set of molecules, and are usually designed to minimize their interactions with other molecules, targeted therapeutics may have fewer adverse side effects.

[00359] Without being bound by theory, some treatments for fibrotic disorders, such as idiopathic pulmonary fibrosis, hepatic fibrosis, and systemic sclerosis, target inflammatory pathways.

[00360] Provided herein are methods of treating a fibrotic disease in a subject, comprising administering a therapeutically effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, to the subject. Also provided herein are methods treating a fibrotic disease in a subject, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, to the subject. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00361] In some embodiments of the methods of treating a fibrotic disease provided herein,

the method administering a compound or pharmaceutically acceptable form thereof that modulates the activity of one or more Ras superfamily protein. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates the activity of one or more Ras superfamily protein by 50% or more at 20 μ M according to a Ras Superfamily Activity. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 9, 10, 11, 12, 13, 16, 18, 22, 23, 24, 27, 28, 32, 33, 36, 37, 38, 39, 40, 57, 62, 75, 84, 86, and 92, or a pharmaceutically acceptable form thereof.

[00362] In some embodiments of the methods of treating a fibrotic disease provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates Erk1/2 activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Erk1/2 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Erk1/2 protein by 80% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Erk1/2 protein by 85% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 19, 20, 21, 49, 51, 53, 56, 67, 68, 79, 80, 81, 82, 89, and 94, or a pharmaceutically acceptable form thereof. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Erk1/2 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Erk1/2

protein by 45% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Erk1/2 protein by 50% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 16, 18, 23, 27, 28, 36, 37, 38, 40, 54, 55, 57, 60, 61, 62, 75, and 83, or a pharmaceutically acceptable form thereof.

[00363] In some embodiments of the methods of treating a fibrotic disease provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates Akt activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Akt protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Akt protein by 85% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 19, 20, 49, 51, 53, 56, 79, 80, 81, and 94, or a pharmaceutically acceptable form thereof. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Akt protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Akt protein by 50% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 18, 22, 27, 28, 32, 36, 37, 38, 39, 40, 47, 54, 55, 57, 59, 60, 61, 62, 66, 67, 74, 75, 76, 83, 84, 86, 87, 88, and 91, or a pharmaceutically acceptable form thereof.

[00364] In some embodiments of the methods of treating a fibrotic disease provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates Smad2/3 activity. In some embodiments, the compound or pharmaceutically

acceptable form thereof inhibits phosphorylation of the Smad2/3 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Smad2/3 protein by 80% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Smad2/3 protein by 85% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound is selected from the group consisting of Compounds 19, 20, 21, 29, 49, 51, 56, 58, 61, 63, 64, 65, 68, 77, 79, 80, 81, 87, 88, 89, and 94, or a pharmaceutically acceptable form thereof. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Smad2/3 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Smad2/3 protein by 50% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound is Compound 12, 14, 25, 26, 31, 32, 33, 37, 78, and 90, or a pharmaceutically acceptable form thereof.

[00365] In some embodiments of the methods of treating a fibrotic disease provided herein, the method administering a compound or pharmaceutically acceptable form that modulates JNK activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the JNK protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the JNK protein by 50% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound is Compound 8, or a pharmaceutically acceptable form thereof. In some embodiments, the

compound or pharmaceutically acceptable form thereof activates phosphorylation of the JNK protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the JNK protein by about 50% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, and 7, or a pharmaceutically acceptable form thereof.

[00366] In some embodiments of the methods of treating a fibrotic disease provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates MAPK p38 activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the MAPK p38 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the MAPK p38 by 50% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the MAPK p38 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the MAPK p38 by 50% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 2, 3, 4, 5, 6, and 7, or a pharmaceutically acceptable form thereof.

[00367] In some embodiments of the methods of treating a fibrotic disease provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates IL-6 activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6. In some embodiments, the compound or pharmaceutically acceptable

form thereof inhibits IL-6 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by 75% or more at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound is selected from the group consisting of Compounds 4, 9, 10, 11, 16, 17, 19, 20, 92, and 94, or a pharmaceutically acceptable form thereof.

[00368] In some embodiments of the methods of treating a fibrotic disease provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates TNF-alpha activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by 75% or more at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound is Compound 20 and 94, or a pharmaceutically acceptable form thereof.

[00369] In some embodiments, the compound of Formula I administered according to any of the methods disclosed herein treats, prevents, or inhibits fibrosis in the subject. In some embodiments, the compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, administered according to any of the methods disclosed herein inhibits fibrosis in the liver, lung, skin, soft tissue, tendons, lymph nodes, lung, kidney, heart, eye, or retroperitoneum of said subject. In some embodiments, the compound administered according to any of the methods disclosed herein treats, prevents, or ameliorates one or more symptoms of a fibrotic disease in the subject. In some embodiments, the compound administered according to any of the methods disclosed herein treats, prevents, or ameliorates the fibrotic disease in the subject. In some embodiments, the fibrotic disease is selected from the group consisting of fibrosis of kidney, fibrosis of cardiovascular system, pulmonary fibrosis, cystic fibrosis, idiopathic fibrosis, fibrosis of the lung, bridging fibrosis, fibrosis of the liver, fibrosis of the intestine, fibrosis of the muscular system, fibrosis of the brain, fibrosis of the joints, fibrosis of the skin, fibrosis of the bone marrow, fibrosis of the heart,

fibrosis of the soft tissue, fibrosis of the tendons, fibrosis of the lymph nodes, fibrosis of the eyes, retroperitoneum, scleroderma and surgical scarring. In some embodiments, the fibrotic disease is fibrosis of the kidney. In some embodiments, the fibrosis of the kidney is progressive kidney disease. In some embodiments, the fibrotic disease is fibrosis of the cardiovascular system. In some embodiments, the fibrosis of the cardiovascular system is atherosclerosis or restenosis. In some embodiments, the fibrotic disease is pulmonary fibrosis. In some embodiments, the fibrotic disease is cystic fibrosis. In some embodiments, the fibrotic disease is idiopathic fibrosis. In some embodiments, the idiopathic fibrosis is idiopathic pulmonary fibrosis. In some embodiments, the fibrotic disease is fibrosis of the lung. In some embodiments, the fibrosis of the lung is progressive massive fibrosis and radiation-induced lung injury. In some embodiments, the fibrotic disease is bridging fibrosis. In some embodiments, the fibrotic disease is fibrosis of the liver. In some embodiments, the fibrosis of the liver is cirrhosis. In some embodiments, the fibrotic disease is fibrosis of the intestine. In some embodiments, the fibrosis of the intestine is Crohn's disease. In some embodiments, the fibrotic disease is fibrosis of the muscular system. In some embodiments, the fibrosis of the muscular system is Duchenne muscular dystrophy (DMD). In some embodiments, the Duchenne muscular dystrophy is Becker Muscular Dystrophy (BMD), an intermediate clinical presentation between DMD and BMD, or DMD-associated dilated cardiomyopathy. In some embodiments, the fibrotic disease is fibrosis of the brain. In some embodiments, the fibrosis of the brain is glial scar. In some embodiments, the fibrotic disease is fibrosis of the joints. In some embodiments, the fibrosis of the joints is arterial stiffness. In some embodiments, the fibrosis of the joints is fibrosis of the knee. In some embodiments, the fibrosis of the joints is fibrosis of the shoulder. In some embodiments, the fibrotic disease is fibrosis of the skin. In some embodiments, the fibrosis of the skin is Keloid. In some embodiments, the fibrotic disease is fibrosis of the bone marrow. In some embodiments, the fibrosis of the bone marrow is Myelofibrosis. In some embodiments, the fibrotic disease is fibrosis of the heart. In some embodiments, the fibrosis of the heart is Myocardial fibrosis. In some embodiments, the fibrotic disease is fibrosis of the soft tissue. In some embodiments, the fibrotic disease is fibrosis of the tendons. In some embodiments, the fibrotic disease is fibrosis of the lymph nodes. In some embodiments, the fibrotic disease is fibrosis of the eyes. In some embodiments, the fibrotic disease is retroperitoneum. In some embodiments, the fibrotic disease is scleroderma. In some embodiments, the fibrotic disease is surgical scarring.

3.6. METHODS OF TREATING INFLAMMATION

[00370] Inflammation is a complex protective biological response of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants, involving immune cells, blood vessels, and molecular mediators. The function of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues damaged from the original insult and the inflammatory process, and to initiate tissue repair. (Ferrero-Miliani L, Nielsen OH, Andersen PS, Girardin SE; Nielsen; Andersen; Girardin (February 2007) Clin. Exp. Immunol. 147)

[00371] Inflammation is classified as either acute or chronic. Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) from the blood into the injured tissues. A series of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue.

[00372] Prolonged inflammation, known as chronic inflammation, is characterized by simultaneous destruction and healing of the tissue from the inflammatory process. It leads to a progressive shift in the type of cells present at the site of inflammation, such as mononuclear cells, and increases in systemic concentrations of cytokines such as TNF- α , IL-6, and CRP. (Petersen, A. M.; Pedersen, B. K. (2005). J Appl Physiol. 98 (4): 1154–1162)

[00373] Many proteins are involved in inflammation. Any of them are susceptible to genetic mutation which may impair or otherwise dysregulate their normal function and expression.

[00374] Both small molecules and biologics are used to treat inflammatory diseases. Most treatments, however, are largely palliative.

[00375] A clear unmet medical need remains to find treatments that can mechanistically reduce chronic inflammatory diseases.

[00376] Provided herein are methods treating an inflammatory disease in a subject, comprising administering a therapeutically effective amount of a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, to the subject. Also provided herein are methods of treating an inflammatory disease in a subject, comprising administering a therapeutically effective amount of a pharmaceutical composition comprising a compound of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable form thereof, to the subject. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2,

3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof.

[00377] In some embodiments of the methods of treating an inflammatory disease provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates the activity of one or more Ras superfamily protein. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 20 μ M according to a Ras Superfamily Activity Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits the activity one or more Ras superfamily protein. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates the activity of one or more Ras superfamily protein by 45% or more at 20 μ M according to a Ras Superfamily Activity. In some embodiments, the compound or pharmaceutically acceptable form thereof modulates the activity of one or more Ras superfamily protein by 50% or more at 20 μ M according to a Ras Superfamily Activity. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 9, 10, 11, 12, 13, 16, 18, 22, 23, 24, 27, 28, 32, 33, 36, 37, 38, 39, 40, 57, 62, 75, 84, 86, and 92, or a pharmaceutically acceptable form thereof.

[00378] In some embodiments of the methods of treating an inflammatory disease provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates Erk1/2 activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Erk1/2 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Erk1/2 protein by 80% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Erk1/2 protein by 85% or more at 10 μ M

according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 19, 20, 21, 49, 51, 53, 56, 67, 68, 79, 80, 81, 82, 89, and 94, or a pharmaceutically acceptable form thereof. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Erk1/2 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Erk1/2 protein by 45% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Erk1/2 protein by 50% or more at 10 μ M according to Erk1/2 Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 16, 18, 23, 27, 28, 36, 37, 38, 40, 54, 55, 57, 60, 61, 62, 75, and 83, or a pharmaceutically acceptable form thereof.

[00379] In some embodiments of the methods of treating an inflammatory disease provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates Akt activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Akt protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Akt protein by 85% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 19, 20, 49, 51, 53, 56, 79, 80, 81, and 94, or a pharmaceutically acceptable form thereof. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Akt protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Akt

Phosphorylation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Akt protein by 50% or more at 10 μ M according to Akt Phosphorylation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 18, 22, 27, 28, 32, 36, 37, 38, 39, 40, 47, 54, 55, 57, 59, 60, 61, 62, 66, 67, 74, 75, 76, 83, 84, 86, 87, 88, and 91, or a pharmaceutically acceptable form thereof.

[00380] In some embodiments of the methods of treating an inflammatory disease provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates Smad2/3 activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Smad2/3 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Smad2/3 protein by 80% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the Smad2/3 protein by 85% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound is selected from the group consisting of Compounds 19, 20, 21, 29, 49, 51, 56, 58, 61, 63, 64, 65, 68, 77, 79, 80, 81, 87, 88, 89, and 94, or a pharmaceutically acceptable form thereof. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Smad2/3 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the Smad2/3 protein by 50% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay. In some embodiments, the compound is Compound 12, 14, 25, 26, 31, 32, 33, 37, 78, and 90, or a pharmaceutically acceptable form thereof.

[00381] In some embodiments of the methods of treating an inflammatory disease provided

herein, the method administering a compound or pharmaceutically acceptable form that modulates JNK activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits JNK by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the JNK protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the JNK protein by about 50% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound is Compound 8, or a pharmaceutically acceptable form thereof. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the JNK protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates JNK by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to JNK Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the JNK protein by about 50% or more at 10 μ M according to JNK Activation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, and 7, or a pharmaceutically acceptable form thereof.

[00382] In some embodiments of the methods of treating an inflammatory disease provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates MAPK p38 activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the MAPK p38 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of the MAPK p38 by about 50% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the MAPK p38 protein. In some embodiments, the compound or pharmaceutically acceptable form thereof activates MAPK p38 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or

more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof activates phosphorylation of the MAPK p38 by about 50% or more at 10 μ M according to MAPK p38 Activation Assay. In some embodiments, the compound is selected from the group consisting of Compounds 2, 3, 4, 5, 6, and 7, or a pharmaceutically acceptable form thereof.

[00383] In some embodiments of the methods of treating an inflammatory disease provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates IL-6 activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits IL-6 by 75% or more at 10 μ M according to IL-6 Quantification Assay. In some embodiments, the compound is selected from the group consisting of Compounds 4, 9, 10, 11, 16, 17, 19, 20, 92, and 94, or a pharmaceutically acceptable form thereof.

[00384] In some embodiments of the methods of treating an inflammatory disease provided herein, the method administering a compound or pharmaceutically acceptable form thereof that modulates TNF-alpha activity. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by 75% or more at 10 μ M according to TNF-alpha Quantification Assay. In some embodiments, the compound is Compound 20 and 94, or a pharmaceutically acceptable form thereof.

[00385] In some embodiments, the inflammatory disease is inflammation-associated cancer development. As disclosed here, the compounds provided herein are useful in treatment of cancer. It is well recognized that the immune inflammatory state serves as a key mediator of the middle stages of tumor development. It is also well known that chronic inflammation can

predispose an individual to cancer. Chronic inflammation is caused by a variety of factors, including bacterial, viral, and parasitic infections. The longer the inflammation persists, the higher the risk of associated carcinogenesis. Anti-inflammatory cancer therapy prevents premalignant cells from turning fully cancerous or impedes existing tumors from spreading to distant sites in the body. Thus, in some embodiments, the compounds provided herein are useful in treating inflammatory cancers. Such cancers, and the chronic inflammatory conditions that predispose susceptible cells to neoplastic transformation, include gastric adenocarcinoma (gastritis), mucosa-associated lymphoid tissue (MALT) lymphoma (gastritis), bladder, liver and rectal carcinomas (schistosomiasis), cholangiocarcinoma and colon carcinoma (cholangitis), gall bladder cancer (chronic cholecystitis), ovarian and cervical carcinoma (pelvic inflammatory disease, chronic cervicitis), skin carcinoma (osteomyelitis), colorectal carcinoma (inflammatory bowel disease), esophageal carcinoma (reflux esophagitis, Barrett's esophagus), bladder cancer (bladder inflammation (cystitis)), mesothelioma and lung carcinoma (asbestosis, silicosis), oral squamous cell carcinoma (gingivitis, lichen planus), pancreatic carcinoma (pancreatitis, protease mutation), vulvar squamous cell carcinoma (lichen sclerosis), salivary gland carcinoma (sialadenitis), lung carcinoma (bronchitis) and MALT lymphoma (Sjogren syndrome, Hashimoto's thyroiditis). Shacter, *et al.*, 2002, *Oncology*, 16(2), 217-26.

[00386] In certain embodiments, the compounds provided herein are useful in treating inflammatory diseases in the airways, such as nonspecific bronchial hyper-reactivity, chronic bronchitis, cystic fibrosis, and acute respiratory distress syndrome (ARDS).

[00387] In certain embodiments, the compounds provided herein are useful in treating asthma and idiopathic lung fibrosis or idiopathic pulmonary fibrosis (IPF), pulmonary fibrosis, and interstitial lung disease. As known to one of skill in the art, the differentiation of fibroblasts into cell types called myofibroblasts occurs during wound healing, when the cells contribute to the deposition of extracellular matrix (ECM) in the transient process of wound repair. In chronic inflammatory diseases such as asthma, pathological tissue remodeling often occurs, and is mediated by the functions of increased numbers of myofibroblasts in the diseased tissue, see Hinz, B. et al. *Am J Pathol.* 2007; 170: 1807–1816. In certain embodiments, the compounds provided herein prevent or reduce TGF- β -induced myofibroblast differentiation, as measured by the expression of alpha smooth muscle actin (α -SMA), a hallmark of myofibroblast differentiation (Serini, G. and Gabbiani, G. 1999; *Exp. Cell Res.* 250: 273-283).

[00388] In certain embodiments, the compounds provided herein are useful in treating psoriasis, chronic plaque psoriasis, psoriatic arthritis, acanthosis, atopic dermatitis, various forms of eczema, contact dermatitis (includes allergic dermatitis), systemic sclerosis (scleroderma), wound healing, and drug eruption.

[00389] In some embodiments, the disease is inflammation, arthritis, rheumatoid arthritis, spondylarthropathies, gouty arthritis, osteoarthritis, juvenile arthritis, and other arthritic conditions, systemic lupus erythematosus (SLE), skin-related conditions, eczema, Sjögren's syndrome, burns, dermatitis, neuroinflammation, allergy pain, autoimmune myositis, neuropathic pain, fever, pulmonary disorders, lung inflammation, adult respiratory distress syndrome, pulmonary sarcoidosis, asthma, silicosis, chronic pulmonary inflammatory disease, and chronic obstructive pulmonary disease (COPD), cardiovascular disease, arteriosclerosis, myocardial infarction (including post-myocardial infarction indications), thrombosis, congestive heart failure, cardiac reperfusion injury, as well as complications associated with hypertension and/or heart failure such as vascular organ damage, restenosis, cardiomyopathy, stroke including ischemic and hemorrhagic stroke, reperfusion injury, renal reperfusion injury, ischemia including stroke and brain ischemia, and ischemia resulting from cardiac/coronary bypass, neurodegenerative disorders, liver disease and nephritis, gastrointestinal conditions, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, ulcerative diseases, gastric ulcers, viral and bacterial infections, sepsis, septic shock, gram negative sepsis, malaria, meningitis, HIV infection, opportunistic infections, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia, herpes virus, myalgias due to infection, influenza, autoimmune disease, graft vs. host reaction and allograft rejections, treatment of bone resorption diseases, osteoporosis, multiple sclerosis, acute gout, pneumonitis, myocarditis, pericarditis, myositis, eczema, alopecia, vitiligo, bullous skin diseases, atherosclerosis, depression, retinitis, uveitis, scleritis, hepatitis, pancreatitis, primary biliary cirrhosis, sclerosing cholangitis, Addison's disease, hypophysitis, thyroiditis, type I diabetes, giant cell arteritis, nephritis including lupus nephritis, vasculitis with organ involvement such as glomerulonephritis, vasculitis including giant cell arteritis, Wegener's granulomatosis, Polyarteritis nodosa, Behcet's disease, Kawasaki disease, Takayasu's Arteritis, vasculitis with organ involvement, acute rejection of transplanted organs. endotoxaemia, systemic inflammatory

response syndrome (SIRS), multi-organ dysfunction syndrome, toxic shock syndrome, acute lung injury, ARDS (adult respiratory distress syndrome), acute renal failure, fulminant hepatitis, burns, acute pancreatitis, postsurgical syndromes, sarcoidosis, Herxheimer reactions, encephalitis, myelitis, SIRS associated with viral infections such as influenza, herpes zoster, herpes simplex, coronavirus or dry eye syndrome (or keratoconjunctivitis sicca (KCS)).

[00390] In certain embodiments, the compounds provided herein are useful in treating neuropathic and nociceptive pain, chronic or acute, such as, without limitation, allodynia, inflammatory pain, inflammatory hyperalgesia, post herpetic neuralgia, neuropathies, neuralgia, diabetic neuropathy, HIV-related neuropathy, nerve injury, rheumatoid arthritic pain, osteoarthritic pain, burns, back pain, ocular pain, visceral pain, cancer pain, dental pain, headache, migraine, carpal tunnel syndrome, fibromyalgia, neuritis, sciatica, pelvic hypersensitivity, pelvic pain, post operative pain, post stroke pain, and menstrual pain.

[00391] In certain embodiments, the compounds provided herein are useful in treating Alzheimer's disease (AD), mild cognitive impairment (MCI), age-associated memory impairment (AAMI), multiple sclerosis, Parkinson's disease, vascular dementia, senile dementia, AIDS dementia, Pick's disease, dementia caused by cerebrovascular disorders, corticobasal degeneration, amyotrophic lateral sclerosis (ALS), Huntington's disease, diminished CNS function associated with traumatic brain injury.

[00392] In some embodiments, the compounds provided herein are useful in treating Alzheimer's disease (AD), ankylosing spondylitis, arthritis (osteoarthritis, rheumatoid arthritis (RA), psoriatic arthritis), asthma, atherosclerosis, Crohn's disease, colitis, dermatitis, diverticulitis, fibromyalgia, hepatitis, irritable bowel syndrome (IBS), systemic lupus, erythematous (SLE), nephritis, Parkinson's disease, ulcerative colitis.

[00393] When used for the treatment of inflammatory disease, the compounds provided herein may be administered in dosages, routes of administration and/or to achieve pK profiles as described herein for the treatment of cancer.

[00394] In some embodiments, the inflammatory disease is inflammation-associated cancer development. As disclosed here, the compounds provided herein are useful in treatment of cancer. It is well recognized that the immune inflammatory state serves as a key mediator of the middle stages of tumor development. It is also well known that chronic inflammation can predispose an individual to cancer. Chronic inflammation is caused by a variety of factors,

including bacterial, viral, and parasitic infections. The longer the inflammation persists, the higher the risk of associated carcinogenesis. Anti-inflammatory cancer therapy prevents premalignant cells from turning fully cancerous or impedes existing tumors from spreading to distant sites in the body. Thus, in some embodiments, the compounds provided herein are useful in treating inflammatory cancers. Such cancers, and the chronic inflammatory conditions that predispose susceptible cells to neoplastic transformation, include gastric adenocarcinoma (gastritis), mucosa-associated lymphoid tissue (MALT) lymphoma (gastritis), bladder, liver and rectal carcinomas (schistosomiasis), cholangiocarcinoma and colon carcinoma (cholangitis), gall bladder cancer (chronic cholecystitis), ovarian and cervical carcinoma (pelvic inflammatory disease, chronic cervicitis), skin carcinoma (osteomyelitis), colorectal carcinoma (inflammatory bowel disease), esophageal carcinoma (reflux esophagitis, Barrett's esophagus), bladder cancer (bladder inflammation (cystitis)), mesothelioma and lung carcinoma (asbestosis, silicosis), oral squamous cell carcinoma (gingivitis, lichen planus), pancreatic carcinoma (pancreatitis, protease mutation), vulvar squamous cell carcinoma (lichen sclerosis), salivary gland carcinoma (sialadenitis), lung carcinoma (bronchitis) and MALT lymphoma (Sjogren syndrome, Hashimoto's thyroiditis). Shacter, et al., 2002, *Oncology*, 16(2), 217-26.

[00395] In certain embodiments, the compounds provided herein are useful in treating inflammatory diseases in the airways, such as nonspecific bronchial hyper-reactivity, chronic bronchitis, cystic fibrosis, and acute respiratory distress syndrome (ARDS).

[00396] In certain embodiments, the compounds provided herein are useful in treating asthma and idiopathic lung fibrosis or idiopathic pulmonary fibrosis (IPF), pulmonary fibrosis, and interstitial lung disease. As known to one of skill in the art, the differentiation of fibroblasts into cell types called myofibroblasts occurs during wound healing, when the cells contribute to the deposition of extracellular matrix (ECM) in the transient process of wound repair. In chronic inflammatory diseases such as asthma, pathological tissue remodeling often occurs, and is mediated by the functions of increased numbers of myofibroblasts in the diseased tissue, see Hinz, B. et al. *Am J Pathol.* 2007; 170: 1807–1816. In certain embodiments, the compounds provided herein prevent or reduce TGF- β -induced myofibroblast differentiation, as measured by the expression of alpha smooth muscle actin (α -SMA), a hallmark of myofibroblast differentiation (Serini, G. and Gabbiani, G. 1999; *Exp. Cell Res.* 250: 273-283).

[00397] In certain embodiments, the compounds provided herein are useful in treating

psoriasis, chronic plaque psoriasis, psoriatic arthritis, acanthosis, atopic dermatitis, various forms of eczema, contact dermatitis (includes allergic dermatitis), systemic sclerosis (scleroderma), wound healing, and drug eruption.

[00398] In some embodiments, the disease is inflammation, arthritis, rheumatoid arthritis, spondylarthropathies, gouty arthritis, osteoarthritis, juvenile arthritis, and other arthritic conditions, systemic lupus erythematosus (SLE), skin-related conditions, eczema, Sjögren's syndrome, burns, dermatitis, neuroinflammation, allergy pain, autoimmune myositis, neuropathic pain, fever, pulmonary disorders, lung inflammation, adult respiratory distress syndrome, pulmonary sarcoidosis, asthma, silicosis, chronic pulmonary inflammatory disease, and chronic obstructive pulmonary disease (COPD), cardiovascular disease, arteriosclerosis, myocardial infarction (including post-myocardial infarction indications), thrombosis, congestive heart failure, cardiac reperfusion injury, as well as complications associated with hypertension and/or heart failure such as vascular organ damage, restenosis, cardiomyopathy, stroke including ischemic and hemorrhagic stroke, reperfusion injury, renal reperfusion injury, ischemia including stroke and brain ischemia, and ischemia resulting from cardiac/coronary bypass, neurodegenerative disorders, liver disease and nephritis, gastrointestinal conditions, inflammatory bowel disease, Crohn's disease, gastritis, irritable bowel syndrome, ulcerative colitis, ulcerative diseases, gastric ulcers, viral and bacterial infections, sepsis, septic shock, gram negative sepsis, malaria, meningitis, HIV infection, opportunistic infections, cachexia secondary to infection or malignancy, cachexia secondary to acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), pneumonia, herpes virus, myalgias due to infection, influenza, autoimmune disease, graft vs. host reaction and allograft rejections, treatment of bone resorption diseases, osteoporosis, multiple sclerosis, acute gout, pneumonitis, myocarditis, pericarditis, myositis, eczema, alopecia, vitiligo, bullous skin diseases, atherosclerosis, depression, retinitis, uveitis, scleritis, hepatitis, pancreatitis, primary biliary cirrhosis, sclerosing cholangitis, Addison's disease, hypophysitis, thyroiditis, type I diabetes, giant cell arteritis, nephritis including lupus nephritis, vasculitis with organ involvement such as glomerulonephritis, vasculitis including giant cell arteritis, Wegener's granulomatosis, Polyarteritis nodosa, Behcet's disease, Kawasaki disease, Takayasu's Arteritis, vasculitis with organ involvement, acute rejection of transplanted organs, endotoxaemia, systemic inflammatory response syndrome (SIRS), multi-organ dysfunction syndrome, toxic shock syndrome, acute

lung injury, ARDS (adult respiratory distress syndrome), acute renal failure, fulminant hepatitis, burns, acute pancreatitis, postsurgical syndromes, sarcoidosis, Herxheimer reactions, encephalitis, myelitis, SIRS associated with viral infections such as influenza, herpes zoster, herpes simplex, coronavirus or dry eye syndrome (or keratoconjunctivitis sicca (KCS)).

[00399] In certain embodiments, the compounds provided herein are useful in treating neuropathic and nociceptive pain, chronic or acute, such as, without limitation, allodynia, inflammatory pain, inflammatory hyperalgesia, post herpetic neuralgia, neuropathies, neuralgia, diabetic neuropathy, HIV-related neuropathy, nerve injury, rheumatoid arthritic pain, osteoarthritic pain, burns, back pain, ocular pain, visceral pain, cancer pain, dental pain, headache, migraine, carpal tunnel syndrome, fibromyalgia, neuritis, sciatica, pelvic hypersensitivity, pelvic pain, post operative pain, post stroke pain, and menstrual pain.

[00400] In certain embodiments, the compounds provided herein are useful in treating Alzheimer's disease (AD), mild cognitive impairment (MCI), age-associated memory impairment (AAMI), multiple sclerosis, Parkinson's disease, vascular dementia, senile dementia, AIDS dementia, Pick's disease, dementia caused by cerebrovascular disorders, corticobasal degeneration, amyotrophic lateral sclerosis (ALS), Huntington's disease, diminished CNS function associated with traumatic brain injury.

[00401] In some embodiments, the compounds provided herein are useful in treating Alzheimer's disease (AD), ankylosing spondylitis, arthritis (osteoarthritis, rheumatoid arthritis (RA), psoriatic arthritis), asthma, atherosclerosis, Crohn's disease, colitis, dermatitis, diverticulitis, fibromyalgia, hepatitis, irritable bowel syndrome (IBS), systemic lupus, erythematosus (SLE), nephritis, Parkinson's disease, ulcerative colitis.

3.7. PHARMACEUTICAL COMPOSITIONS

[00402] The pharmaceutical compositions provided herein contain therapeutically effective amounts of one or more of compounds provided herein (e.g. compounds of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), and a pharmaceutically acceptable carrier, diluent or excipient.

[00403] The compounds can be formulated into suitable pharmaceutical preparations such as solutions, suspensions, tablets, dispersible tablets, pills, capsules, powders, sustained release formulations or elixirs, for oral administration or in sterile solutions or suspensions for ophthalmic or parenteral administration, as well as transdermal patch preparation and dry powder

inhalers. Typically the compounds described above are formulated into pharmaceutical compositions using techniques and procedures well known in the art (*see, e.g.*, Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems, Twelfth Edition 2021).

[00404] In the compositions, effective concentrations of one or more compounds or pharmaceutically acceptable salts is (are) mixed with a suitable pharmaceutical carrier or vehicle. In certain embodiments, the concentrations of the compounds in the compositions are effective for delivery of an amount, upon administration, that treats, prevents, or ameliorates one or more of the symptoms and/or progression of a disease or disorder disclosed herein.

[00405] Typically, the compositions are formulated for single dosage administration. To formulate a composition, the weight fraction of compound is dissolved, suspended, dispersed or otherwise mixed in a selected vehicle at an effective concentration such that the treated condition is relieved or ameliorated. Pharmaceutical carriers or vehicles suitable for administration of the compounds provided herein include any such carriers known to those skilled in the art to be suitable for the particular mode of administration.

[00406] In addition, the compounds may be formulated as the sole pharmaceutically active ingredient in the composition or may be combined with other active ingredients. Liposomal suspensions, including tissue-targeted liposomes, such as tumor-targeted liposomes, may also be suitable as pharmaceutically acceptable carriers. These may be prepared according to methods known to those skilled in the art. For example, liposome formulations may be prepared as known in the art. Briefly, liposomes such as multilamellar vesicles (MLV's) may be formed by drying down egg phosphatidyl choline and brain phosphatidyl serine (7:3 molar ratio) on the inside of a flask. A solution of a compound provided herein in phosphate buffered saline lacking divalent cations (PBS) is added and the flask shaken until the lipid film is dispersed. The resulting vesicles are washed to remove unencapsulated compound, pelleted by centrifugation, and then resuspended in PBS.

[00407] The active compound is included in the pharmaceutically acceptable carrier in an amount sufficient to exert a therapeutically useful effect in the absence of undesirable side effects on the subject treated. The therapeutically effective concentration may be determined empirically by testing the compounds in *in vitro* and *in vivo* systems described herein and then extrapolated therefrom for dosages for humans. In some embodiments, the active compound is administered in a method to achieve a therapeutically effective concentration of the drug. In

some embodiments, a companion diagnostic (see, e.g., Olsen D and Jorgensen JT, *Front. Oncol.*, 2014 May 16, 4:105, doi: 10.3389/fonc.2014.00105) is used to determine the therapeutic concentration and safety profile of the active compound in specific subjects or subject populations.

[00408] The concentration of active compound in the pharmaceutical composition will depend on absorption, tissue distribution, inactivation and excretion rates of the active compound, the physicochemical characteristics of the compound, the dosage schedule, and amount administered as well as other factors known to those of skill in the art. For example, the amount that is delivered is sufficient to ameliorate one or more of the symptoms of a disease or disorder disclosed herein.

[00409] In certain embodiments, a therapeutically effective dosage should produce a serum concentration of active ingredient of from about 0.1 ng/mL to about 50-100 µg/mL. In some embodiments, the pharmaceutical compositions provide a dosage of from about 0.001 mg to about 2000 mg of compound per kilogram of body weight per day. Pharmaceutical dosage unit forms are prepared to provide from about 1 mg to about 1000 mg and in certain embodiments, from about 10 to about 500 mg of the essential active ingredient or a combination of essential ingredients per dosage unit form.

[00410] The active ingredient may be administered at once, or may be divided into a number of smaller doses to be administered at intervals of time. It is understood that the precise dosage and duration of treatment is a function of the disease being treated and may be determined empirically using known testing protocols or by extrapolation from in vivo or in vitro test data. It is to be noted that concentrations and dosage values may also vary with the severity of the condition to be alleviated. It is to be further understood that for any particular subject, specific dosage regimens should be adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions, and that the concentration ranges set forth herein are exemplary only and are not intended to limit the scope or practice of the claimed compositions.

[00411] Thus, effective concentrations or amounts of one or more of the compounds described herein or pharmaceutically acceptable salts thereof are mixed with a suitable pharmaceutical carrier or vehicle for systemic, topical or local administration to form pharmaceutical compositions. Compounds are included in an amount effective for ameliorating one or more

symptoms of, or for treating, retarding progression, or preventing. The concentration of active compound in the composition will depend on absorption, tissue distribution, inactivation, excretion rates of the active compound, the dosage schedule, amount administered, particular formulation as well as other factors known to those of skill in the art.

[00412] The compositions are intended to be administered by a suitable route, including but not limited to oral, parenteral, subcutaneous, intravenous, intramuscular, intraperitoneal, intrathecal, mucosal, dermal, transdermal, buccal, rectal, topical, local, nasal or inhalation. For oral administration, capsules and tablets can be formulated. The compositions are in liquid, semi-liquid or solid form and are formulated in a manner suitable for each route of administration.

[00413] Solutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application can include any of the following components: a sterile diluent, such as water for injection, saline solution, fixed oil, polyethylene glycol, glycerine, propylene glycol, dimethyl acetamide or other synthetic solvent; antimicrobial agents, such as benzyl alcohol and methyl parabens; antioxidants, such as ascorbic acid and sodium bisulfite; chelating agents, such as ethylenediaminetetraacetic acid (EDTA); buffers, such as acetates, citrates and phosphates; and agents for the adjustment of tonicity such as sodium chloride or dextrose. Parenteral preparations can be enclosed in ampules, pens, disposable syringes or single or multiple dose vials made of glass, plastic or other suitable material.

[00414] In instances in which the compounds exhibit insufficient solubility, methods for solubilizing compounds may be used. Such methods are known to those of skill in this art, and include, but are not limited to, using cosolvents, such as dimethylsulfoxide (DMSO), using surfactants, such as TWEEN®, or dissolution in aqueous sodium bicarbonate.

[00415] Upon mixing or addition of the compound(s), the resulting mixture may be a solution, suspension, emulsion or the like. The form of the resulting mixture depends upon a number of factors, including the intended mode of administration and the solubility of the compound in the selected carrier or vehicle. The effective concentration is sufficient for ameliorating the symptoms of the disease, disorder or condition treated and may be empirically determined.

[00416] The pharmaceutical compositions are provided for administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, sterile parenteral solutions or suspensions, and oral solutions or suspensions, and oil water emulsions containing

suitable quantities of the compounds or pharmaceutically acceptable salts thereof. The pharmaceutically therapeutically active compounds and salts thereof are formulated and administered in unit dosage forms or multiple dosage forms. Unit dose forms as used herein refer to physically discrete units suitable for human and animal subjects and packaged individually as is known in the art. Each unit dose contains a predetermined quantity of the therapeutically active compound sufficient to produce the desired therapeutic effect, in association with the required pharmaceutical carrier, vehicle or diluent. Examples of unit dose forms include ampules and syringes and individually packaged tablets or capsules. Unit dose forms may be administered in fractions or multiples thereof. A multiple dose form is a plurality of identical unit dosage forms packaged in a single container to be administered in segregated unit dose form. Examples of multiple dose forms include vials, bottles of tablets or capsules or bottles of pints or gallons. Hence, multiple dose form is a multiple of unit doses which are not segregated in packaging.

[00417] Sustained-release preparations can also be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the compound provided herein, which matrices are in the form of shaped articles, e.g., films, or microcapsule. Examples of sustained-release matrices include iontophoresis patches, polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides, copolymers of L-glutamic acid and ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT™ (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated compound remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at 37 °C, resulting in a loss of biological activity and possible changes in their structure. Rational strategies can be devised for stabilization depending on the mechanism of action involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through thio-disulfide interchange, stabilization may be achieved by modifying sulfhydryl residues, lyophilizing from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

[00418] Dosage forms or compositions containing active ingredient in the range of 0.005% to 100% with the balance made up from non toxic carrier may be prepared. For oral administration, a pharmaceutically acceptable non toxic composition is formed by the incorporation of any of the normally employed excipients, such as, for example pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, talcum, cellulose derivatives, sodium crosscarmellose, glucose, sucrose, magnesium carbonate or sodium saccharin. Such compositions include solutions, suspensions, tablets, capsules, powders and sustained release formulations, such as, but not limited to, implants and microencapsulated delivery systems, and biodegradable, biocompatible polymers, such as collagen, ethylene vinyl acetate, polyanhydrides, polyglycolic acid, polyorthoesters, polylactic acid and others. Methods for preparation of these compositions are known to those skilled in the art. The contemplated compositions may contain about 0.001% to 100% active ingredient, in certain embodiments, about 0.1 85% or about 75-95%.

[00419] The active compounds or pharmaceutically acceptable salts may be prepared with carriers that protect the compound against rapid elimination from the body, such as time release formulations or coatings.

[00420] The compositions may include other active compounds to obtain desired combinations of properties. The compounds provided herein, or pharmaceutically acceptable salts thereof as described herein, may also be advantageously administered for therapeutic or prophylactic purposes together with another pharmacological agent known in the general art to be of value in treating one or more of the diseases or medical conditions referred to hereinabove, such as diseases related to oxidative stress. It is to be understood that such combination therapy constitutes a further aspect of the compositions and methods of treatment provided herein.

[00421] Lactose-free compositions provided herein can contain excipients that are well known in the art and are listed, for example, in the U.S. Pharmacopia (USP) SP (XXI)/NF (XVI). In general, lactose-free compositions contain an active ingredient, a binder/filler, and a lubricant in pharmaceutically compatible and pharmaceutically acceptable amounts. Exemplary lactose-free dosage forms contain an active ingredient, microcrystalline cellulose, pre-gelatinized starch and magnesium stearate.

[00422] Further encompassed are anhydrous pharmaceutical compositions and dosage forms containing a compound provided herein. For example, the addition of water (e.g., 5%) is widely accepted in the pharmaceutical arts as a means of simulating long-term storage in order to

determine characteristics such as shelf-life or the stability of formulations over time. See, e.g., Jens T. Carstensen, *Drug Stability: Principles & Practice*, 2d. Ed., Marcel Dekker, NY, NY, 1995, pp. 379-80. In effect, water and heat accelerate the decomposition of some compounds. Thus, the effect of water on a formulation can be of great significance since moisture and/or humidity are commonly encountered during manufacture, handling, packaging, storage, shipment and use of formulations.

[00423] Anhydrous pharmaceutical compositions and dosage forms provided herein can be prepared using anhydrous or low moisture containing ingredients and low moisture or low humidity conditions. Pharmaceutical compositions and dosage forms that comprise lactose and at least one active ingredient that comprises a primary or secondary amine are anhydrous if substantial contact with moisture and/or humidity during manufacturing, packaging, and/or storage is expected.

[00424] An anhydrous pharmaceutical composition should be prepared and stored such that its anhydrous nature is maintained. Accordingly, anhydrous compositions are packaged using materials known to prevent exposure to water such that they can be included in suitable formulary kits. Examples of suitable packaging include, but are not limited to, hermetically sealed foils, plastics, unit dose containers (e.g., vials), blister packs and strip packs.

Articles of Manufacture

[00425] The compounds of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable forms thereof, provided herein, and the pharmaceutical compositions comprising the same with a pharmaceutically acceptable carrier, diluent or excipient, can be contained in a pharmaceutical kit or pharmaceutical packaging (sometimes referred to as articles of manufacture). Such articles of manufacture can be used for treatment, prevention or amelioration of one or more symptoms or progression of a disease or disorder disclosed herein, and a label that indicates that the compound or pharmaceutically acceptable salt thereof is used for treatment, prevention or amelioration of one or more symptoms or progression of a disease or disorder disclosed herein.

[00426] In certain embodiments, provided herein is a pharmaceutical kit, which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active ingredients to a subject. In certain embodiments, the pharmaceutical kit provided herein includes a container and a dosage form of a compound provided herein, including a single enantiomer or a

mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

[00427] In certain embodiments, the pharmaceutical kit includes a container comprising a dosage form of the compound provided herein, including a single enantiomer or a mixture of diastereomers thereof; or a pharmaceutically acceptable salt, solvate, or prodrug thereof, in a container comprising one or more other therapeutic agent(s) described herein.

[00428] Pharmaceutical kits provided herein can further include devices that are used to administer the active ingredients. Examples of such devices include, but are not limited to, syringes, needle-less injectors drip bags, patches, and inhalers. The kits provided herein can also include condoms for administration of the active ingredients.

[00429] Pharmaceutical kits provided herein can further include pharmaceutically acceptable vehicles that can be used to administer one or more active ingredients. For example, if an active ingredient is provided in a solid form that must be reconstituted for parenteral administration, the kit can comprise a sealed container of a suitable vehicle in which the active ingredient can be dissolved to form a particulate-free sterile solution that is suitable for parenteral administration. Examples of pharmaceutically acceptable vehicles include, but are not limited to: aqueous vehicles, including, but not limited to, Water for Injection USP, Sodium Chloride Injection, Ringer's Injection, Dextrose Injection, Dextrose and Sodium Chloride Injection, and Lactated Ringer's Injection; water-miscible vehicles, including, but not limited to, ethyl alcohol, polyethylene glycol, and polypropylene glycol; and non-aqueous vehicles, including, but not limited to, corn oil, cottonseed oil, peanut oil, sesame oil, ethyl oleate, isopropyl myristate, and benzyl benzoate.

3.8. DOSING

[00430] The compounds of Formula I, IA, IA(1), IB, IB(1), IB(2), II, IIA, IIA(1), IIB, IIB(1), or IIB(2), or pharmaceutically acceptable forms thereof, and pharmaceutical compositions comprising the same, provided herein may be dosed in certain therapeutically or prophylactically effective amounts, certain time intervals, certain dosage forms, and certain dosage administration methods as described below.

[00431] In certain embodiments, a therapeutically or prophylactically effective amount of the compound is from about 0.005 to about 1,000 mg per day, from about 0.01 to about 500 mg per day, from about 0.01 to about 250 mg per day, from about 0.01 to about 100 mg per day, from

about 0.1 to about 100 mg per day, from about 0.5 to about 100 mg per day, from about 1 to about 100 mg per day, from about 0.01 to about 50 mg per day, from about 0.1 to about 50 mg per day, from about 0.5 to about 50 mg per day, from about 1 to about 50 mg per day, from about 0.02 to about 25 mg per day, from about 0.05 to about 10 mg per day, from about 0.05 to about 5 mg per day, from about 0.1 to about 5 mg per day, or from about 0.5 to about 5 mg per day.

[00432] In certain embodiments, the therapeutically or prophylactically effective amount is about 0.1, about 0.2, about 0.5, about 1, about 2, about 3, about 4, about 5, about 6, about 7, about 8, about 9, about 10, about 15, about 20, about 25, about 30, about 40, about 45, about 50, about 60, about 70, about 80, about 90, about 100, or about 150 mg per day.

[00433] In some embodiments, the recommended daily dose range of the compound provided herein, or a derivative thereof, for the conditions described herein lie within the range of from about 0.5 mg to about 50 mg per day, in some embodiments given as a single once-a-day dose, or in divided doses throughout a day. In some embodiments, the dosage ranges from about 1 mg to about 50 mg per day. In other embodiments, the dosage ranges from about 0.5 to about 5 mg per day. Specific doses per day include 0.1, 0.2, 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49 or 50 mg per day.

[00434] In a specific embodiment, the recommended starting dosage may be 0.5, 1, 2, 3, 4, 5, 10, 15, 20, 25 or 50 mg per day. In another embodiment, the recommended starting dosage may be 0.5, 1, 2, 3, 4, or 5 mg per day. The dose may be escalated to 15, 20, 25, 30, 35, 40, 45 and 50 mg/day. In a specific embodiment, the compound can be administered in an amount of about 25 mg/day. In a particular embodiment, the compound can be administered in an amount of about 10 mg/day. In a particular embodiment, the compound can be administered in an amount of about 5 mg/day. In a particular embodiment, the compound can be administered in an amount of about 4 mg/day. In a particular embodiment, the compound can be administered in an amount of about 3 mg/day.

[00435] In certain embodiments, the therapeutically or prophylactically effective amount is from about 0.001 to about 100 mg/kg/day, from about 0.01 to about 50 mg/kg/day, from about 0.01 to about 25 mg/kg/day, from about 0.01 to about 10 mg/kg/day, from about 0.01 to about 9 mg/kg/day, 0.01 to about 8 mg/kg/day, from about 0.01 to about 7 mg/kg/day, from about 0.01 to about 6 mg/kg/day, from about 0.01 to about 5 mg/kg/day, from about 0.01 to about 4

mg/kg/day, from about 0.01 to about 3 mg/kg/day, from about 0.01 to about 2 mg/kg/day, from about 0.01 to about 1 mg/kg/day, or from about 0.01 to about 0.05 mg/kg/day.

[00436] The administered dose can also be expressed in units other than mg/kg/day. For example, doses for parenteral administration can be expressed as mg/m²/day. One of ordinary skill in the art would readily know how to convert doses from mg/kg/day to mg/m²/day to given either the height or weight of a subject or both (see, e.g., Nair AB, Jacob S. A simple practice guide for dose conversion between animals and human. J Basic Clin Pharma 2016;7:27-31). For example, a dose of 1 mg/kg/day for a 60 kg human is approximately equal to 37 mg/m²/day.

[00437] In certain embodiments, the amount of the compound administered is sufficient to provide a plasma concentration of the compound at steady state, ranging from about 0.001 to about 500 μ M, about 0.002 to about 200 μ M, about 0.005 to about 100 μ M, about 0.01 to about 50 μ M, from about 1 to about 50 μ M, about 0.02 to about 25 μ M, from about 0.05 to about 20 μ M, from about 0.1 to about 20 μ M, from about 0.5 to about 20 μ M, or from about 1 to about 20 μ M.

[00438] In other embodiments, the amount of the compound administered is sufficient to provide a plasma concentration of the compound at steady state, ranging from about 5 to about 100 nM, about 5 to about 50 nM, about 10 to about 100 nM, about 10 to about 50 nM or from about 50 to about 100 nM.

[00439] As used herein, the term “plasma concentration at steady state” is the concentration reached after a period of administration of a compound provided herein, or a derivative thereof. Once steady state is reached, there are minor peaks and troughs on the time dependent curve of the plasma concentration of the compound.

[00440] In certain embodiments, the amount of the compound administered is sufficient to provide a maximum plasma concentration (peak concentration) of the compound, ranging from about 0.001 to about 500 μ M, about 0.002 to about 200 μ M, about 0.005 to about 100 μ M, about 0.01 to about 50 μ M, from about 1 to about 50 μ M, about 0.02 to about 25 μ M, from about 0.05 to about 20 μ M, from about 0.1 to about 20 μ M, from about 0.5 to about 20 μ M, or from about 1 to about 20 μ M.

[00441] In certain embodiments, the amount of the compound administered is sufficient to provide a minimum plasma concentration (trough concentration) of the compound, ranging from about 0.001 to about 500 μ M, about 0.002 to about 200 μ M, about 0.005 to about 100 μ M, about

0.01 to about 50 μ M, from about 1 to about 50 μ M, about 0.01 to about 25 μ M, from about 0.01 to about 20 μ M, from about 0.02 to about 20 μ M, from about 0.02 to about 20 μ M, or from about 0.01 to about 20 μ M.

[00442] In certain embodiments, the amount of the compound administered is sufficient to provide an area under the curve (AUC) of the compound, ranging from about 100 to about 100,000 ng*hr/mL, from about 1,000 to about 50,000 ng*hr/mL, from about 5,000 to about 25,000 ng*hr/mL, or from about 5,000 to about 10,000 ng*hr/mL.

[00443] The methods provided herein encompass treating a patient regardless of subject's age, although some diseases or disorders are more common in certain age groups.

[00444] Depending on the disease to be treated and the subject's condition, the compound provided herein, or a derivative thereof, may be administered by oral, parenteral (e.g., intramuscular, intraperitoneal, intravenous, CIV, intracisternal injection or infusion, subcutaneous injection, or implant), inhalation, nasal, vaginal, rectal, sublingual, or topical (e.g., transdermal or local) routes of administration. The compound provided herein, or a derivative thereof, may be formulated, alone or together, in suitable dosage unit with pharmaceutically acceptable excipients, carriers, adjuvants and vehicles, appropriate for each route of administration.

[00445] In some embodiments, the compound provided herein, or a derivative thereof, is administered orally. In another embodiment, the compound provided herein, or a derivative thereof, is administered parenterally. In yet another embodiment, the compound provided herein, or a derivative thereof, is administered intravenously.

[00446] The compound provided herein, or a derivative thereof, can be delivered as a single dose such as, e.g., a single bolus injection, or oral tablets or pills; or over time, such as, e.g., continuous infusion over time or divided bolus doses over time. The compound can be administered repeatedly if necessary, for example, until the subject experiences stable disease or regression, or until the subject experiences disease progression or unacceptable toxicity. For example, stable disease for solid tumors generally means that the perpendicular diameter of measurable lesions has not increased by 25% or more from the last measurement. Response Evaluation Criteria in Solid Tumors (RECIST) Guidelines, Journal of the National Cancer Institute 92(3): 205-216 (2000). Stable disease or lack thereof is determined by methods known in the art such as evaluation of patient symptoms, physical examination, visualization of the

tumor that has been imaged using X-ray, CAT, PET, or MRI scan and other commonly accepted evaluation modalities.

[00447] The compound provided herein, or a derivative thereof, can be administered once daily (QD), or divided into multiple daily doses such as twice daily (BID), three times daily (TID), and four times daily (QID). In addition, the administration can be continuous (i.e., daily for consecutive days or every day), intermittent, e.g., in cycles (i.e., including days, weeks, or months of rest without drug). As used herein, the term “daily” is intended to mean that a therapeutic compound, such as the compound provided herein, or a derivative thereof, is administered once or more than once each day, for example, for a period of time. The term “continuous” is intended to mean that a therapeutic compound, such as the compound provided herein or a derivative thereof, is administered daily for an uninterrupted period of at least 10 days to 52 weeks. The term “intermittent” or “intermittently” as used herein is intended to mean stopping and starting at either regular or irregular intervals. For example, intermittent administration of the compound provided herein or a derivative thereof is administration for one to six days per week, administration in cycles (e.g., daily administration for two to eight consecutive weeks, then a rest period with no administration for up to one week), or administration on alternate days. The term “cycling” as used herein is intended to mean that a therapeutic compound, such as the compound provided herein or a derivative thereof, is administered daily or continuously but with a rest period. In some such embodiments, administration is once a day for two to six days, then a rest period with no administration for five to seven days.

[00448] In some embodiments, the frequency of administration is in the range of about a daily dose to about a monthly dose. In certain embodiments, administration is once a day, twice a day, three times a day, four times a day, once every other day, twice a week, once every week, once every two weeks, once every three weeks, or once every four weeks. In some embodiments, the compound provided herein, or a derivative thereof, is administered once a day. In another embodiment, the compound provided herein, or a derivative thereof, is administered twice a day. In yet another embodiment, the compound provided herein, or a derivative thereof, is administered three times a day. In still another embodiment, the compound provided herein, or a derivative thereof, is administered four times a day.

[00449] In certain embodiments, the compound provided herein, or a derivative thereof, is

administered once per day from one day to six months, from one week to three months, from one week to four weeks, from one week to three weeks, or from one week to two weeks. In certain embodiments, the compound provided herein, or a derivative thereof, is administered once per day for one week, two weeks, three weeks, or four weeks. In some embodiments, the compound provided herein, or a derivative thereof, is administered once per day for 4 days. In some embodiments, the compound provided herein, or a derivative thereof, is administered once per day for 5 days. In some embodiments, the compound provided herein, or a derivative thereof, is administered once per day for 6 days. In some embodiments, the compound provided herein, or a derivative thereof, is administered once per day for one week. In another embodiment, the compound provided herein, or a derivative thereof, is administered once per day for two weeks. In yet another embodiment, the compound provided herein, or a derivative thereof, is administered once per day for three weeks. In still another embodiment, the compound provided herein, or a derivative thereof, is administered once per day for four weeks.

Combination Therapy With A Second Active Agent

[00450] The compound provided herein, or a derivative thereof, can also be combined or used in combination with other therapeutic agents useful in the treatment and/or prevention of cancers, inflammatory diseases, rasopathies, or fibrotic disease.

[00451] In some embodiments, provided herein is a method of treating, preventing, or managing cancers, inflammatory diseases, rasopathies, and fibrotic disease, comprising administering to a subject a compound provided herein, or a derivative thereof, in combination with one or more second active agents.

[00452] As used herein, the term “in combination” includes the use of more than one therapy (e.g., one or more prophylactic and/or therapeutic agents). However, the use of the term “in combination” does not restrict the order in which therapies (e.g., prophylactic and/or therapeutic agents) are administered to a subject with a disease or disorder. A first therapy (e.g., a prophylactic or therapeutic agent such as a compound provided herein, a compound provided herein, e.g., the compound provided herein, or a derivative thereof) can be administered prior to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours, 96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks before), concomitantly with, or subsequent to (e.g., 5 minutes, 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, 4 hours, 6 hours, 12 hours, 24 hours, 48 hours, 72 hours,

96 hours, 1 week, 2 weeks, 3 weeks, 4 weeks, 5 weeks, 6 weeks, 8 weeks, or 12 weeks after) the administration of a second therapy (e.g., a prophylactic or therapeutic agent) to the subject.

Triple therapy is also contemplated herein.

[00453] Administration of the compound provided herein, or a derivative thereof and one or more second active agents to a subject can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease or disorder being treated.

[00454] The route of administration of the compound provided herein, or a derivative thereof, is independent of the route of administration of a second therapy. In some embodiments, the compound provided herein, or a derivative thereof, is administered orally. In another embodiment, the compound provided herein, or a derivative thereof, is administered intravenously. Thus, in accordance with these embodiments, the compound provided herein, or a derivative thereof, is administered orally or intravenously, and the second therapy can be administered orally, parenterally, intraperitoneally, intravenously, intraarterially, transdermally, sublingually, intramuscularly, rectally, transbuccally, intranasally, liposomally, via inhalation, vaginally, intraocularly, via local delivery by catheter or stent, subcutaneously, intraadiposally, intraarticularly, intrathecally, or in a slow release dosage form. In some embodiments, the compound provided herein, or a derivative thereof, and a second therapy are administered by the same mode of administration, orally or by IV. In another embodiment, the compound provided herein, or a derivative thereof, is administered by one mode of administration, e.g., by IV, whereas the second agent is administered by another mode of administration, e.g., orally.

[00455] In some embodiments, the second active agent is administered intravenously or subcutaneously and once or twice daily in an amount of from about 1 to about 1000 mg, from about 5 to about 500 mg, from about 10 to about 350 mg, or from about 50 to about 200 mg. The specific amount of the second active agent will depend on the specific agent used, the type of disease being treated or managed, the severity and stage of disease, and the amount of the compound provided herein, or a derivative thereof, and any optional additional active agents concurrently administered to the subject.

[00456] One or more second active ingredients or agents can be used together with the

compound provided herein, or a derivative thereof, in the methods and compositions provided herein. Second active agents can be large molecules (e.g., proteins) or small molecules (e.g., synthetic inorganic, organometallic, or organic molecules).

[00457] Examples of large molecule active agents include, but are not limited to, hematopoietic growth factors, cytokines, and monoclonal and polyclonal antibodies, particularly, therapeutic antibodies to cancer antigens. Typical large molecule active agents are biological molecules, such as naturally occurring or synthetic or recombinant proteins.

[00458] In some embodiments, the compound provided herein, or a derivative thereof, can be administered in an amount ranging from about 0.1 to about 150 mg, from about 1 to about 25 mg, or from about 2 to about 10 mg orally and daily alone, or in combination with a second active agent, prior to, during, or after the use of conventional therapy.

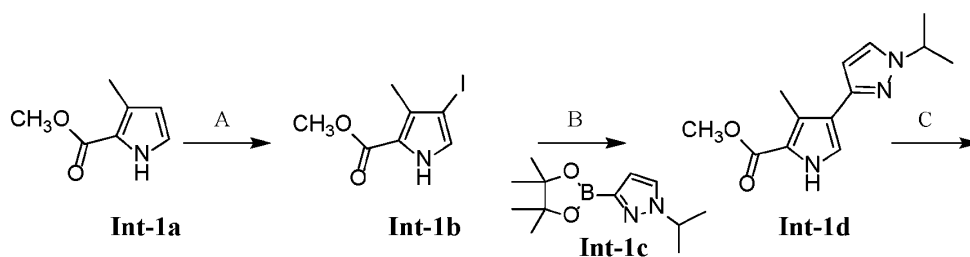
4. EXAMPLES

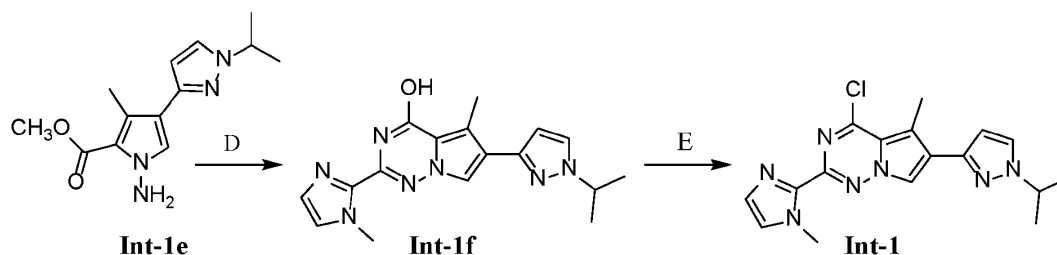
[00459] The present disclosure will now be described with reference to specific example(s) which should not be construed as in any way limiting. International Patent Application No. PCT/US2023/65530, is incorporated herein by reference in its entirety, including the synthetic and purification procedures disclosed therein.

4.1 Synthetic Examples

[00460] Example Int-1: Synthesis of Intermediate Int-1

Scheme 1: The Synthesis of Intermediate Int-1





[00461] **Step A:** Methyl 4-iodo-3-methyl-1*H*-pyrrole-2-carboxylate **Int-1b**.

[00462] N-Iodosuccinimide (33.95 g, 150.91 mmol) was added portionwise to the solution of methyl 3-methyl-1*H*-pyrrole-2-carboxylate **Int-1a** (20.0 g, 143.73 mmol) in DMF (100.0 mL) at 0°C. The reaction mixture was stirred at room temperature for 16 h. Then, the mixture was poured in ice water. The formed precipitate was collected by filtration, washed with water (2×50 mL) and dried *in vacuo* to afford methyl 4-iodo-3-methyl-1*H*-pyrrole-2-carboxylate **Int-1b** (29.0 g, 109.41 mmol, 76.1% yield) as yellow powder.

[00463] **Step B:** Methyl 4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-1d**.

[00464] Methyl 4-iodo-3-methyl-1*H*-pyrrole-2-carboxylate **Int-1b** (26.94 g, 101.64 mmol), 1-isopropyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole **Int-1c** (24.0 g, 101.64 mmol), cesium carbonate (66.24 g, 203.29 mmol) and Pd(dppf)Cl₂ (8.3 g, 10.16 mmol) were dissolved in degassed dioxane (80 mL) under Ar atmosphere. 3.8 mL of water was added *via* syringe and the reaction mixture was stirred at 80°C for 16 h. The mixture was cooled to room temperature, filtered through celite pad and concentrated under reduced pressure. The residue was purified by column chromatography (eluted by Hex:EtOAc 20:1 to 1:2) to afford methyl 4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-1d** (7.5 g, 30.33 mmol, 29.8% yield) as dark-yellow powder.

[00465] **Step C:** Methyl 1-amino-4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-1e**.

[00466] To a solution of methyl 4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-1d** (5.8 g, 22.19 mmol) in DMF (75 mL), sodium hydride (1.15 g, 48.09 mmol) was added at 0°C. The resulting mixture was stirred for 1 h at room temperature and the solution of *O*-(2,4-dinitrophenyl)hydroxylamine (5.75 g, 28.85 mmol) in DMF (50 mL) was added dropwise at 0°C. The reaction mixture was stirred at RT overnight. Then, the aqueous solution of

NH₄Cl (20 mL) was added dropwise to reaction mixture at cooling to 0°C. The product was extracted with EtOAc (3×35 mL) and combined organic layers was washed with water (5×20 mL). The organic extracts were dried over Na₂SO₄ and concentrated *in vacuo* to afford methyl 1-amino-4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-1d** (4.9 g, 73.5% purity, 13.03 mmol, 58.7% yield).

[00467] Step D: 6-(1-Isopropyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-1f**.

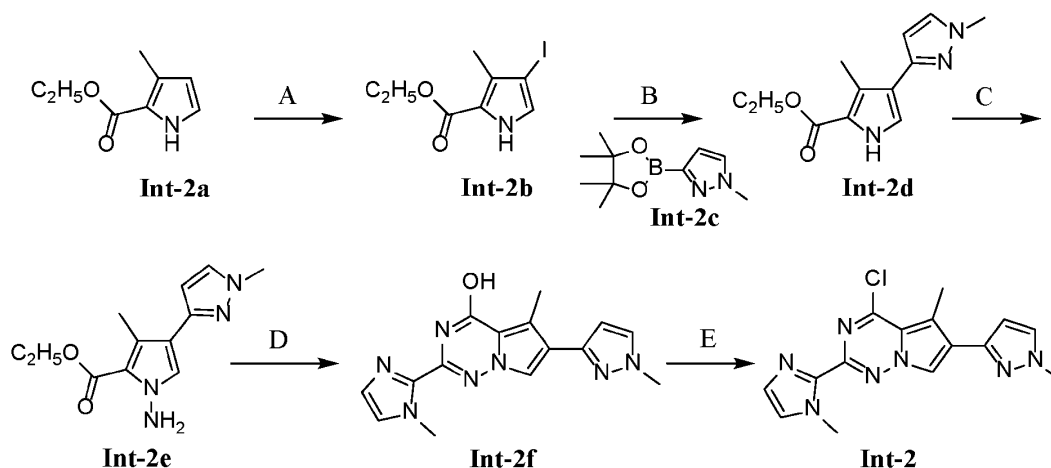
[00468] Sodium hydride (1.77 g, 73.71 mmol) (60% in mineral oil) was added portionwise (over 3 min) to the solution of methyl 1-amino-4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-1d** (5.8 g, 22.11 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (2.37 g, 22.11 mmol) in dioxane (20 mL). The reaction mixture was heated under reflux for 16 h. Then, the mixture was cooled to the room temperature, poured in ice water and neutralized by acetic acid (6.64 g, 110.56 mmol). The formed particulate was collected by filtration, washed with water (2×10 mL) and purified by column chromatography (eluted Hex:EtOAc 10:1 to EtOAc 100%) to afford 6-(1-isopropyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-1f** (1.8 g, 5.34 mmol, 24.1% yield) as dark-yellow solid.

[00469] Step E: 4-Chloro-6-(1-isopropyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine Intermediate **Int-1**.

[00470] 6-(1-Isopropyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-1f** (1.8 g, 5.34 mmol) was dissolved in phosphoryl trichloride (9.81 g, 64.01 mmol, 5.97 mL, 12.0 equiv). The mixture was stirred at 100°C for 16 h. The reaction mixture was concentrated *in vacuo*, poured in ice water (5 mL) and neutralized by K₂CO₃ (pH ~ 9!). The mixture was extracted three times with DCM, dried over Na₂SO₄ and concentrated under reduced pressure to afford 4-chloro-6-(1-isopropyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine intermediate **Int-1** (1.3 g, 3.65 mmol, 68.5% yield) as dark-brown oil.

[00471] Example Int-2: Synthesis of Intermediate Int-2

[00472] Scheme 2: The Synthesis of Intermediate **Int-2**.



[00473] **Step A:** Ethyl 4-iodo-3-methyl-1H-pyrrole-2-carboxylate **Int-2b**.

[00474] N-iodosuccinimide (35.62 g, 158.31 mmol) was added portionwise to the solution of ethyl 3-methyl-1H-pyrrole-2-carboxylate (**Int-2a**) (25.0 g, 163.21 mmol) in DMF (600 mL). The mixture was stirred at ambient temperature for 16h. The mixture was poured into ice water. The formed precipitate was filtered through celite and dried *in vacuo*. Ethyl 4-iodo-3-methyl-1H-pyrrole-2-carboxylate **Int-2b** (33.0 g, 118.25 mmol, 72.5% yield) was obtained.

[00475] **Step B:** Ethyl 3-methyl-4-(1-methyl-1H-pyrazol-3-yl)-1H-pyrrole-2-carboxylate **Int-2d**.

[00476] Ethyl 4-iodo-3-methyl-1H-pyrrole-2-carboxylate **Int-2b** (21.24 g, 76.1 mmol), 1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole **Int-2c** (19.0 g, 91.32 mmol), Pd(dppf)Cl₂·2DCM (6.21 g, 7.61 mmol) and cesium carbonate (49.59 g, 152.2 mmol) was dissolved in degassed dioxane (600 mL) under Ar atmosphere. 30 mL of water was added *via* syringe. The reaction mixture was heated to 100°C and stirred at this temperature for 48 h. The mixture was cooled to room temperature, filtered through celite and concentrated. The residue was purified by column chromatography (SiO₂, Eluted by Hex:EtOAc 20:1 to 1:4). Ethyl 3-methyl-4-(1-methyl-1H-pyrazol-3-yl)-1H-pyrrole-2-carboxylate **Int-2d** (7.0 g, 30.01 mmol, 39.4% yield) was obtained.

[00477] **Step C:** Ethyl 1-amino-3-methyl-4-(1-methyl-1H-pyrazol-3-yl)-1H-pyrrole-2-carboxylate **Int-2e**.

[00478] Sodium hydride (913.91 mg, 38.08 mmol)(60% in mineral oil) was added portionwise to a solution of Ethyl 3-methyl-4-(1-methyl-1H-pyrazol-3-yl)-1H-pyrrole-2-carboxylate **Int-2d**

(4.1 g, 17.58 mmol) in DMF (10 mL) at 0°C. The mixture was stirred for 1 h at room temperature. Then the mixture was cooled to 0°C and O-(2,4-dinitrophenyl)hydroxylamine (4.55 g, 22.85 mmol) was added portionwise. The mixture was stirred for 16 h at room temperature. Then the mixture was poured in ice water, diluted with EtOAc (10 mL), washed with water (5*5 mL), dried *in vacuo* and purified by HPLC (0-2-10 min 30-50 % H₂O/MeOH/0.1NH₄OH, flow 30 mL/min ((loading pump 4 mL MeOH); column: Chromatorex C18 SMB100-5T 100*19 mm, 5 microM). Ethyl 1-amino-3-methyl-4-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate **Int-2e** (3.8 g, 15.31 mmol, 87.1% yield) was obtained.

[00479] **Step D:** 5-Methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-2f**.

[00480] Sodium hydride (1.48 g, 61.76 mmol) (60% in mineral oil) was added portionwise (during 3 min) to the solution of ethyl 1-amino-3-methyl-4-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate **Int-2e** (4.6 g, 18.53 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (2.38 g, 22.23 mmol, 2.38 mL) in dioxane (20 mL). The reaction mixture was heated under reflux for 16 h. Then, the mixture was cooled to room temperature, poured in ice water and neutralized by acetic acid. The formed precipitate was collected by filtration, washed by water (2*10 mL) and dried *in vacuo* and purified by flash chromatography (SiO₂, Hexane-EtOAc). 5-Methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-2f** (1.85 g, 5.98 mmol, 32.3% yield) was obtained. ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm) 2.65 (s, 3H), 3.82 (s, 3H), 3.97 (s, 3H), 6.50 (d, 1H), 7.12 (s, 1H), 7.47 (d, 1H), 7.58 (d, 1H), 7.87 (d, 1H), 11.04 (br s, 1H). LCMS(ESI): MS Calculated [M+1] 310.2. Found [M+1] 310.2; Rt = 1.112 min.

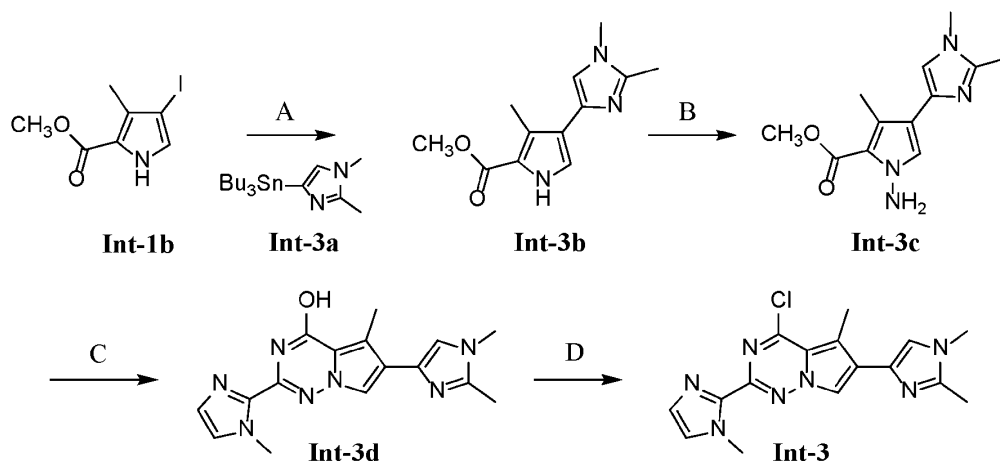
[00481] **Step E:** 4-Chloro-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine Intermediate **Int-2**.

[00482] 5-Methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-2f** (1.85 g, 5.98 mmol) was dissolved in phosphoryl trichloride (9.17 g, 59.8 mmol, 5.57 mL). The mixture was heated to 100°C and stirred at this temperature for 16 h. The reaction mixture was concentrated *in vacuo*, poured in ice water (5 mL) and neutralized by K₂CO₃. The formed precipitate was collected by filtration, washed by water (2*20 mL) and dried *in vacuo*. 4-Chloro-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine intermediate **Int-2** (1.7 g, 5.19 mmol, 86.7% yield) was obtained.

[00483] LCMS(ESI): MS Calculated [M+1] 328.0. Found [M+1] 328.0; Rt = 1.014 min.

[00484] **Example Int-3: Synthesis of Intermediate Int-3**

[00485] Scheme 3. The Synthesis of Intermediate **Int-3**.



[00486] **Step A:** Methyl 4-(1,2-dimethyl-1*H*-imidazol-4-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-3b**.

[00487] Methyl 4-iodo-3-methyl-1*H*-pyrrole-2-carboxylate **Int-1b** (3.0 g, 11.32 mmol) and 1,2-dimethyl-4-(tributylstannyl)-1*H*-imidazole **Int-3a** (6 g 15.58 mmol), Pd(dppf)Cl₂ (1.27 g 1.556 mmol) and CuI (0.3 g 1.578 mmol) were suspended in degassed THF (50 mL). The reaction mixture was stirred under argon at 60 °C overnight, cooled to rt, and diluted with ethyl acetate. The organic layer was washed with water and brine, dried over MgSO₄, filtered, concentrated *in vacuo* and purified by FCC (Interchim; 330 g SiO₂, chloroform/acetonitrile with acetonitrile from 50~100% further acetonitrile/methanol with methanol from 0~32% flow rate = 130 mL/min, R_v = 6.5-8 CV) to give methyl 4-(1,2-dimethyl-1*H*-imidazol-4-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-3b** (1.59 g, 95.0% purity, 6.46 mmol, 57% yield).

[00488] **Step B:** Methyl 1-amino-4-(1,2-dimethyl-1*H*-imidazol-4-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-3c**.

[00489] Sodium hydride (0.4g, 10 mmol) (60% on mineral oil), was added portion wise to a solution of methyl 4-(1,2-dimethyl-1*H*-imidazol-4-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-3b** (1.59 g, 6.8 mmol) in DMF (15 mL) at 0°C. The mixture was stirred for 1h at room temperature. Then the mixture was cooled to 0°C and O-(2,4-dinitrophenyl)hydroxylamine (1.93 g, 9.69 mmol) was added portion-wise. The mixture was stirred for 16 h at room temperature.

Then the mixture was poured in ice water and extracted with EtOAc (3*40 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give methyl 1-amino-4-(1,2-dimethyl-1*H*-imidazol-4-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-3c** (6.75 g, 4.0% purity, 1.09 mmol, 16.8% yield) and used for the next step without further purification.

[00490] Step C: 6-(1,2-Dimethyl-1*H*-imidazol-4-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-3d**.

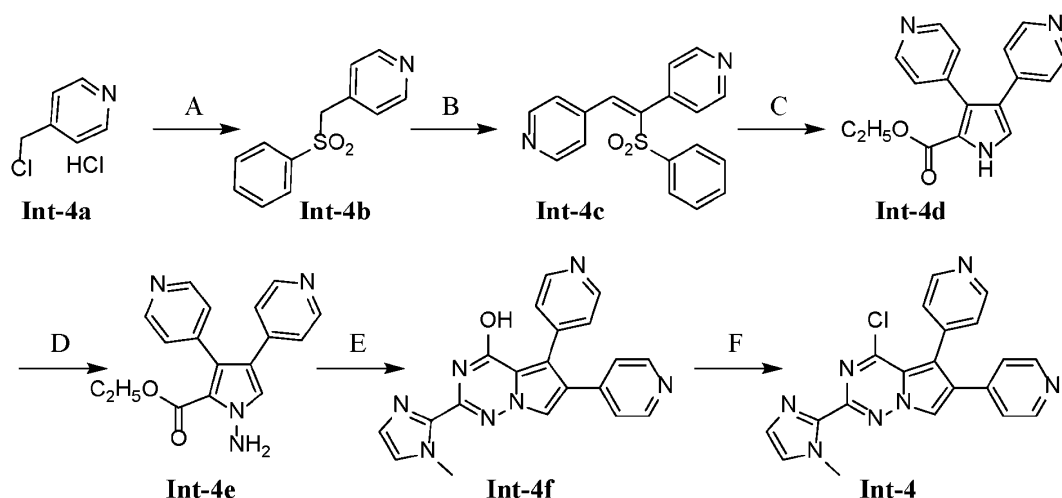
[00491] Sodium hydride (0.65 g, 16 mmol) (60% on mineral oil) was added portion wise to the solution of methyl 1-amino-4-(1,2-dimethyl-1*H*-imidazol-4-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-3c** (6.75 g, 27.2 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (174.8 mg, 1.63 mmol) in dry dioxane (40 mL). The reaction mixture was heated to 80°C and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured in ice water, neutralized with acetic acid, and extracted with EtOAc (3*40 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo*, and purified by FCC to give 6-(1,2-dimethyl-1*H*-imidazol-4-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-3d** (100.0 mg, 95.0% purity, 293.8 μmol, 27% yield).

[00492] Step D: 4-Chloro-6-(1,2-dimethyl-1*H*-imidazol-4-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-3**.

[00493] To the solution of 6-(1,2-dimethyl-1*H*-imidazol-4-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-3d** (99.52 mg, 307.97 μmol) in CH₃CN (3 mL), phosphoryl trichloride (1.78 g, 11.7 mmol, 1.08 mL, 40.0 equiv) was added dropwise. The mixture was heated to 80°C, stirred at this temperature for 16h, and concentrated *in vacuo*. The residue was dissolved in EtOAc/CH₃CN 5 mL/5 mL washed with ice-cold NaHCO₃, brine, dried over Na₂SO₄, concentrated *in vacuo*, to give 4-Chloro-6-(1,2-dimethyl-1*H*-imidazol-4-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-3** (45.0 mg, 131.66 μmol, 45% yield).

[00494] Example Int-4: Synthesis of Intermediate Int-4

[00495] Scheme 4: The Synthesis of Intermediate **Int-4**.



[00496] **Step A:** 4-((Phenylsulfonyl)methyl)pyridine **Int-4b**.

[00497] Potassium acetate (13.22 g, 134.97 mmol) was added in one portion to a stirred solution of 4-(chloromethyl)pyridine hydrochloride (20.0 g, 122.7 mmol) and sodium benzenesulfonate (22.13 g, 134.97 mmol) in isopropyl alcohol (300 mL). The mixture was heated to 80°C and stirred at this temperature overnight. Then, the reaction mixture was concentrated *in vacuo*, diluted with ice water (150 mL) and extracted 3 times with EtOAc (3*150 mL). The organic phase was washed with water, and brine, dried over Na₂SO₄ and concentrated *in vacuo* to give 4-((phenylsulfonyl)methyl)pyridine **Int-4b** (24.3 g, 95.0% purity, 98.96 mmol, 80.6% yield) as a yellow solid.

[00498] **Step B:** (Z)-4,4'-(1-(Phenylsulfonyl)ethene-1,2-diyl)dipyridine **Int-1c**.

[00499] 4-((phenylsulfonyl)methyl)pyridine **Int-4b** (14.3 g, 61.36 mmol) in THF (400 mL) was added LiHMDS (1.1 M in THF/ ethylbenzene, 77.8 mL), at -78°C and the mixture was stirred for 10 min. To the solution was added isonicotinaldehyde (9.85 g, 92.04 mmol), and the mixture was stirred for 1 hr. Diethyl chlorophosphonate (12.66 g, 73.63 mmol) was added, and the mixture was stirred for 1 hr. Then LiHMDS (1.1 M in THF/ ethylbenzene, 62.2 mL) was added at -78°C, and the mixture was stirred to ambient temperature. The resulting mixture was poured into saturated aq NH₄Cl (400 mL) and extracted with EtOAc (3*300 mL). The organic phase was washed with water, and brine, dried over Na₂SO₄, concentrated *in vacuo*, and purified by FCC to give (Z)-4,4'-(1-(phenylsulfonyl)ethene-1,2-diyl)dipyridine **Int-1c** (3.7 g, 90.0% purity, 10.33 mmol, 16.8% yield).

[00500] **Step C:** Ethyl 3,4-di(pyridin-4-yl)-1*H*-pyrrole-2-carboxylate **Int-4d**.

[00501] Potassium *t*-butoxide (1.29 g, 11.49 mmol) was added portionwise to the solution of (Z)-4,4'-(1-(phenylsulfonyl)ethene-1,2-diyl)dipyridine **Int-1c** (3.7 g, 11.49 mmol) and ethyl 2-isocyanoacetate (1.3 g, 11.49 mmol) in dry THF (60 mL) at (-10°C), and stirred at room temperature overnight. The reaction mixture was diluted with ice water (60 mL) and extracted 3 times by EtOAc (3*60 mL). The organic phase washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Column Interchim, 120 g SiO₂, chloroform/acetonitrile (0-100%), further acetonitrile/TEA (2,5%), flow rate = 80 ml/min, 27,1-32,1CV.) to give ethyl 3,4-di(pyridin-4-yl)-1*H*-pyrrole-2-carboxylate **Int-4d** (1.2 g, 95.0% purity, 3.89 mmol, 33.8% yield).

[00502] **Step D:** Ethyl 1-amino-3,4-di(pyridin-4-yl)-1*H*-pyrrole-2-carboxylate **Int-4e**.

[00503] Sodium hydride (245 mg, 6.125 mmol)(60% in mineral oil), was added portionwise to a solution of ethyl 3,4-di(pyridin-4-yl)-1*H*-pyrrole-2-carboxylate **Int-4d** (1.2 g, 4.09 mmol) in DMF (30 mL) at 0°C. The mixture was stirred for 1 h at room temperature. Then the mixture was cooled to 0°C O-(2,4-dinitrophenyl)hydroxylamine (1.06 g, 5.32 mmol) was added portionwise. The mixture was stirred for 16 h at room temperature. Then the mixture was poured into ice water, and extracted with EtOAc (3*15 mL). The organic phase was washed with water, and brine, dried over Na₂SO₄, and concentrated *in vacuo* to give ethyl 1-amino-3,4-di(pyridin-4-yl)-1*H*-pyrrole-2-carboxylate **Int-4e** (1.8 g, 70.0% purity, 4.09 mmol, 99.8% yield) as dark oil.

[00504] **Step E:** 2-(1-Methyl-1*H*-imidazol-2-yl)-5,6-di(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-4f**.

[00505] Sodium hydride (0.46 g, 11.5 mmol) (60% in mineral oil) was added portionwise to the solution of ethyl 1-amino-3,4-di(pyridin-4-yl)-1*H*-pyrrole-2-carboxylate **Int-4e** (1.8 g, 5.84 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (938.1 mg, 8.76 mmol) in dry dioxane (12 mL). The reaction mixture was heated 80°C and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured in ice water, neutralized with acetic acid, and extracted with EtOAc (3*15 mL). The organic phase washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* to give 2-(1-methyl-1*H*-imidazol-2-yl)-5,6-di(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-4f** (900.0 mg, 50.0% purity, 1.22 mmol, 20.9% yield) and used for the next step without further purification.

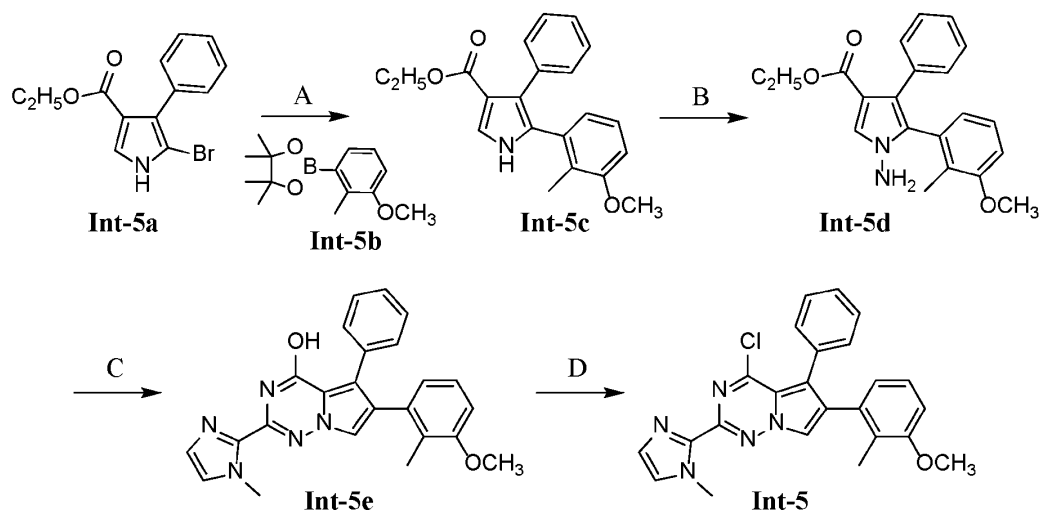
[00506] **Step F:** 4-Chloro-2-(1-methyl-1*H*-imidazol-2-yl)-5,6-di(pyridin-4-yl)pyrrolo[2,1-

f[1,2,4]triazine **Int-4**.

[00507] To the solution of 2-(1-methyl-1*H*-imidazol-2-yl)-5,6-di(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-4f** (900.0 mg, 2.44 mmol) in CH₃CN (20 mL), phosphoryl trichloride (1.48 g, 9.76 mmol) was added dropwise. The mixture was heated to 80°C and stirred at this temperature for 16 h and then concentrated *in vacuo*, poured in ice water (5 mL) and neutralized by NaHCO₃ (aq soln). The obtained precipitate was collected by filtration, washed by water (2*20 mL) and dried *in vacuo*, to give 4-chloro-2-(1-methyl-1*H*-imidazol-2-yl)-5,6-di(pyridin-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-4** (500.0 mg, 72.0% purity, 928.25 μmol, 38.1% yield) as yellow solid.

[00508] **Example Int-5: Synthesis of Intermediate Int-5**

[00509] Scheme 5: The Synthesis of Intermediate **Int-5**.



[00510] **Step A:** Ethyl 5-(3-methoxy-2-methylphenyl)-4-phenyl-1*H*-pyrrole-3-carboxylate **Int-5c**.

[00511] Ethyl 4-bromo-3-phenyl-1*H*-pyrrole-2-carboxylate **Int-5a** (7.95 g, 27.13 mmol), 2-(3-methoxy-2-methylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane **Int-5b** (7.41 g, 29.85 mmol), cesium carbonate (17.68 g, 54.26 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (2.21 g, 2.71 mmol) were suspended in degassed dioxane : water (80 mL : 10 mL). The mixture was heated under argon at 90°C overnight. After cooling to room temperature, the mixture was diluted with ethyl acetate (150 mL), the organic layer was washed with water (150 mL) and saturated brine

(150 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography to afford ethyl 5-(3-methoxy-2-methylphenyl)-4-phenyl-1*H*-pyrrole-3-carboxylate **Int-5c** (5.2 g, 15.5 mmol, 57.1% yield).

[00512] Step B: Ethyl 1-amino-5-(3-methoxy-2-methylphenyl)-4-phenyl-1*H*-pyrrole-3-carboxylate **Int-5d**.

[00513] To a solution of ethyl 5-(3-methoxy-2-methylphenyl)-4-phenyl-1*H*-pyrrole-3-carboxylate **Int-5c** (670.01 mg, 2.0 mmol) in DMF (15 mL) sodium hydride (103.87 mg, 4.33 mmol) was added at 0°C. After 1 h O-(2,4-dinitrophenyl)hydroxylamine (517.11 mg, 2.6 mmol) was added portion-wise at 0°C. The reaction mixture was stirred at room temperature overnight. An aqueous solution of NH₄Cl was added to reaction mixture, extracted with EtOAc (3*75 mL), combined EtOAc was washed with water (7*30 mL), dried and evaporated under reduce pressure to give ethyl 1-amino-5-(3-methoxy-2-methylphenyl)-4-phenyl-1*H*-pyrrole-3-carboxylate **Int-5d** (620 mg, 1.77 mmol, 88.5% yield).

[00514] Step C: 6-(3-Methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-5e**.

[00515] Sodium hydride (571.09 mg, 23.8 mmol) (60% on mineral oil) was added portionwise (during 3 min) to the solution of ethyl 1-amino-5-(3-methoxy-2-methylphenyl)-4-phenyl-1*H*-pyrrole-3-carboxylate **Int-5d** (2.0 g, 5.71 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (1.22 g, 11.42 mmol) in dioxane (20 mL). The reaction mixture was heated to reflux and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured in ice water (30 mL), and neutralized with acetic acid. The formed precipitate was collected by filtration, washed with water (2*100 mL), dried *in vacuo*. 6-(3-Methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-5e** (1.8 g, 4.37 mmol, 76.6% yield) was obtained.

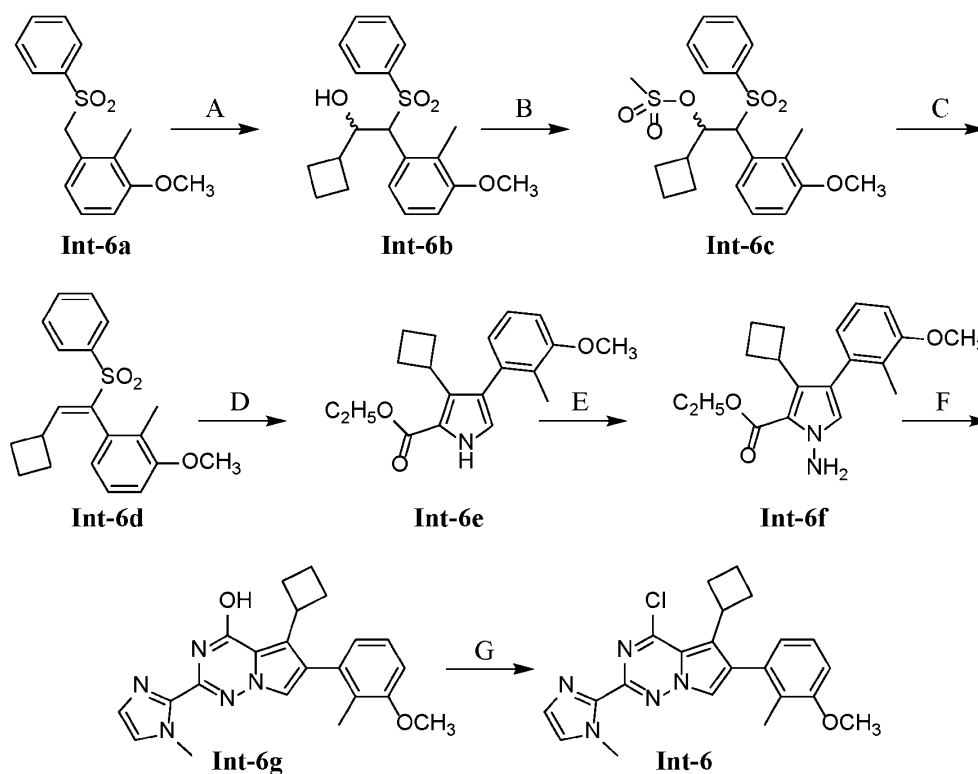
[00516] Step D: 4-Chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-phenylpyrrolo[2,1-*f*][1,2,4]triazine **Int-5**.

[00517] 6-(3-Methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-phenylpyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-5e** (1.8 g, 4.38 mmol) was suspended in 15 mL POCl₃. The mixture was heated to 100°C and stirred at this temperature for 16 h. The reaction mixture was concentrated *in vacuo*, poured in ice water (50 mL) and neutralized with K₂CO₃. The formed precipitate was collected by filtration, washed with water (2*75 mL), and dried *in vacuo*. 4-Chloro-6-(3-

methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-phenylpyrrolo[2,1-*f*][1,2,4]triazine
Int-5 (1.75 g, 4.07 mmol, 93% yield) was obtained and used in next step without further purification.

[00518] Example Int-6: Synthesis of Intermediate Int-5

[00519] Scheme 6: The Synthesis of Intermediate Int-6.



[00520] Step A: 1-Cyclobutyl-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethan-1-ol
Int 6b.

[00521] To 1-methoxy-2-methyl-3-((phenylsulfonyl)methyl)benzene **Int 6b** (3.01 g, 10.88 mmol) in THF (200 mL) was added LiHMDS (1.1 M in THF/ ethylbenzene, 10.8 mL), at -78°C and the mixture was stirred for 1 hr. To the resulting mixture was added cyclobutanecarbaldehyde (1.83 g, 21.77 mmol), and followed by tetrachlorotitanium (2.25 g, 11.97 mmol, 1.3 mL, 1.1 equiv). The mixture was stirred for 1 h at -78°C, and then to ambient temperature overnight. The resulting mixture was poured into sat. aq NH₄Cl (150 mL) and extracted with EtOAc (3*100 mL). The organic phase washed with water, brine, dried over

Na₂SO₄, concentrated *in vacuo* to give 1-cyclobutyl-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethan-1-ol **Int-6b** (4.12 g, 85.0% purity, 9.72 mmol, 89.2% yield).

[00522] Step B: 1-Cyclobutyl-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethyl methanesulfonate **Int-6c**.

[00523] Methanesulfonyl chloride (3.91 g, 34.29 mmol) was added dropwise at 0°C to a stirred solution of 1-cyclobutyl-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethan-1-ol **Int-6b** (4.12 g, 11.43 mmol) in pyridine (40 mL). The mixture was stirred at room temperature overnight. Then reaction mixture was concentrated *in vacuo*, diluted with ice water (50 mL) and extracted 3 times by EtOAc (3*50 mL). The organic phase was washed with 1N HCl (20 mL), water, and brine, dried over Na₂SO₄ and concentrated *in vacuo* to give 1-cyclobutyl-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethyl methanesulfonate **Int-6c** (3.4 g, 80.0% purity, 6.2 mmol, 54.3% yield).

[00524] Step C: (*E*)-1-(2-Cyclobutyl-1-(phenylsulfonyl)vinyl)-3-methoxy-2-methylbenzene **Int-6c**.

[00525] DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (1.2 g, 7.91 mmol) was added dropwise at room temperature to a stirred solution of 1-cyclobutyl-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethyl methanesulfonate **Int-6c** (2.89 g, 6.59 mmol) in CH₂Cl₂ (40 mL). The mixture was stirred at 45°C overnight. Then reaction mixture was washed with 1N HCl (20 mL), water, and brine, dried over Na₂SO₄ and concentrated *in vacuo* to give (*E*)-1-(2-cyclobutyl-1-(phenylsulfonyl)vinyl)-3-methoxy-2-methylbenzene **Int-6c** (2.38 g, 65.0% purity, 4.52 mmol, 68.5% yield).

[00526] Step D: Ethyl 3-cyclobutyl-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-6e**.

[00527] Potassium t-butoxide (1.2 g, 10.73 mmol) was added portion wise to the solution of (*E*)-1-(2-cyclobutyl-1-(phenylsulfonyl)vinyl)-3-methoxy-2-methylbenzene **Int-6c** (2.45 g, 7.15 mmol) and ethyl 2-isocynoacetate (1.21 g, 10.73 mmol) in dry THF (60 mL) at (-10°C) and stirred at room temperature overnight. The reaction mixture was diluted with ice water (40 mL) and extracted 3 times by EtOAc (3*40 mL). The organic phase washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (2d: Interchim; 40 g SiO₂, chloroform/MeCN with MeCN from 0~7%, flow rate = 40 mL/min, R_v = 5-6CV) to give ethyl 3-cyclobutyl-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-6e** (1.0 g, 80.0%

purity, 2.55 mmol, 35.7% yield).

[00528] Step E: Ethyl 1-amino-3-cyclobutyl-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-6f**.

[00529] Sodium hydride (0.2g, 5 mmol) (60% in mineral oil), was added portion-wise to a solution of ethyl 3-cyclobutyl-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-6e** (1.0 g, 3.19 mmol) in DMF (12 mL) at 0°C. The mixture was stirred for 1 h at room temperature. Then the mixture was cooled to 0°C and O-(2,4-dinitrophenyl)hydroxylamine (761.78 mg, 3.83 mmol) was added portion wise. The mixture was stirred for 16 h at room temperature. Then the mixture was poured in ice water and extracted with EtOAc (3*30 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* to give ethyl 1-amino-3-cyclobutyl-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-6f** (2.4 g, 32.0% purity, 2.34 mmol, 91.6% yield) and used for the next step without further purification.

[00530] Step F: 5-Cyclobutyl-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-6g**.

[00531] Sodium hydride (0.58 g, 14.5 mmol) (60% in mineral oil) was added portion wise to the solution of ethyl 1-amino-3-cyclobutyl-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-6f** (2.4 g, 7.31 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (375.61 mg, 3.51 mmol) in dry dioxane (24 mL). The reaction mixture was heated 80°C and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured in ice water, neutralized with acetic acid, and extracted with EtOAc (3*30 mL). The organic phase washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 80g SiO₂, chloroform/MeCN with MeCN from 0~25%, flow rate = 85 mL/min, R_v = 7-9 CV) to give 5-cyclobutyl-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-6g** (580.0 mg, 95.0% purity, 1.41 mmol, 60.5% yield).

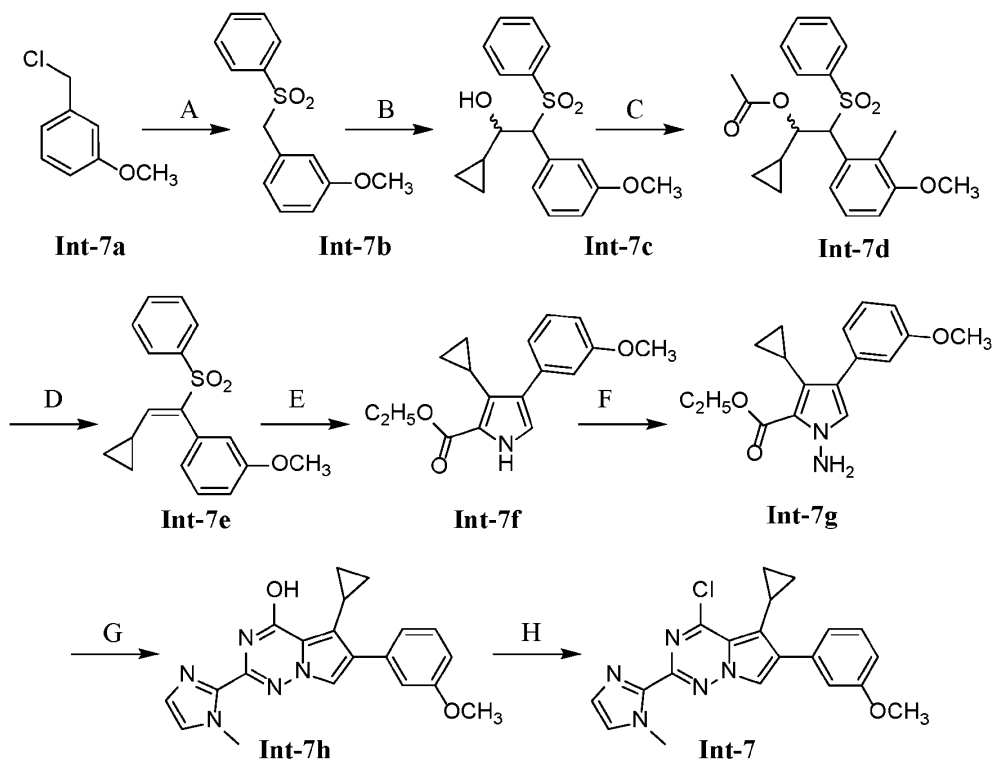
[00532] Step G: 4-Chloro-5-cyclobutyl-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-6**.

[00533] To the solution of 5-cyclobutyl-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-6g** (579.55 mg, 1.49 mmol) in CH₃CN (15 mL), phosphoryl trichloride (9.05 g, 59.57 mmol, 5.5 mL, 40.0 equiv) was added dropwise. The mixture was heated to 80°C and stirred at this temperature for 16 h and then concentrated *in vacuo*, dissolved in EtOAc/CH₃CN 30 mL/30 mL washed by ice-cold NaHCO₃, brine, dried over

Na₂SO₄, concentrated *in vacuo*, to give 4-chloro-5-cyclobutyl-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-6h** (380.0 mg, 95.0% purity, 885.03 μmol, 59.5% yield).

[00534] Example Int-7: Synthesis of Intermediate Int-7

[00535] Scheme 7: The Synthesis of Intermediate **Int-7**.



[00536] Step A: 1-Methoxy-3-((phenylsulfonyl)methyl)benzene **Int-7b**.

[00537] To the solution of 1-(chloromethyl)-3-methoxybenzene **Int-7a** (5.4 g, 34.61 mmol) in dry IPA (80 mL), sodium benzenesulfinate (5.96 g, 36.34 mmol) was added portion wise at room temperature, and heated 80°C overnight. Afterwards the reaction mixture was evaporated under reduced pressure, diluted with water (100 mL) and extracted 3 times by EtOAc (3*100 mL). The organic phase washed with water, brine, dried over Na₂SO₄ and concentrated *in vacuo* to give 1-methoxy-3-((phenylsulfonyl)methyl)benzene **Int-7b** (6.63 g, 95.0% purity, 24.01 mmol, 69.4% yield).

[00538] Step B: 1-Cyclopropyl-2-(3-methoxyphenyl)-2-(phenylsulfonyl)ethan-1-ol **Int-7c**.

[00539] To 1-methoxy-3-((phenylsulfonyl)methyl)benzene **Int-7b** (3.0 g, 11.45 mmol) in

THF (60 mL) was added LiHMDS (1.1 M in THF/ ethylbenzene, 12 mL), at -78°C and the mixture was stirred for 1 h. To the resulting mixture was added cyclopropanecarbaldehyde (1.6 g, 22.89 mmol), followed by tetrachlorotitanium (2.36 g, 12.59 mmol). The mixture was stirred for 1 h at -78°C, and then to ambient temperature overnight. The resulting mixture was poured into saturated aq NH₄Cl (50 mL) and extracted with EtOAc (3*50 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to afford 1-cyclopropyl-2-(3-methoxyphenyl)-2-(phenylsulfonyl)ethan-1-ol **Int-7c** (4.0 g, 60.0% purity, 7.22 mmol, 63.1% yield).

[00540] Step C: 1-Cyclopropyl-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethyl acetate **Int-7d**.

[00541] Acetyl acetate (644.56 mg, 6.32 mmol) was added dropwise at room temperature to a stirred solution of 1-cyclopropyl-2-(3-methoxyphenyl)-2-(phenylsulfonyl)ethan-1-ol **Int-7c** (2.0 g, 6.02 mmol) in pyridine (20 mL). The mixture was stirred at room temperature overnight. Then reaction mixture was concentrated *in vacuo*, diluted with EtOAc, washed with 1N HCl (20 mL), water, and brine, dried over Na₂SO₄, and concentrated *in vacuo* to give 1-cyclopropyl-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethyl acetate **Int-7d** (2.12 g, 70.0% purity, 3.96 mmol, 94.1% yield).

[00542] Step D: (*E*)-1-(2-Cyclopropyl-1-(phenylsulfonyl)vinyl)-3-methoxybenzene **Int-7e**.

[00543] DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) (723.5 mg, 4.76 mmol) was added dropwise at room temperature to a stirred solution of 1-cyclopropyl-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethyl acetate **Int-7d** (2.12 g, 5.66 mmol) in CH₂Cl₂ (25 mL). The mixture was stirred at 45°C overnight. Then reaction mixture was washed with 1N HCl (20 mL), water, and brine, dried over Na₂SO₄ and concentrated *in vacuo* to give (*E*)-1-(2-cyclopropyl-1-(phenylsulfonyl)vinyl)-3-methoxybenzene **Int-7e** (1.3 g, 70.0% purity, 2.89 mmol, 73% yield).

[00544] Step E: Ethyl 3-cyclopropyl-4-(3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate **Int-7f**.

[00545] Potassium *t*-butoxide (486.46 mg, 4.34 mmol) was added portion wise to the solution of (*E*)-1-(2-cyclopropyl-1-(phenylsulfonyl)vinyl)-3-methoxybenzene **Int-7e** (1.3 g, 4.13 mmol) and ethyl 2-isocyanoacetate (490.88 mg, 4.34 mmol) in dry THF (60 mL) at (-10°C), and stirred at room temperature overnight. Then reaction mixture was diluted with ice water (40 mL) and extracted 3 times by EtOAc (3*40 mL). The organic phase washed with water, brine, dried over

Na₂SO₄, concentrated *in vacuo*. The residue was purified by FCC (Interchim; 40 g SiO₂, hexane/MtBE with MtBE from 0~40%, flow rate = 40mL/min, R_v = 9-10CV) to give ethyl 3-cyclopropyl-4-(3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate **Int-7f** (500.0 mg, 90.0% purity, 1.58 mmol, 54.5% yield).

[00546] Step F: Ethyl 1-amino-3-cyclopropyl-4-(3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate **Int-7g**.

[00547] Sodium hydride (0.1g, 2.5 mmol)(60% in mineral oil), was added portion wise to a solution of ethyl 3-cyclopropyl-4-(3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate **Int-7f** (500.0 mg, 1.75 mmol) in DMF (5 mL) at 0°C. The mixture was stirred for 1 h at room temperature. Then the mixture was cooled to 0°C and O-(2,4-dinitrophenyl)hydroxylamine (522.82 mg, 2.63 mmol) was added portion wise. The mixture was stirred for 16 h at room temperature. Then the mixture was poured in ice water, and extracted with EtOAc (3*10 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* to give ethyl 1-amino-3-cyclopropyl-4-(3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate **Int-7g** (740.0 mg, 60.0% purity, 1.48 mmol, 84.4% yield) and used for the next step without further purification.

[00548] Step G: 5-Cyclopropyl-6-(3-methoxyphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-7h**.

[00549] Sodium hydride (0.2g, 5 mmol) (60% in mineral oil) was added portion wise to the solution of ethyl 1-amino-3-cyclopropyl-4-(3-methoxyphenyl)-1*H*-pyrrole-2-carboxylate **Int-7g** (740.0 mg, 2.46 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (237.26 mg, 2.22 mmol) in dry dioxane (8 mL). Then reaction mixture was heated to 80°C and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured in ice water, neutralized with acetic acid and extracted with EtOAc (3*10 mL). The organic phase washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 12g SiO₂, hexane /MtBE/methanol with methanol from 0~15%, flow rate =15 mL/min, R_v = 27-36 CV) to give 5-cyclopropyl-6-(3-methoxyphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-7h** (90.0 mg, 88.0% purity, 219.15 μmol, 14.8% yield).

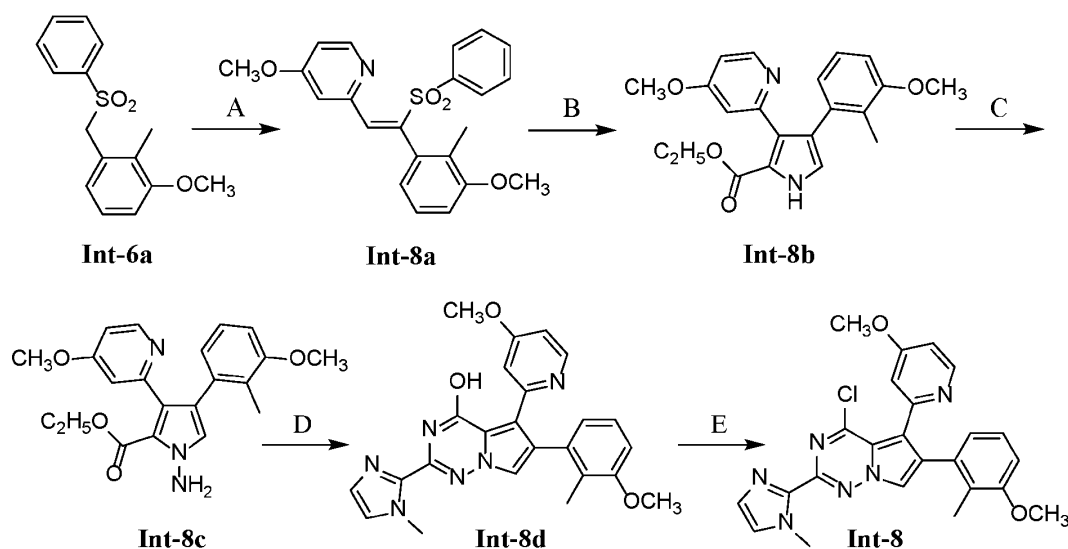
[00550] Step H: 4-Chloro-5-cyclopropyl-6-(3-methoxyphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-7**.

[00551] To the solution of 5-cyclopropyl-6-(3-methoxyphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-7h** (90.0 mg, 249.03 μmol) in CH₃CN (1.5 mL),

phosphoroyl trichloride (1.33 g, 8.76 mmol) was added dropwise. The mixture was heated to 80°C and stirred at this temperature for 16 h and then concentrated *in vacuo*, dissolved in EtOAc/CH₃CN 10 mL/10 mL and washed with ice cold NaHCO₃, brine, dried over Na₂SO₄, concentrated *in vacuo*, to give 4-chloro-5-cyclopropyl-6-(3-methoxyphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-7** (50.0 mg, 90.0% purity, 118.47 μmol, 54.1% yield).

[00552] Example Int-8: Synthesis of Intermediate Int-8

[00553] Scheme 8: The Synthesis of Intermediate Int-8.



[00554] Step A: (Z)-4-Methoxy-2-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)pyridine **Int-8a**.

[00555] To 1-methoxy-2-methyl-3-((phenylsulfonyl)methyl)benzene **Int-6a** (5.0 g, 18.09 mmol) in THF (200 mL) was added LiHMDS (1.1 M in THF/ ethylbenzene, 20ml), at -78°C and the mixture was stirred for 45 min. To this solution was added 4-methoxypyridine-2-carbaldehyde (2.98 g, 21.71 mmol), and the mixture was stirred for 1 h. Then diethyl chlorophosphate (3.73 g, 21.71 mmol) was added, and the mixture was stirred for 1 h, LiHMDS (1.1 M in THF/ ethylbenzene, 20 ml) was added at -78°C, and the mixture was stirred to ambient temperature. The resulting mixture was poured into saturated aq NH₄Cl (80ml) and extracted with EtOAc (3*80 mL). The organic phase washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* to give (Z)-4-methoxy-2-(2-(3-methoxy-2-methylphenyl)-2-

(phenylsulfonyl)vinyl)pyridine **Int-8a** (10.5 g, 65.0% purity, 17.26 mmol, 95% yield) and used for the next step without further purification.

[00556] Step B: Ethyl 4-(3-methoxy-2-methylphenyl)-3-(4-methoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-8b**.

[00557] Potassium *t*-butoxide (2.9 g, 25.88 mmol) was added portion wise to the solution of (Z)-4-methoxy-2-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)pyridine **Int-8a** (10.5 g, 26.55 mmol) and ethyl 2-isocyanoacetate (2.93 g, 25.88 mmol) in dry THF (150 mL) at (-10°C), and stirred at room temperature overnight. Then the reaction mixture was diluted with ice water (100 mL) and extracted 3 times with EtOAc (3*80 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 220g SiO₂, chloroform/acetonitrile with acetonitrile from 0~50%, flow rate =100 mL/min, Rv = 14-18CV) to give ethyl 4-(3-methoxy-2-methylphenyl)-3-(4-methoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-8b** (2.47 g, 95.0% purity, 6.4 mmol, 37% yield).

[00558] Step C: Ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(4-methoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-8c**.

[00559] Sodium hydride (0.4 g, 10 mmol) (60% in mineral oil), was added portion wise to a solution of ethyl 4-(3-methoxy-2-methylphenyl)-3-(4-methoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-8b** (2.47 g, 6.74 mmol) in DMF (30 mL) at 0°C, and stirred for 1h at this temperature. Then O-(2,4-dinitrophenyl)hydroxylamine (2.01 g, 10.11 mmol) was added in one portion at -10°C. The mixture was stirred for 16 h at room temperature. Then the mixture was poured in ice water (250 mL), and extracted with EtOAc (3*100 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* to give ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(4-methoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-8c** (2.95 g, 70.0% purity, 5.41 mmol, 80% yield).

[00560] Step D: 6-(3-Methoxy-2-methylphenyl)-5-(4-methoxypyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-8d**.

[00561] Sodium hydride (0.62 g, 15 mmol) (60% in mineral oil) was added portion wise to the solution of ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(4-methoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-8c** (2.95 g, 7.73 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (869.15 mg, 8.12 mmol) in dry dioxane (40 mL). Then the reaction mixture was heated 80°C and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured in

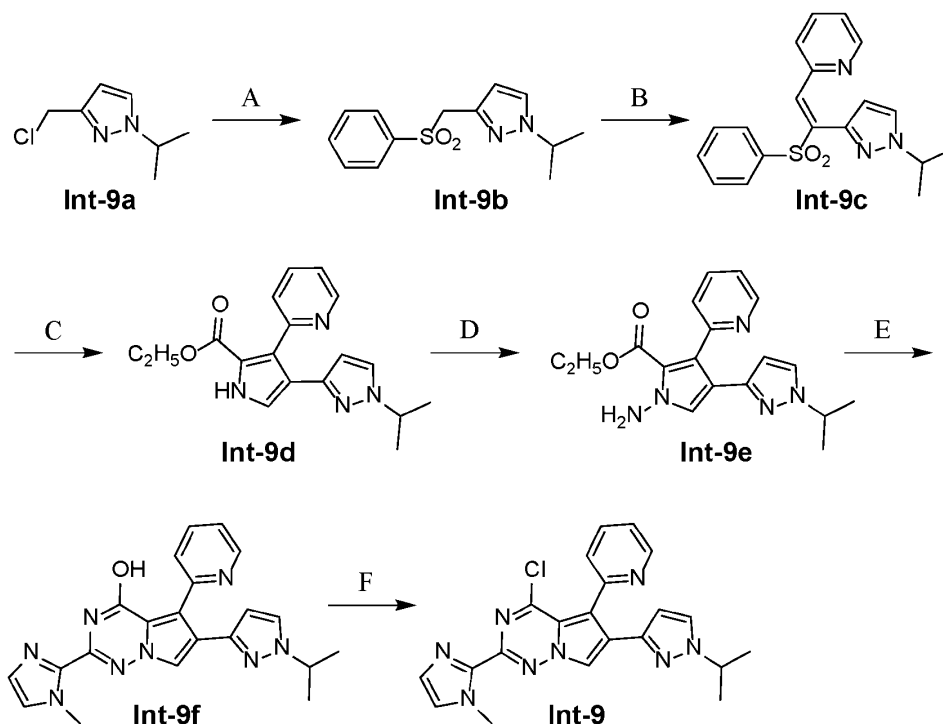
ice water, neutralized with acetic acid, and extracted with EtOAc (3*50 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim, 120 g SiO₂, chloroform/acetonitrile(0-100%)/methanol (0-70%) flow rate = 80 mL/min, 26,5-28,5CV.) to give 6-(3-methoxy-2-methylphenyl)-5-(4-methoxypyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-8d** (950.0 mg, 80.0% purity, 1.72 mmol, 31% yield).

[00562] Step E: 4-Chloro-6-(3-methoxy-2-methylphenyl)-5-(4-methoxypyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-8**.

[00563] To the solution of 6-(3-methoxy-2-methylphenyl)-5-(4-methoxypyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-8d** (500.0 mg, 1.13 mmol) in CH₃CN (12 mL), phosphoryl trichloride (6.87 g, 45.21 mmol) was added dropwise. The mixture was heated to 80°C and stirred at this temperature for 16 h and then concentrated *in vacuo*, dissolved in EtOAc/CH₃CN 10 mL /10 mL, washed with ice cold NaHCO₃, brine, dried over Na₂SO₄, concentrated *in vacuo*, to give 4-chloro-6-(3-methoxy-2-methylphenyl)-5-(4-methoxypyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-8** (520.0 mg, 90.0% purity, 1.02 mmol, 89% yield).

[00564] Example Int-9: Synthesis of Intermediate Int-9

[00565] Scheme 9: The Synthesis of Intermediate **Int-9**



[00566] **Step A:** 1-Isopropyl-3-((phenylsulfonyl)methyl)-1H-pyrazole **Int-9b**.

[00567] To the solution of 3-(chloromethyl)-1-isopropyl-1H-pyrazole **Int-9a** (10.5 g, 66.43 mmol) in dry isopropanol (75 mL), sodium benzenesulfinate (11.98 g, 73.07 mmol) was added portionwise at RT and heated 80°C overnight. Afterwards the reaction mixture was evaporated under reduced pressure, diluted with water (50 mL) and extracted 3 times with ethyl acetate (3*50 mL). The organic phase was washed with water, brine, dried over Na₂SO₄ and concentrated *in vacuo* to give 1-isopropyl-3-((phenylsulfonyl)methyl)-1H-pyrazole **Int-9b** (14.0 g, 95.0% purity, 50.31 mmol, 75% yield).

[00568] **Step B:** (E)-2-(2-(1-Isopropyl-1H-pyrazol-3-yl)-2-(phenylsulfonyl)vinyl)pyridine **Int-9c**.

[00569] To 1-isopropyl-3-((phenylsulfonyl)methyl)-1H-pyrazole **Int-9b** (9.0 g, 34.05 mmol) in THF (270 mL) was added LiHMDS (1.1 M in THF/ ethylbenzene, 37 mL), at -78°C and the mixture was stirred for 45 min. To the solution was added pyridine-2-carbaldehyde (4.37 g, 40.85 mmol), and the mixture was stirred for 1 h. Diethyl phosphorochloridate (7.03 g, 40.85 mmol) was added, and the mixture was stirred for 1 h. Then LiHMDS (1.1 M in THF/

ethylbenzene, 37 ml) was added at -78°C, and the mixture was stirred to ambient temperature. The resulting mixture was poured into saturated aq. NH₄Cl (80 mL) and extracted with ethyl acetate (3*80 mL). The organic phase washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give (*E*)-2-(2-(1-isopropyl-1*H*-pyrazol-3-yl)-2-(phenylsulfonyl)vinyl)pyridine **Int-9c** (13.1 g, 60.0% purity, 22.24 mmol, 65% yield) and used for the next step without further purification.

[00570] **Step C:** Ethyl 4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-9d**.

[00571] Potassium *t*-butoxide (3.74 g, 33.36 mmol) was added portionwise to the solution of (*E*)-2-(2-(1-isopropyl-1*H*-pyrazol-3-yl)-2-(phenylsulfonyl)vinyl)pyridine **Int-9c** (13.1 g, 60.0% purity, 22.24 mmol) and ethyl 2-isocyanoacetate (3.77 g, 33.36 mmol) in dry THF (200 mL) at (-10°C), and stirred at room temperature overnight. Then reaction mixture was diluted with ice water (100 mL) and extracted 3 times with ethyl acetate (3*80 mL). The organic phase washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 220g SiO₂, chloroform/acetonitrile with acetonitrile from 0~75%, flow rate =100 mL/min, Rv = 11,3-17,5CV) to give ethyl 4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-9d** (5.8 g, 95.0% purity, 16.99 mmol, 76% yield).

[00572] **Step D:** Ethyl 1-amino-4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-9e**.

[00573] Sodium hydride (0.637g, 15 mmol) (60% in mineral oil), was added portionwise to a solution of ethyl 4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-9d** (3.0 g, 9.25 mmol) in DMF (30 mL) at 0°C. The mixture was stirred for 1h at room temperature. Then the mixture was cooled to 0°C and O-(2,4-dinitrophenyl)hydroxylamine (2.76 g, 13.87 mmol) was added portionwise. The mixture was stirred for 16 h at room temperature. Then the mixture poured in ice water and extracted with ethyl acetate (3*20 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* to give ethyl 1-amino-4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-9e** (2.95 g, 77.0% purity, 6.69 mmol, 72% yield) and used for the next step without further purification.

[00574] **Step E:** 6-(1-Isopropyl-1*H*-pyrazol-3-yl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-9f**.

[00575] Sodium hydride (0.637 g, 15 mmol) (60% in mineral oil) was added portionwise to

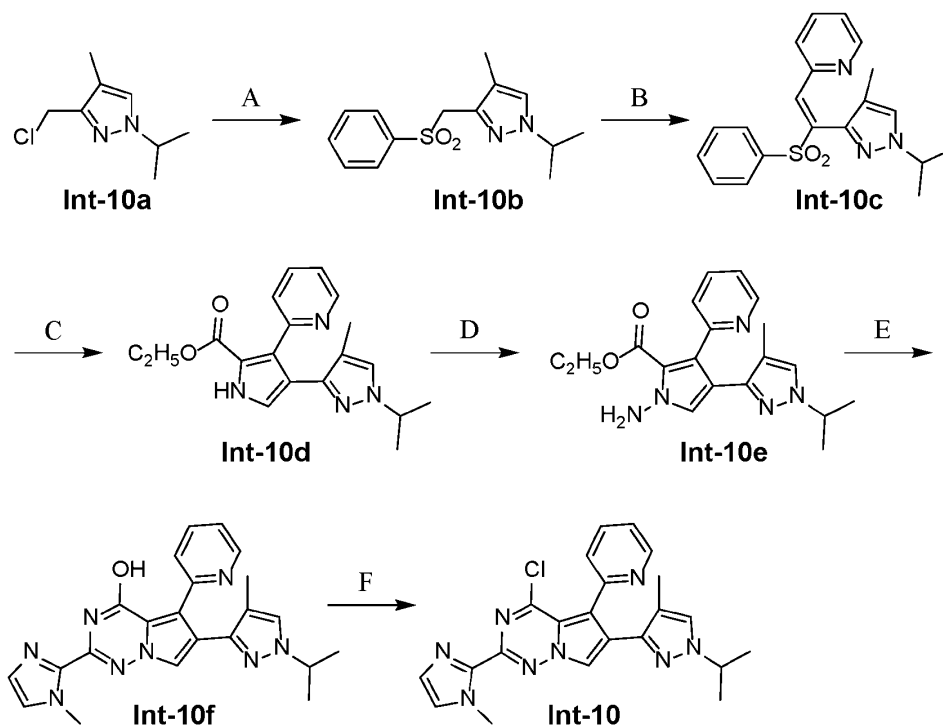
the solution of ethyl 1-amino-4-(1-isopropyl-1*H*-pyrazol-3-yl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-9e** (2.97 g, 77.0% purity, 6.74 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (1.08 g, 10.11 mmol) in dry dioxane (60 mL). Then reaction mixture was heated to 80°C and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured in ice water, neutralized with acetic acid and extracted with ethyl acetate (3*50 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim, 80 g SiO₂, methyl *t*-butyl ether/methanol with methanol from 0~20%, flow rate = 60 mL/min, R_v = 8-13 CV) to give 6-(1-isopropyl-1*H*-pyrazol-3-yl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-9f** (750.0 mg, 95.0% purity, 1.78 mmol, 26% yield) .

[00576] Step F: 4-Chloro-6-(1-isopropyl-1*H*-pyrazol-3-yl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-9**.

[00577] To the solution of 6-(1-isopropyl-1*H*-pyrazol-3-yl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-9f** (750.43 mg, 1.87 mmol) in acetonitrile (15 mL), phosphoryl trichloride (11.38 g, 74.95 mmol, 6.92 mL, 40.0 eq) was added dropwise. The mixture was heated to 100°C in a sealed tube and stirred at this temperature for 16 h then concentrated *in vacuo*, dissolved in ethyl acetate/ acetonitrile 30 mL/30 mL, washed with ice cold aq. NaHCO₃, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give 4-chloro-6-(1-isopropyl-1*H*-pyrazol-3-yl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-9** (500.0 mg, 95.0% purity, 1.13 mmol, 60% yield) .

[00578] Example Int-10: Synthesis of Intermediate Int-10

[00579] Scheme 10: The Synthesis of Intermediate **Int-10**



[00580] **Step A:** 1-Isopropyl-4-methyl-3-((phenylsulfonyl)methyl)-1H-pyrazole **Int-10b**.

[00581] To a solution of 3-(chloromethyl)-1-isopropyl-4-methyl-1H-pyrazole **Int-10a** (6.9 g, 40.1 mmol) in dry isopropanol (75 mL), sodium benzenesulfinate (7.23 g, 44.11 mmol) was added portionwise at RT and heated at 80°C overnight. Afterwards the reaction mixture was evaporated under reduced pressure, diluted with water (50 mL) and extracted 3 times with ethyl acetate (3*50 mL). The organic phase was washed with water, brine, dried over Na₂SO₄ and concentrated *in vacuo* to give 1-isopropyl-4-methyl-3-((phenylsulfonyl)methyl)-1H-pyrazole **Int-10b** (6.3 g, 95.0% purity, 21.5 mmol, 53% yield).

[00582] **Step B:** (E)-2-(2-(1-Isopropyl-4-methyl-1H-pyrazol-3-yl)-2-(phenylsulfonyl)vinyl)pyridine **Int-10c**.

[00583] To 1-isopropyl-4-methyl-3-((phenylsulfonyl)methyl)-1H-pyrazole **Int-10b** (2.5 g, 8.98 mmol) in THF (70 mL) was added LiHMDS (1.1 M in THF/ ethylbenzene, 10 mL) at -78°C and the mixture was stirred for 45 min. To the solution was added pyridine-2-carbaldehyde (1.15 g, 10.78 mmol) and the mixture was stirred for 1 h. Diethyl phosphorochloridate (1.85 g, 10.78 mmol) was added and the mixture was stirred for 1 h. Then LiHMDS (1.1 M in THF/

ethylbenzene, 10 mL) was added at -78°C , and the mixture was stirred to ambient temperature. The resulting mixture was poured into saturated aq. NH_4Cl (80 mL) and extracted with ethyl acetate (3*80 mL). The organic phase was washed with water, brine, dried over Na_2SO_4 , and concentrated *in vacuo* to give (*E*)-2-(2-(1-isopropyl-4-methyl-1*H*-pyrazol-3-yl)-2-(phenylsulfonyl)vinyl)pyridine **Int-10c** (3.7 g, 58.0% purity, 5.84 mmol, 65% yield) and used for the next step without further purification.

[00584] Step C: Ethyl 4-(1-isopropyl-4-methyl-1*H*-pyrazol-3-yl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-10d**.

[00585] Potassium *t*-butoxide (1.1 g, 9.82 mmol) was added portionwise to the solution of (*E*)-2-(2-(1-isopropyl-4-methyl-1*H*-pyrazol-3-yl)-2-(phenylsulfonyl)vinyl)pyridine **Int-10c** (3.7 g, 65.0% purity, 6.54 mmol) and ethyl 2-isocyanoacetate (1.11 g, 9.82 mmol) in dry THF (50 mL) at (-10°C) , and stirred at room temperature overnight. Then the reaction mixture was diluted with ice water (30 mL) and extracted 3 times with ethyl acetate (3*30 mL). The organic phase was washed with water, brine, dried over Na_2SO_4 , concentrated *in vacuo* and purified by FCC (Interchim; 120 g SiO_2 , chloroform/acetonitrile with acetonitrile from 0~100%, flow rate = 85 mL/min, $\text{R}_v = 9.5\text{-}15.8\text{CV}$) to give ethyl 4-(1-isopropyl-4-methyl-1*H*-pyrazol-3-yl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-10d** (2.2 g, 95.0% purity, 6.18 mmol, 94% yield).

[00586] Step D: Ethyl 1-amino-4-(1-isopropyl-4-methyl-1*H*-pyrazol-3-yl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-10e**.

[00587] Sodium hydride (0.4 g, 10 mmol) (60% in mineral oil), was added portionwise to a solution of ethyl 4-(1-isopropyl-4-methyl-1*H*-pyrazol-3-yl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-10d** (2.25 g, 6.65 mmol) in DMF (30 mL) at 0°C . The mixture was stirred for 1 h at room temperature. Then the mixture was cooled to 0°C and O-(2,4-dinitrophenyl)hydroxylamine (1.99 g, 9.97 mmol) was added portionwise. The mixture was stirred for 16 h at room temperature. Then the mixture poured into ice water and extracted with ethyl acetate (3*20 mL). The organic phase washed with water, brine, dried over Na_2SO_4 , and concentrated *in vacuo* to give ethyl 1-amino-4-(1-isopropyl-4-methyl-1*H*-pyrazol-3-yl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-10e** (2.55 g, 45.0% purity, 3.25 mmol, 48.8% yield) and used for the next step without further purification.

[00588] Step E: 6-(1-Isopropyl-4-methyl-1*H*-pyrazol-3-yl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-10f**.

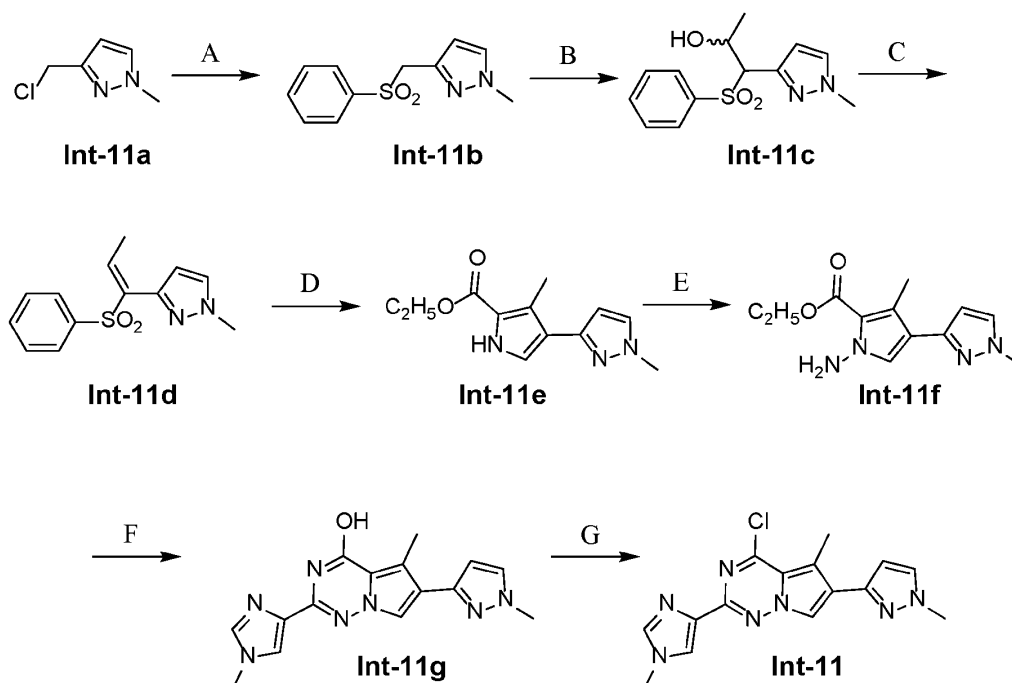
[00589] Sodium hydride (0.577 g, 14 mmol) (60% in mineral oil) was added portionwise to the solution of ethyl 1-amino-4-(1-isopropyl-4-methyl-1*H*-pyrazol-3-yl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-10e** (2.55 g, 45.0% purity, 3.25 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (521.47 mg, 4.87 mmol) in dry dioxane (40 mL). Then the reaction mixture was heated to 80°C and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured into ice water, neutralized with acetic acid and extracted with ethyl acetate (3*50 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 80 g SiO₂, chloroform/acetonitrile/methanol with methanol from 0~25%, flow rate =65 mL/min, R_v = 28-31CV) to give 6-(1-isopropyl-4-methyl-1*H*-pyrazol-3-yl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-10f** (850.0 mg, 95.0% purity, 1.95 mmol, 60% yield).

[00590] **Step F:** 4-Chloro-6-(1-isopropyl-4-methyl-1*H*-pyrazol-3-yl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-10**.

[00591] To the solution of 6-(1-isopropyl-4-methyl-1*H*-pyrazol-3-yl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-10f** (851.12 mg, 2.05 mmol) in acetonitrile (15ml), phosphoryl trichloride (12.47 g, 82.1 mmol, 7.58 mL, 40.0 equiv) was added dropwise. The mixture was heated to 100°C in a sealed tube and stirred at this temperature for 16 h, then concentrated *in vacuo*, dissolved in ethyl acetate/acetonitrile (30 mL/30 mL), washed with ice cold aq. NaHCO₃, brine, and dried over Na₂SO₄ and concentrated *in vacuo* to give 4-chloro-6-(1-isopropyl-4-methyl-1*H*-pyrazol-3-yl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-10** (800.0 mg, 98.0% purity, 1.81 mmol, 88.2% yield).

[00592] **Example Int-11: Synthesis of Intermediate Int-11**

[00593] Scheme 11: The Synthesis of Intermediate **Int-11**



[00594] Step A: 1-Methyl-3-((phenylsulfonyl)methyl)-1*H*-pyrazole **Int-11b**.

[00595] To the solution of 3-(chloromethyl)-1-methyl-1*H*-pyrazole **Int-11a** (100.0 g, 602.39 mmol) and potassium acetate (64.92 g, 662.63 mmol) in dry isopropanol (800 mL), sodium benzenesulfinate (108.66 g, 662.63 mmol) was added portionwise at RT, and heated at 80°C overnight. Afterwards the reaction mixture was filtered, washed with isopropanol and dried *in vacuo* to give 1-methyl-3-((phenylsulfonyl)methyl)-1*H*-pyrazole **Int-11b** (141.0 g, 95.0% purity, 566.89 mmol, 94.1% yield).

[00596] Step B: 1-(1-Methyl-1*H*-pyrazol-3-yl)-1-(phenylsulfonyl)propan-2-ol **Int-11c**.

[00597] To 1-methyl-3-((phenylsulfonyl)methyl)-1*H*-pyrazole **Int-11b** (25.01 g, 105.84 mmol) in THF (500 mL) was added LiHMDS (1.1 M in THF/ ethylbenzene, 192 mL), at -78°C and the mixture was stirred for 1 h. To the resulting mixture was added acetaldehyde (9.32 g, 211.68 mmol) followed by tetrachlorotitanium (21.87 g, 116.42 mmol, 12.64 mL, 1.1 equiv). The mixture was stirred for 1 h at -78°C, and then stirred at ambient temperature overnight. The resulting mixture was poured into saturated aq. NH₄Cl (50 mL), filtered through a pad of Celite and extracted with ethyl acetate (3*50 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give 1-(1-methyl-1*H*-pyrazol-3-yl)-1-

(phenylsulfonyl)propan-2-ol **Int-11c** (16.6 g, 50.0% purity, 29.61 mmol, 28% yield) and used for the next step without further purification.

[00598] Step C: (*E*)-1-Methyl-3-(1-(phenylsulfonyl)prop-1-en-1-yl)-1*H*-pyrazole **Int-11d**.

[00599] Methanesulfonyl chloride (16.38 g, 143.77 mmol, 11.07 mL, 3.0 equiv) was added dropwise at 0°C to a stirred solution of 1-(1-methyl-1*H*-pyrazol-3-yl)-1-(phenylsulfonyl)propan-2-ol **Int-11c** (16.79 g, 80.0% purity, 47.92 mmol) in pyridine (40 mL). The mixture was stirred at RT overnight. Then the reaction mixture was concentrated *in vacuo*, diluted with ice water (50 mL) and extracted 3 times with ethyl acetate (3*50 mL). The organic phase was washed with 1N HCl (20 mL), water, brine, dried over Na₂SO₄ and concentrated *in vacuo* to give (*E*)-1-methyl-3-(1-(phenylsulfonyl)prop-1-en-1-yl)-1*H*-pyrazole **Int-11d** (19.4 g, 60.0% purity, 44.37 mmol, 92.6% yield) and used for the next step without further purification.

[00600] Step D: Ethyl 3-methyl-4-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate **Int-11e**.

[00601] Potassium *t*-butoxide (7.46 g, 66.56 mmol) was added portionwise to the solution of (*E*)-1-methyl-3-(1-(phenylsulfonyl)prop-1-en-1-yl)-1*H*-pyrazole **Int-11d** (19.4 g, 60.0% purity, 44.37 mmol) and ethyl 2-isocyanoacetate (7.52 g, 66.56 mmol) in dry THF (60 mL) at (-10°C) and stirred at room temperature overnight. Then the reaction mixture was diluted with ice water (40 mL) and extracted 3 times with ethyl acetate (3*40 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 330 g SiO₂, chloroform/acetonitrile with acetonitrile from 0~40%, flow rate = 127 mL/min, Rv = 8-12CV) to give ethyl 3-methyl-4-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate **Int-11e** (6.7 g, 95.0% purity, 27.29 mmol, 61.5% yield).

[00602] Step E: Ethyl 1-amino-3-methyl-4-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate **Int-11f**.

[00603] Sodium hydride (0.95 g, 23.7 mmol) (60% in mineral oil), was added portionwise to a solution of ethyl 3-methyl-4-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate **Int-11e** (3.7 g, 15.87 mmol) in DMF (37 mL) at 0°C. The mixture was stirred for 1 h at 0°C. Then O-(2,4-dinitrophenyl)hydroxylamine (4.74 g, 23.81 mmol) was added in one portion. The mixture was stirred for 16 h at room temperature. Then the mixture was poured into ice water and extracted with ethyl acetate (3*100 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give ethyl 1-amino-3-methyl-4-(1-methyl-1*H*-pyrazol-3-

yl)-1*H*-pyrrole-2-carboxylate **Int-11f** (5.13 g, 70.0% purity, 14.46 mmol, 91% yield) and used for the next step without further purification.

[00604] Step F: 5-Methyl-2-(1-methyl-1*H*-imidazol-4-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-11g**.

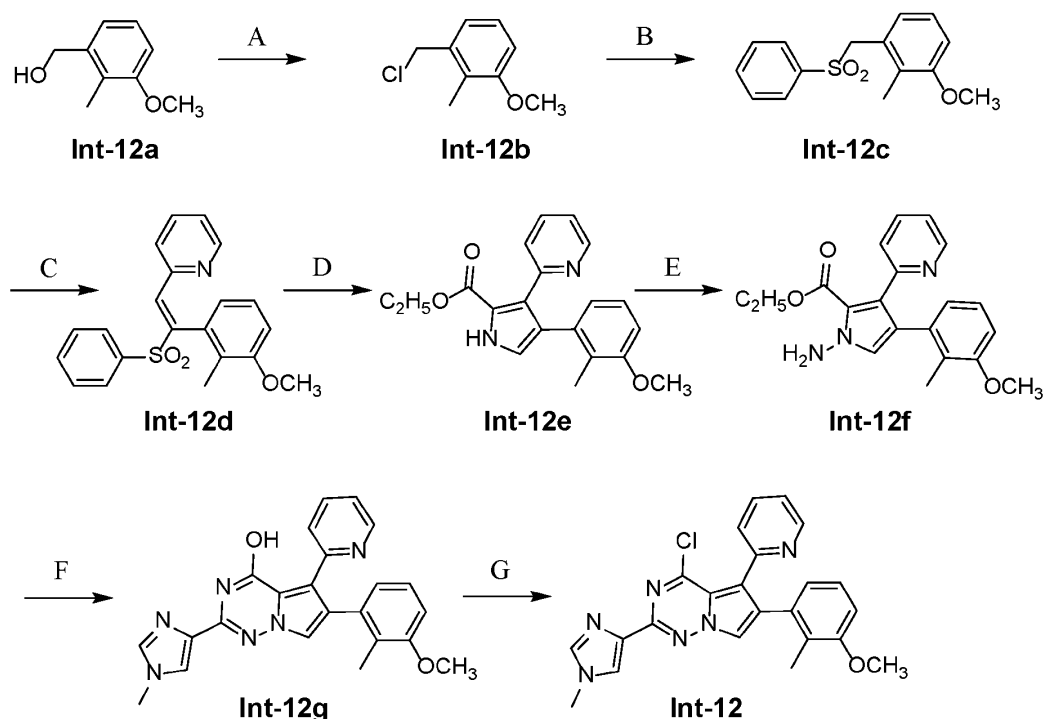
[00605] Sodium hydride (1.65 g, 41.2 mmol) (60% in mineral oil) was added portionwise to the solution of 1-amino-3-methyl-4-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate **Int-11f** (5.13 g, 70.0% purity, 14.47 mmol) and 1-methyl-1*H*-imidazole-4-carbonitrile (2.32 g, 21.71 mmol) in dry dioxane (70 mL). Then the reaction mixture was heated to 80°C and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured into ice water, neutralized with acetic acid and extracted with ethyl acetate (3*100 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim, 120 g SiO₂, methyl *t*-butyl ether/methanol with methanol from 0~60%, flow rate = 85 mL/min, R_v = 20-23 CV;) to give 5-methyl-2-(1-methyl-1*H*-imidazol-4-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-11g** (780.0 mg, 95.0% purity, 2.4 mmol, 16% yield).

[00606] Step G: 4-Chloro-5-methyl-2-(1-methyl-1*H*-imidazol-4-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-11**.

[00607] To the solution of 5-methyl-2-(1-methyl-1*H*-imidazol-4-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-11g** (620.0 mg, 2.0 mmol) in toluene (12 mL), phosphoryl trichloride (12.18 g, 80.18 mmol) was added dropwise. The mixture was heated to 110°C and stirred at this temperature for 3 days then concentrated *in vacuo*, dissolved in ethyl acetate/acetonitrile 10 mL/10 mL, washed with ice cold aq. NaHCO₃, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give 4-chloro-5-methyl-2-(1-methyl-1*H*-imidazol-4-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-11** (450.0 mg, 85.0% purity, 1.17 mmol, 58% yield).

[00608] Example Int-12: Synthesis of Intermediate Int-12

[00609] Scheme 12: The Synthesis of Intermediate **Int-12**



[00610] **Step A:** 1-(Chloromethyl)-3-methoxy-2-methylbenzene **Int-12b**.

[00611] To the solution of (3-methoxy-2-methylphenyl)methanol **Int-12a** (5.0 g, 32.88 mmol) in dry methylene chloride (200 mL) and 2 drops of DMF, sulfuryl dichloride (8.53 g, 72.33 mmol) was added dropwise at RT, then stirred overnight. Afterwards the reaction mixture was evaporated under reduced pressure to give 1-(chloromethyl)-3-methoxy-2-methylbenzene **Int-12b** (5.6 g, 95.0% purity, 31.18 mmol, 94.8% yield).

[00612] **Step B:** 1-Methoxy-2-methyl-3-((phenylsulfonyl)methyl)benzene **Int-12c**.

[00613] To the solution of 1-(chloromethyl)-3-methoxy-2-methylbenzene **Int-12b** (5.6 g, 32.93 mmol) in dry isopropanol (75 mL), sodium benzenesulfinate (5.64 g, 34.41 mmol) was added portionwise at RT, and heated 80 °C overnight. Afterwards the reaction mixture was evaporated under reduced pressure, diluted with water (50 mL) and extracted 3 times with ethyl acetate (3*50 mL). The organic phase was washed with water, brine, dried over Na₂SO₄ and concentrated *in vacuo* to give 1-methoxy-2-methyl-3-((phenylsulfonyl)methyl)benzene **Int-12c** (6.57 g, 90.0% purity, 21.4 mmol, 68.4% yield). LCMS(ESI): [M+H]⁺ m/z: calcd 276.2; found 276.2; Rt = 3.056 min.

[00614] **Step C:** (*E*)-2-(2-(3-Methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)pyridine **Int-12d**.

[00615] To 1-methoxy-2-methyl-3-((phenylsulfonyl)methyl)benzene **Int-12c** (6.57 g, 23.77 mmol) in THF (200 mL) was added LiHMDS (1.1 M in THF/ethylbenzene, 26 mL), at -78 °C and the mixture was stirred for 45 min. To the solution was added pyridine-2-carbaldehyde (3.05 g, 28.53 mmol), and the mixture was stirred for 1 h. Diethyl chlorophosphonate (4.91 g, 28.53 mmol) was added, and the mixture was stirred for 1 h. Then LiHMDS (1.1 M in THF/ethylbenzene, 26 mL) was added at -78°C, and the mixture was stirred to ambient temperature. The resulting mixture was poured into saturated aq NH₄Cl (80 mL) and extracted with ethyl acetate (3*80 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give (*E*)-2-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)pyridine **Int-12d** (9.6 g, 60.0% purity, 15.76 mmol, 66.3% yield) and used for the next step without further purification. LCMS(ESI): [M+H]⁺ m/z: calcd 366.2; found 366.2; Rt = 3.451 min.

[00616] **Step D:** Ethyl 4-(3-methoxy-2-methylphenyl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-12e**.

[00617] Potassium *t*-butoxide (2.65 g, 23.64 mmol) was added portionwise to the solution of (*E*)-2-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)pyridine **Int-12d** (9.6 g, 26.27 mmol) and ethyl 2-isocyanoacetate (2.67 g, 23.64 mmol) in dry THF (200 mL) at (-10°C), and stirred at room temperature overnight. Then reaction mixture was diluted with ice water (100 mL) and extracted 3 times with ethyl acetate (3*80 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 220 g SiO₂, petroleum ether/ethyl acetate with ethyl acetate from 0-30%, flow rate = 100 mL/min, Rv = 8-10 CV) to give ethyl 4-(3-methoxy-2-methylphenyl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-12e** (2.7 g, 95.0% purity, 7.63 mmol, 48.4% yield). LCMS(ESI): [M+H]⁺ m/z: calcd 337.2; found 337.2; Rt = 0.869 min.

[00618] **Step E:** Ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-12f**.

[00619] Sodium hydride (0.48g, 12 mmol) (60% in mineral oil), was added portionwise to a solution of ethyl 4-(3-methoxy-2-methylphenyl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-12e** (2.7 g, 8.03 mmol) in DMF (30 mL) at 0°C. The mixture was stirred for 1 h at room

temperature. Then the mixture was cooled to 0°C and O-(2,4-dinitrophenyl)hydroxylamine (2.4 g, 12.04 mmol) was added portionwise. The mixture was stirred for 16 h at room temperature. Then the mixture was poured into ice water and extracted with ethyl acetate (3*20 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-12f** (4.4 g, 60.0% purity, 7.51 mmol, 93.6% yield) as a dark oil.

[00620] Step F: 6-(3-Methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-4-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-12g**.

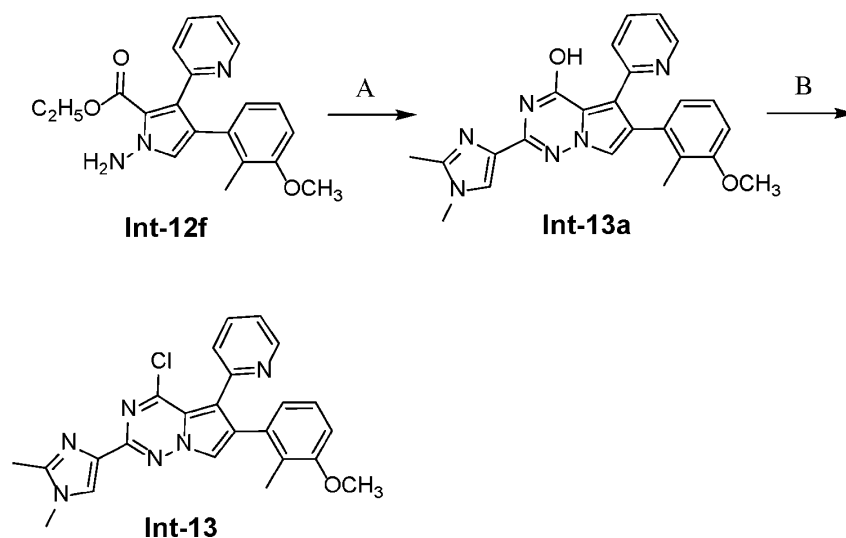
[00621] Sodium hydride (0.2 g, 5.1 mmol) (60% in mineral oil) was added portionwise to the solution of ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-12f** (900.0 mg, 2.56 mmol) and 1-methyl-1*H*-imidazole-4-carbonitrile (411.12 mg, 3.84 mmol) in dry dioxane (16 mL) at RT. Then the reaction mixture was heated to 80°C and stirred at this temperature for 16 h. After the mixture was cooled to room temperature, it was poured into ice water, neutralized with acetic acid and extracted with ethyl acetate (3*100 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 40 g SiO₂, chloroform/acetonitrile/methanol with methanol from 0~30%, flow rate = 85 mL/min, R_v = 30 -35 CV) to give 6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-4-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-12g** (400.0 mg, 95.0% purity, 921.34 μmol, 36% yield).

[00622] Step G: 4-Chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-4-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-12**.

[00623] To the solution of 6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-4-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-12g** (400.0 mg, 969.83 μmol) in acetonitrile (15 mL), phosphoryl trichloride (11.79 g, 77.61 mmol) was added dropwise. The mixture was heated to 100°C in a sealed tube and stirred at this temperature for 16 h, then concentrated *in vacuo*, dissolved in ethyl acetate/acetonitrile 10 mL/10 mL, washed with ice cold aq. NaHCO₃, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give 4-chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-4-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-12** (360.0 mg, 90.0% purity, 751.93 μmol, 77% yield).

[00624] Example Int-13: Synthesis of Intermediate Int-13

[00625] Scheme 13: The Synthesis of Intermediate **Int-13**



[00626] Step A: 2-(1,2-Dimethyl-1*H*-imidazol-4-yl)-6-(3-methoxy-2-methylphenyl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-13a**.

[00627] Sodium hydride (0.17 g, (60% in mineral oil)) was added portionwise to the solution of ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-12f** (prepared as described herein) (1.0 g, 2.85 mmol) and 1,2-dimethyl-1*H*-imidazole-4-carbonitrile (361.85 mg, 2.99 mmol) in dry dioxane (30 mL) at RT. Then the reaction mixture was heated to 80°C and stirred at this temperature for 16 h. Afterwards the mixture was cooled to room temperature, poured into ice water, neutralized with acetic acid and extracted with ethyl acetate (3*50 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 12 g SiO₂, chloroform/acetonitrile/methanol with methanol from 0~30%, flow rate = 15 mL/min, R_v = 43 - 46 CV) to give 2-(1,2-dimethyl-1*H*-imidazol-4-yl)-6-(3-methoxy-2-methylphenyl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-13a** (80.0 mg, 187.59 μmol, 6% yield).

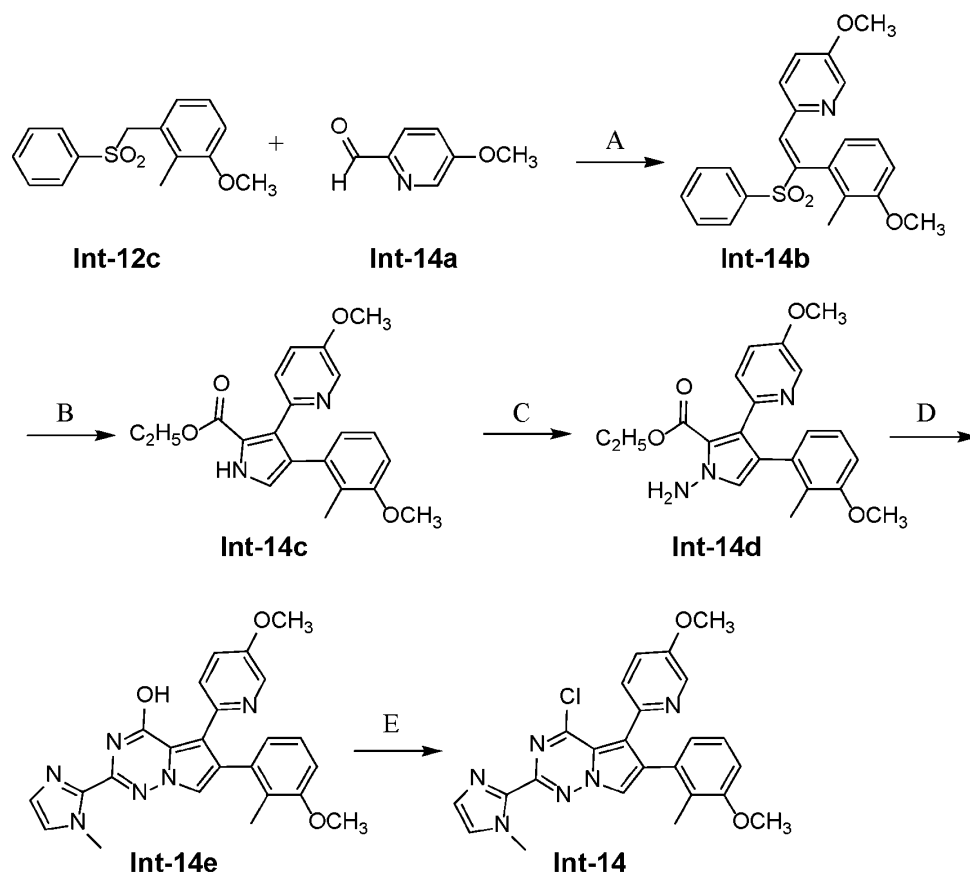
[00628] Step B: 4-Chloro-2-(1,2-dimethyl-1*H*-imidazol-4-yl)-6-(3-methoxy-2-methylphenyl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-13**.

[00629] To the solution of 2-(1,2-dimethyl-1*H*-imidazol-4-yl)-6-(3-methoxy-2-methylphenyl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-13a** (79.65 mg, 186.78 μmol) in acetonitrile (15 mL), phosphoryl trichloride (2.27 g, 14.94 mmol, 1.38 mL, 80.0 equiv) was added dropwise. The mixture was heated to 100°C in a sealed tube and stirred at this temperature

for 16 h, then concentrated *in vacuo*, dissolved in ethyl acetate/acetonitrile 10 mL/10 mL, washed with ice cold aq. NaHCO₃, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give 4-chloro-2-(1,2-dimethyl-1*H*-imidazol-4-yl)-6-(3-methoxy-2-methylphenyl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-13** (60.0 mg, 95.0% purity, 128.11 μmol, 68% yield).

[00630] Example Int-14: Synthesis of Intermediate Int-14

[00631] Scheme 14: The Synthesis of Intermediate Int-14



[00632] Step A: (*E*)-5-methoxy-2-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)pyridine **Int-14b**.

[00633] To 1-methoxy-2-methyl-3-((phenylsulfonyl)methyl)benzene **Int-12c** (prepared as described herein) (2.51 g, 9.08 mmol) in THF (100 mL) was added LiHMDS (1.1 M in THF/ethylbenzene, 10 mL), at -78°C and the mixture was stirred for 45 min. To the solution was added 5-methoxypicolinaldehyde **Int-14a** (1.49 g, 10.9 mmol) and the mixture was stirred for 1

h. Diethyl phosphorochloridate (1.87 g, 10.9 mmol) was added and the mixture was stirred for 1 h. Then LiHMDS (1.1 M in THF/ ethylbenzene, 10 mL) was added at -78°C, and the mixture was stirred to ambient temperature. The resulting mixture was poured into saturated aq. NH₄Cl (80 mL) and extracted with ethyl acetate (3*80 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give (*E*)-5-methoxy-2-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)pyridine **Int-14b** (4.4 g, 66.0% purity, 7.34 mmol, 80% yield) and used for the next step without further purification.

[00634] **Step B:** Ethyl 4-(3-methoxy-2-methylphenyl)-3-(5-methoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-14c**.

[00635] Potassium *t*-butoxide (1.23 g, 11.02 mmol) was added portionwise to the solution of (*E*)-5-methoxy-2-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)pyridine **Int-14b** (4.4 g, 66.0% purity, 7.34 mmol) and ethyl 2-isocyanoacetate (1.25 g, 11.02 mmol) in dry THF (100 mL) at (-10°C), and stirred at room temperature overnight. Then the reaction mixture was diluted with ice water (100 mL) and extracted 3 times with ethyl acetate (3*80 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 120 g SiO₂, chloroform/acetonitrile with acetonitrile from 0~50%, flow rate =85mL/min, R_v = 9-10.9 CV) to give ethyl 4-(3-methoxy-2-methylphenyl)-3-(5-methoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-14c** (900.0 mg, 90.0% purity, 2.21 mmol, 30% yield).

[00636] **Step C:** Ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(5-methoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-14d**.

[00637] Sodium hydride (0.15g, 60% in mineral oil), was added portionwise to a solution of ethyl 4-(3-methoxy-2-methylphenyl)-3-(5-methoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-14c** (900.0 mg, 90.0% purity, 2.21 mmol) in DMF (20 mL) at 0°C. The mixture was stirred for 1 h at room temperature. Then the mixture was cooled to 0°C and O-(2,4-dinitrophenyl)hydroxylamine (659.8 mg, 3.32 mmol) was added portionwise. The mixture was stirred for 16 h at room temperature. Then the mixture was poured into ice water and extracted with ethyl acetate (3*20 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(5-methoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-14d** (820.0 mg, 63.0% purity, 1.35 mmol, 61% yield).

[00638] **Step D:** 6-(3-Methoxy-2-methylphenyl)-5-(5-methoxypyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-14e**.

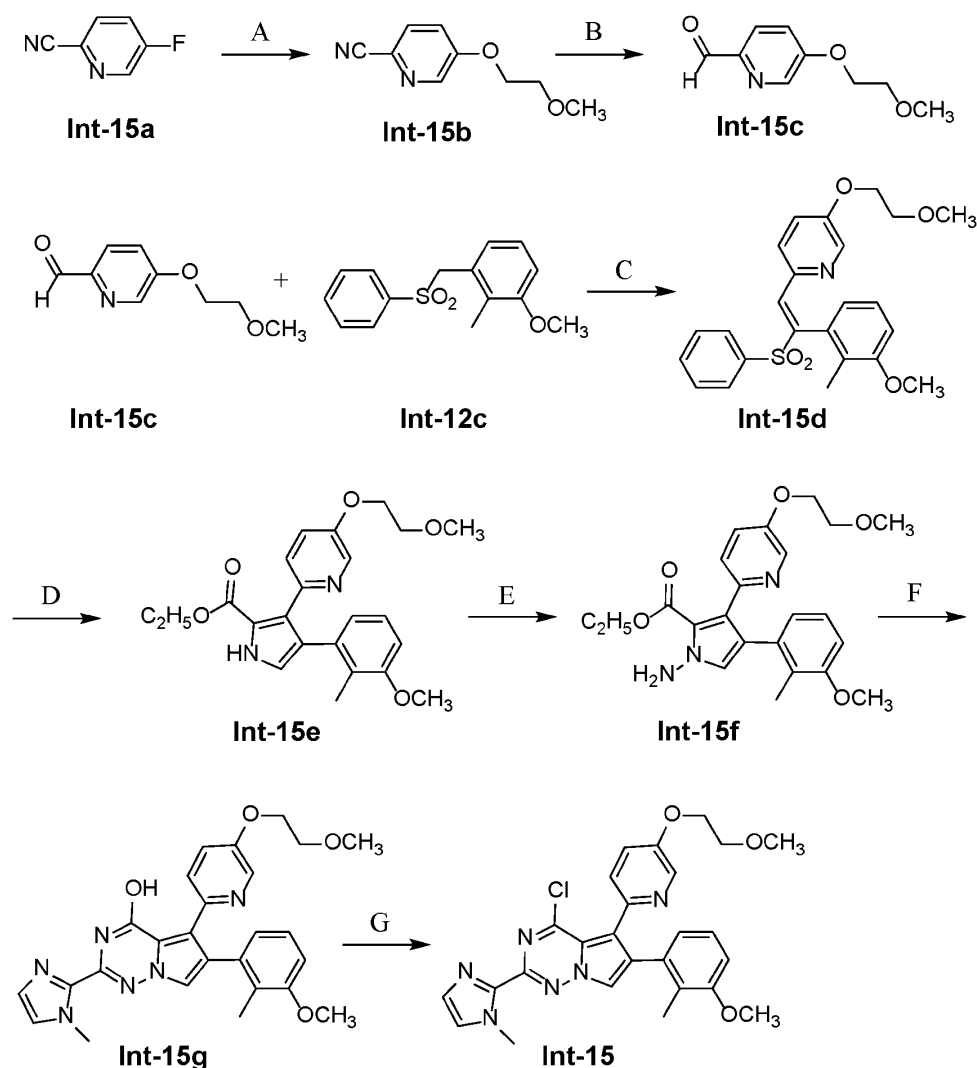
[00639] Sodium hydride (0.17 g, (60% in mineral oil)) was added portionwise to the solution of ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(5-methoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-14d** (820.0 mg, 63.0% purity, 1.35 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (217.38 mg, 2.03 mmol) in dry dioxane (10 mL). Then reaction mixture was heated 80°C and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured into ice water, neutralized with acetic acid and extracted with ethyl acetate (3*20 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 40 g SiO₂, acetonitrile /methanol with methanol from 0-70%, flow rate =40 mL/min, Rv = 24-25.4 CV) to give 6-(3-methoxy-2-methylphenyl)-5-(5-methoxypyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-14e** (250.0 mg, 99.0% purity, 559.36 μmol, 41% yield).

[00640] **Step E:** 4-Chloro-6-(3-methoxy-2-methylphenyl)-5-(5-methoxypyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-14**.

[00641] To the solution of 6-(3-methoxy-2-methylphenyl)-5-(5-methoxypyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-14e** (254.39 mg, 574.94 μmol) in acetonitrile (10 mL), phosphoryl trichloride (6.99 g, 46.0 mmol, 4.25 mL, 80.0 equiv) was added dropwise. The mixture was heated to 80°C and stirred at this temperature for 16 h and then concentrated *in vacuo*, poured in ice water (50 mL) and neutralized with NaHCO₃. The resulting precipitate was collected by filtration, washed with water (2*10 mL) and dried *in vacuo*, to give 4-chloro-6-(3-methoxy-2-methylphenyl)-5-(5-methoxypyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-14** (240.0 mg, 94.0% purity, 489.46 μmol, 85% yield).

[00642] **Example Int-15: Synthesis of Intermediate Int-15**

[00643] Scheme 15: The Synthesis of Intermediate **Int-15**



[00644] Step A: 5-(2-Methoxyethoxy)picolinonitrile Int-15b.

[00645] Sodium hydride (9.83g, 0.245mol) (60% in mineral oil) was added portionwise to the solution of 2-methoxyethan-1-ol (9.35 g, 122.92 mmol) in DMF (250 mL). The mixture was stirred at room temperature for 30 min, then 5-fluoropicolinonitrile **Int-15a** (15.0 g, 122.92 mmol) was added portionwise, and stirred at RT overnight. After this time the resulting mixture was quenched with NH_4Cl aq. and extracted with ethyl acetate (4*100 mL). The organic phase was washed with water, brine, dried over Na_2SO_4 , concentrated *in vacuo* and purified by FCC (Interchim; 330 g SiO_2 , chloroform/acetonitrile with acetonitrile from 0-10%, flow rate =127

mL/min, Rv = 5-9 CV) to give 5-(2-methoxyethoxy)picolinonitrile **Int-15b** (16.6 g, 95.0% purity, 88.5 mmol, 72% yield).

[00646] **Step B:** 5-(2-Methoxyethoxy)picolinaldehyde **Int-15c**.

[00647] To a stirred solution of 5-(2-methoxyethoxy)picolinonitrile **Int-15b** (6.0 g, 33.69 mmol) in tetrahydrofuran (120 mL) at -78°C, DIBAL (50 mL, 1N in cyclohexane) was added and the reaction mixture was stirred for 1 h at -78°C. The reaction mixture was monitored by TLC and quenched with 2N HCl (42 mL) and extracted with dichloromethane (3x80 mL). The organics were washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 80 g SiO₂, hexane/ methyl *t*-butyl ether from 0~80%, flow rate =65 mL/min, Rv = 17 -125 CV) to give 5-(2-methoxyethoxy)picolinaldehyde **Int-15c** (1.27 g, 95.0% purity, 6.66 mmol, 19% yield).

[00648] **Step C:** (*E*)-2-(2-(3-Methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)-5-(2-methoxyethoxy)pyridine **Int-15d**.

[00649] To 1-methoxy-2-methyl-3-((phenylsulfonyl)methyl)benzene **Int-12c** (prepared as described herein) (1.76 g, 6.37 mmol) in THF (50 mL) was added LiHMDS (1.1 M in THF/ethylbenzene, 7 mL), at -78°C and the mixture was stirred for 45 min. To the solution was added 5-(2-methoxyethoxy)picolinaldehyde **Int-15c** (1.27 g, 7.01 mmol) and the mixture was stirred for 1 h. Then diethyl phosphorochloridate (1.31 g, 7.64 mmol) was added, and the mixture was stirred for 1 h. Then LiHMDS (1.1 M in THF/ ethylbenzene, 7 ml) was added at -78°C, and the mixture was stirred to ambient temperature. The resulting mixture was poured into saturated aq. NH₄Cl (50 mL) and extracted with ethyl acetate (3*50 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give (*E*)-2-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)-5-(2-methoxyethoxy)pyridine **Int-15d** (4.16 g, 60.0% purity, 5.68 mmol, 89% yield) and used for the next step without further purification.

[00650] **Step D:** Ethyl 4-(3-methoxy-2-methylphenyl)-3-(5-(2-methoxyethoxy)pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-15e**.

[00651] Potassium *t*-butoxide (954.31 mg, 8.52 mmol) was added portionwise to the solution of (*E*)-2-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)-5-(2-methoxyethoxy)pyridine **Int-15d** (4.16 g, 60.0% purity, 5.68 mmol) and ethyl 2-isocyanoacetate (962.99 mg, 8.52 mmol) in dry THF (100 mL) at (-10°C), and stirred at room temperature overnight. Then the reaction mixture was diluted with ice water (100 mL) and extracted 3 times with ethyl acetate (3*80

mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 120 g SiO₂, chloroform/acetonitrile with acetonitrile from 0~50%, flow rate = 85 mL/min, R_v = 25 -32 min) to give ethyl 4-(3-methoxy-2-methylphenyl)-3-(5-(2-methoxyethoxy)pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-15e** (1.25 g, 95.0% purity, 2.89 mmol, 50% yield).

[00652] Step E: Ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(5-(2-methoxyethoxy)pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-15f**.

[00653] Sodium hydride (0.18g, 60% in mineral oil), was added portionwise to a solution of ethyl 4-(3-methoxy-2-methylphenyl)-3-(5-(2-methoxyethoxy)pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-15e** (1.25 g, 3.05 mmol) in DMF (20 mL) at 0°C. The mixture was stirred for 1 h at 0°C. Then the mixture was cooled to -5°C and O-(2,4-dinitrophenyl)hydroxylamine (909.33 mg, 4.57 mmol) was added portionwise. The mixture was stirred for 16 h at room temperature. Then the mixture was poured into ice water and extracted with ethyl acetate (3*20 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(5-(2-methoxyethoxy)pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-15f** (1.32 g, 60.0% purity, 1.86 mmol, 61% yield).

[00654] Step F: 6-(3-Methoxy-2-methylphenyl)-5-(5-(2-methoxyethoxy)pyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-15g**.

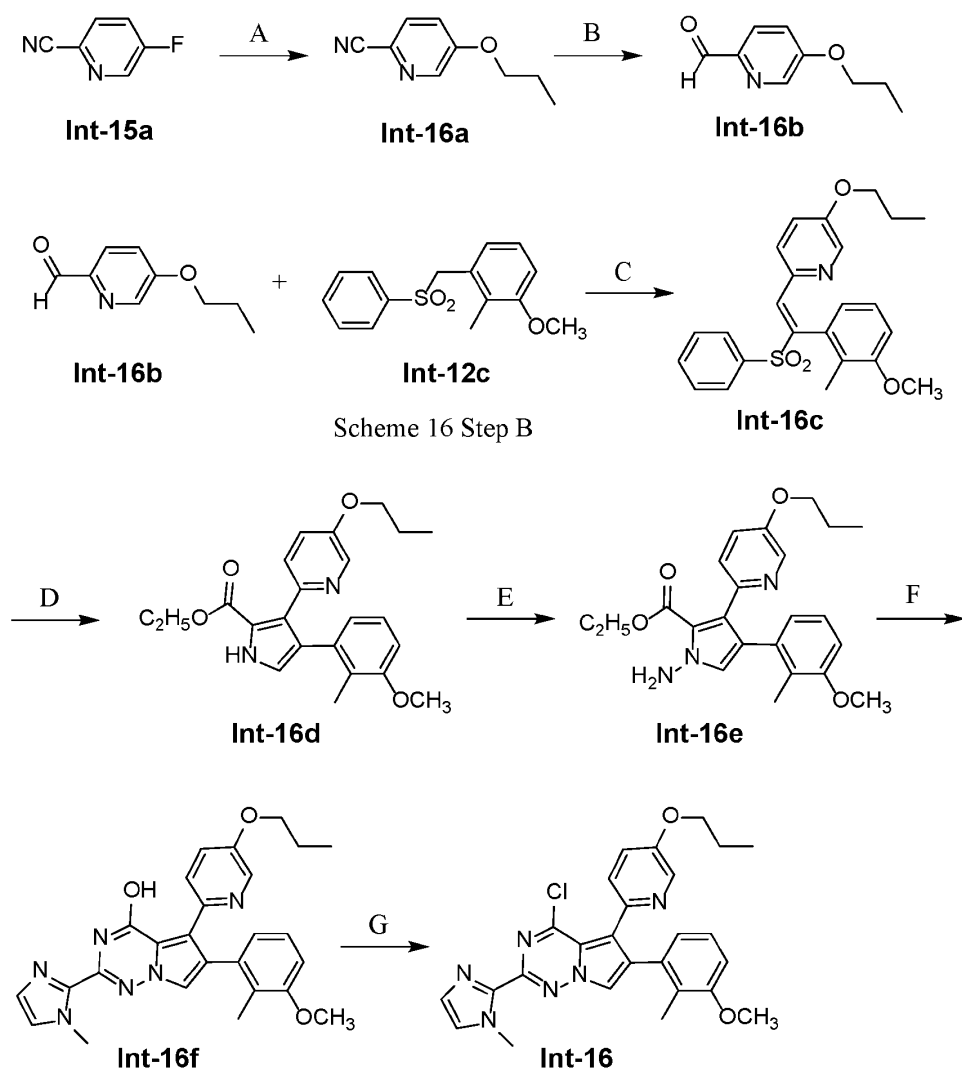
[00655] Sodium hydride (1 g, 25 mmol) (60% in mineral oil) was added portionwise to the solution of ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(5-(2-methoxyethoxy)pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-15f** (1.35 g, 60.0% purity, 1.9 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (305.62 mg, 2.85 mmol) in dry dioxane (40 mL) at RT. Then the reaction mixture was heated to 80°C and stirred at this temperature for 16 h. Afterwards the mixture was cooled to room temperature, poured in ice water, neutralized with acetic acid and extracted with ethyl acetate (3*100 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 80 g SiO₂, acetonitrile\methanol with methanol from 0-50%, flow rate = 60 mL/min, R_v = 23-25 CV) to give 6-(3-methoxy-2-methylphenyl)-5-(5-(2-methoxyethoxy)pyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-15g** (410.0 mg, 95.0% purity, 800.58 μmol, 42% yield).

[00656] Step G: 4-Chloro-6-(3-methoxy-2-methylphenyl)-5-(5-(2-methoxyethoxy)pyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-15**.

[00657] To the solution of 6-(3-methoxy-2-methylphenyl)-5-(5-(2-methoxyethoxy)pyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-15g** (410.44 mg, 843.62 μ mol) in acetonitrile (15 mL), phosphoryl trichloride (10.25 g, 67.48 mmol, 6.23 mL, 80.0 equiv) was added dropwise. The mixture was heated to 100°C in a sealed tube and stirred at this temperature for 16 h then concentrated *in vacuo*, dissolved in ethyl acetate/acetonitrile 10 mL/10 mL, washed with ice cold aq. NaHCO₃, brine, dried over Na₂SO₄, and concentrated *in vacuo* to 4-chloro-6-(3-methoxy-2-methylphenyl)-5-(5-(2-methoxyethoxy)pyridin-2-yl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-15** (400.0 mg, 94.0% purity, 744.6 μ mol, 88% yield).

[00658] **Example Int-16: Synthesis of Intermediate Int-16**

[00659] Scheme 16: The Synthesis of Intermediate **Int-16**



[00660] Step A: 5-Propoxypicolonitrile Int-16a.

[00661] Sodium hydride (9.83g, 0.245 mol) (60% in mineral oil) was added in portionwise to the solution of propan-1-ol (10.0 g, 166.51 mmol) in DMF (200 mL). The mixture was stirred at room temperature for 30 min, then 5-fluoropicolinonitrile **Int-15a** (20.32 g, 166.51 mmol) was added portionwise, and stirred at RT overnight. After this time the resulting mixture was quenched with NH_4Cl aq. and extracted with ethyl acetate (4*100 mL). The organic phase was washed with water, brine, dried over Na_2SO_4 , concentrated *in vacuo* and purified by FCC (Interchim; 220 g SiO_2 , hexane/methyl *t*-butyl ether with methyl *t*-butyl ether from 0~35%, flow

rate = 100 mL/min, Rv = 7-11 CV) to give 5-propoxypicolinonitrile **Int-16a** (5.0 g, 95.0% purity, 29.29 mmol, 17% yield).

[00662] Step B: 5-Propoxypicolinaldehyde **Int-16b**.

[00663] To a stirred solution of 5-propoxypicolinonitrile **Int-16a** (4.75 g, 29.31 mmol) in tetrahydrofuran (100 mL) at -78°C, DIBAL (44 mL, 1M in cyclohexane) was added, and the reaction mixture was stirred for 1 h at -78°C. The reaction mixture was monitored by TLC and quenched with 2N HCl (36 mL) and extracted with dichloromethane (3x80 mL). The organics were washed with water, brine, dried over Na₂SO₄, concentrated in vacuo and purified by FCC (Interchim; 60 g SiO₂, hexane/ methyl *t*-butyl ether with methyl *t*-butyl ether from 0~35%, flow rate = 65 mL/min, Rv = 7,5 -10 CV) to give 5-propoxypicolinaldehyde **Int-16b** (1.82 g, 95.0% purity, 10.47 mmol, 35% yield).

[00664] Step C: (*E*)-2-(2-(3-Methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)-5-propoxypyridine **Int-16c**.

[00665] To the solution of 1-methoxy-2-methyl-3-((phenylsulfonyl)methyl)benzene **Int-12c** (prepared as described herein) (2.5 g, 9.05 mmol) in THF (80 mL) was added LiHMDS (1.1 M in THF/ ethylbenzene, 10 mL), at -78°C and the mixture was stirred for 45 min. To the solution was added 5-propoxypicolinaldehyde **Int-16b** (1.79 g, 10.85 mmol), and the mixture was stirred for 1 h. Then diethyl phosphorochloridate (1.87 g, 10.85 mmol) was added, and the mixture was stirred for 1 h. Then LiHMDS (1.1 M in THF/ethylbenzene, 10 mL) was added at -78°C, and the mixture was stirred to ambient temperature. The resulting mixture was poured into saturated NH₄Cl (80 mL) and extracted with ethyl acetate (3*80 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give (*E*)-2-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)-5-propoxypyridine **Int-16c** (5.3 g, 70.0% purity, 8.76 mmol, 96% yield) and used for the next step without further purification.

[00666] Step D: Ethyl 4-(3-methoxy-2-methylphenyl)-3-(5-propoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-16d**.

[00667] Potassium *t*-butoxide (1.47 g, 13.14 mmol) was added portionwise to the solution of (*E*)-2-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)-5-propoxypyridine **Int-16c** (5.3 g, 70.0% purity, 8.76 mmol) and ethyl 2-isocyanoacetate (1.49 g, 13.14 mmol) in dry THF (100 mL) at (-10°C), and stirred at room temperature overnight. Then the reaction mixture was diluted with ice water (100 mL) and extracted 3 times with ethyl acetate (3*80 mL). The organic phase

was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 120 g SiO₂, chloroform/acetonitrile with acetonitrile from 0~30%, flow rate =85 mL/min, Rv = 9-12 CV) to give ethyl 4-(3-methoxy-2-methylphenyl)-3-(5-propoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-16d** (1.28 g, 95.0% purity, 3.08 mmol, 35% yield).

[00668] Step E: Ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(5-propoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-16e**.

[00669] Sodium hydride (0.175 g, 60% in mineral oil), was added portionwise to a solution of ethyl 4-(3-methoxy-2-methylphenyl)-3-(5-propoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-16d** (1.15 g, 2.92 mmol) in DMF (20 mL) at 0°C. The mixture was stirred for 1 h at 0°C. Then the mixture was cooled to -5°C and O-(2,4-dinitrophenyl)hydroxylamine (870.5 mg, 4.37 mmol) was added in one portion. The mixture was stirred for 16 h at room temperature. Then the mixture was poured into ice water and extracted with ethyl acetate (3*20 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* to give ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(5-propoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-16e** (1.65 g, 50.0% purity, 2.01 mmol, 69% yield) and used for the next step without further purification.

[00670] Step F: 6-(3-Methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(5-propoxypyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-16f**.

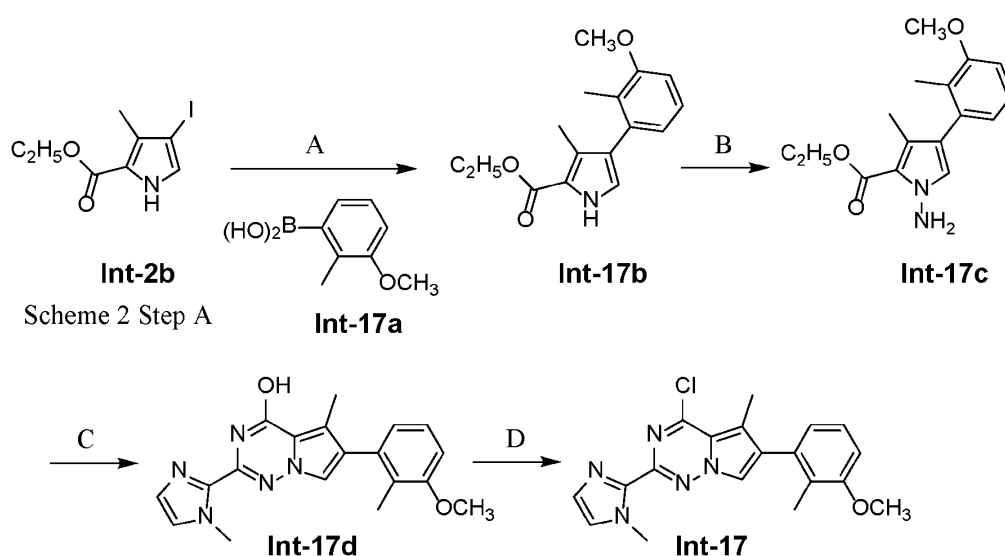
[00671] Sodium hydride (1 g, 25 mmol) (60% in mineral oil) was added portionwise to the solution of ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(5-propoxypyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-16e** (1.65 g, 50.0% purity, 2.01 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (323.52 mg, 3.02 mmol) in dry dioxane (40 mL) at RT. Then reaction mixture was heated to 80°C and stirred at this temperature for 16 h. Afterwards the mixture was cooled to room temperature, poured into ice water, neutralized with acetic acid and extracted with ethyl acetate (3*100 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 80 g SiO₂, chloroform/acetonitrile with acetonitrile from 0-100%, flow rate =60 mL/min, Rv = 16-20 CV) to give 6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(5-propoxypyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-16f** (380.0 mg, 98.0% purity, 791.46 μmol, 39% yield).

[00672] Step G: 4-Chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(5-propoxypyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-16**.

[00673] To the solution of 6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(5-propoxypyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-16f** (380.0 mg, 807.61 μ mol) in acetonitrile (12 mL), phosphoryl trichloride (9.82 g, 64.63 mmol) was added dropwise. The mixture was heated to 90°C and stirred at this temperature for 16 h and then concentrated *in vacuo*, dissolved in ethyl acetate/acetonitrile 10 mL/10 mL, washed with ice cold aq. NaHCO₃, brine, dried over Na₂SO₄, and concentrated *in vacuo*, to give 4-chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(5-propoxypyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-16** (290.0 mg, 92.0% purity, 545.64 μ mol, 67% yield).

[00674] **Example Int-17: Synthesis of Intermediate Int-17**

[00675] Scheme 17: The Synthesis of Intermediate **Int-17**



[00676] **Step A:** Ethyl 4-(3-methoxy-2-methylphenyl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-17b**.

[00677] A mixture of ethyl 4-iodo-3-methyl-1*H*-pyrrole-2-carboxylate **Int-2b** (prepared as described herein) (9.5 g, 34.05 mmol), (3-methoxy-2-methylphenyl)boronic acid **Int-17b** (6.22 g, 37.46 mmol), cesium carbonate (22.19 g, 68.11 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (2.77 g, 3.41 mmol) in dioxane/H₂O (200 mL/10 mL) was heated at 100°C under Argon atmosphere overnight. The reaction mixture was evaporated, and the crude compound was purified by flash chromatography to give ethyl 4-(3-methoxy-2-methylphenyl)-3-methyl-1*H*-pyrrole-2-

carboxylate **Int-17b** (5.4 g, 98% purity, 58.2% yield).

[00678] Step B: Ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-17c**.

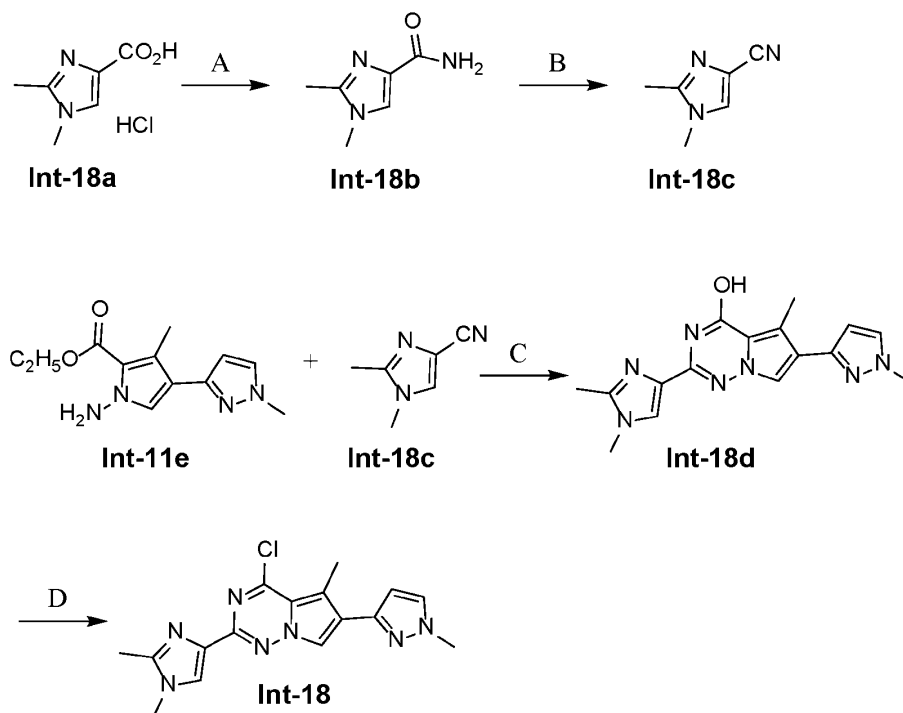
[00679] To solution of ethyl 4-(3-methoxy-2-methylphenyl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-17b** (5.4 g, 19.76 mmol) in DMF (15 mL), sodium hydride (1.03 g, 60.0% purity, 25.69 mmol) was added at 0°C. After 1 h, O-(2,4-dinitrophenyl)hydroxylamine (5.11 g, 25.69 mmol) was added portionwise at 0°C. The reaction mixture was stirred at RT overnight. An aqueous solution of NH₄Cl was added to reaction mixture which was extracted with ethyl acetate (3*50 mL). The combined ethyl acetate layers were washed with water (7*10 mL), dried and evaporated under reduced pressure to give ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-17c** (5.5 g, 85.3% purity, 82.3% yield).

[00680] Step C: 6-(3-Methoxy-2-methylphenyl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-17d**.

[00681] To a mixture of 1-amino-4-(3-methoxy-2-methylphenyl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-17c** (5.5 g, 19.07 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (2.04 g, 19.07 mmol) in dioxane (70 mL), sodium hydride (2.29 g, 60.0% purity, 57.22 mmol) was added under cooling with ice. The reaction mixture was stirred at 100°C overnight. An aqueous solution of NH₄Cl was added to reaction mixture which was then extracted with ethyl acetate (3*30 mL), dried and evaporated under reduce pressure to give 6-(3-methoxy-2-methylphenyl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-17d** (6.8 g, 61.3% purity, 62.2% yield).

[00682] Step D: 4-Chloro-6-(3-methoxy-2-methylphenyl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-17**.

[00683] The starting material 6-(3-methoxy-2-methylphenyl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-17d** (6.9 g, 19.75 mmol) was suspended in phosphoryl trichloride (29.99 g, 197.45 mmol, 18.23 mL, 10.0 equiv) and the reaction mixture was heated at 100°C overnight. The solution was cooled to RT, evaporated under reduced pressure, poured into an aqueous solution of NaHCO₃ and the product was extracted with chloroform (3*50 mL), and evaporated to give 4-chloro-6-(3-methoxy-2-methylphenyl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-17** (5.9 g, 93% purity, 76.2% yield).

[00684] **Example Int-18: Synthesis of Intermediate Int-18**[00685] **Scheme 18: The Synthesis of Intermediate Int-18**[00686] **Step A:** 1,2-Dimethyl-1H-imidazole-4-carboxamide **Int-18b**.

[00687] To the solution of 1,2-dimethyl-1H-imidazole-4-carboxylic acid hydrochloride salt **Int-18a** (15.0 g, 85.21 mmol) in acetonitrile (150 mL), 1,1'-carbonyldiimidazole (20.71 g, 127.81 mmol) was added portionwise. After gas evolution ceased, ammonia gas was bubbled through the reaction mixture and left to stir overnight. Afterwards the reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate, washed with H₂O then with saturated brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 300 g SiO₂, chloroform/methanol with methanol from 0~15%, flow rate = 127 mL/min, R_v = 5-8) to give 1,2-dimethyl-1H-imidazole-4-carboxamide **Int-18b** (8.8 g, 95.0% purity, 60.08 mmol, 70% yield).

[00688] **Step B:** 1,2-Dimethyl-1H-imidazole-4-carbonitrile **Int-18c**.

[00689] To a stirred solution 1,2-dimethyl-1H-imidazole-4-carboxamide **Int-18b** (8.8 g, 63.27 mmol) in pyridine (45 mL) was added trifluoroacetic anhydride (33.21 g, 158.16 mmol, 22.17 mL, 2.5 equiv) and the solution was stirred at room temperature for 2 h. The solvent was

removed under reduced pressure and the residue was dissolved in ethyl acetate, washed with H₂O, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim, 330 g SiO₂, chloroform/acetonitrile (20-40%), flow rate = 127 mL/min, 5,1-8,5 CV) to give 1,2-dimethyl-1*H*-imidazole-4-carbonitrile **Int-18c** (1.1 g, 95.0% purity, 8.63 mmol, 13% yield).

[00690] Step C: 2-(1,2-Dimethyl-1*H*-imidazol-4-yl)-5-methyl-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-18d**.

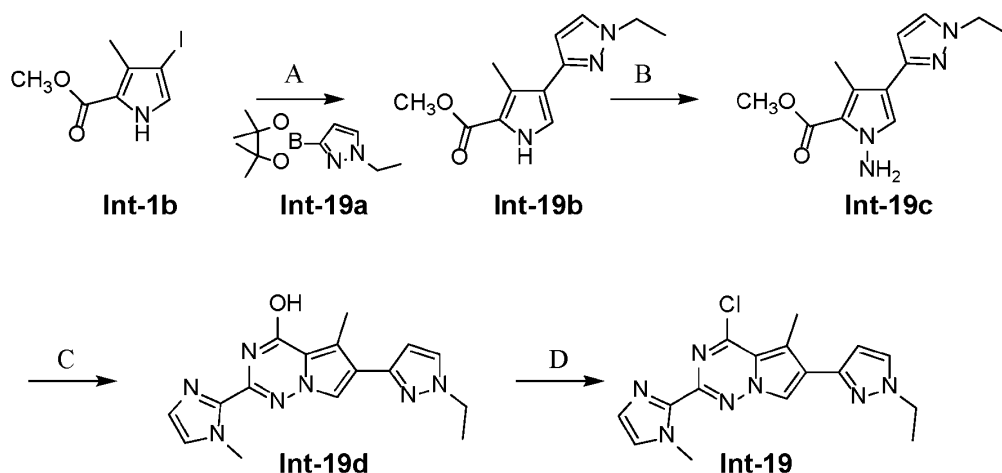
[00691] Sodium hydride (0.52 g (60% in mineral oil)) was added portion-wise to the solution of ethyl 1-amino-3-methyl-4-(1-methyl-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate **Int-11e** (prepared as described herein) (2.13 g, 8.58 mmol) and 1,2-dimethyl-1*H*-imidazole-4-carbonitrile **Int-18c** (1.09 g, 9.01 mmol) in dry dioxane (40 mL). Then the reaction mixture was heated to 80°C and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured into ice water, neutralized with acetic acid and extracted with ethyl acetate (3*50 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim, 40 g SiO₂, chloroform/acetonitrile (0-100%)/methanol (0-50%) flow rate = 40 mL/min, 32-33,4 CV; 2); Interchim, 12 g SiO₂, { ethyl acetate + 2% TEA }/ { methanol + 2% TEA } (0-100), flow rate = 25 mL/min, 9,5-11,3) to give 2-(1,2-dimethyl-1*H*-imidazol-4-yl)-5-methyl-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-18d** (180.0 mg, 95.0% purity, 528.83 µmol, 6% yield).

[00692] Step D: 4-Chloro-2-(1,2-dimethyl-1*H*-imidazol-4-yl)-5-methyl-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-18**.

[00693] To the solution of 2-(1,2-dimethyl-1*H*-imidazol-4-yl)-5-methyl-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-18d** (479.64 mg, 1.48 mmol) in chloroform (12 mL), phosphoryl trichloride (9.01 g, 59.36 mmol, 5.48 mL, 40.0 equiv) was added dropwise. The mixture was heated to 110°C and stirred at this temperature for 3 days then concentrated *in vacuo*, dissolved in ethyl acetate/acetonitrile 10 mL/10 mL washed with ice cold aq. NaHCO₃, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give 4-chloro-2-(1,2-dimethyl-1*H*-imidazol-4-yl)-5-methyl-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-18** (250.0 mg, 90.0% purity, 658.28 µmol, 44% yield).

[00694] Example Int-19: Synthesis of Intermediate Int-19

[00695] Scheme 19: The Synthesis of Intermediate **Int-19**



[00696] Step A: Methyl 4-(1-ethyl-1*H*-pyrazol-3-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-19b**.

[00697] Methyl 4-iodo-3-methyl-1*H*-pyrrole-2-carboxylate **Int-1b** (prepared as described in herein) (2.0 g, 7.55 mmol), 1-ethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole **Int-19a** (2.01 g, 9.05 mmol), cesium carbonate (6.15 g, 18.86 mmol) were dissolved in degassed dioxane/water (40 mL/4 mL). Pd(dppf)Cl₂·CH₂Cl₂ (614.9 mg, 754.5 μmol) was added under an argon flow and the mixture was stirred at 100°C overnight. The mixture was diluted with ethyl acetate/water, the organic layer was washed with brine, dried over Na₂SO₄ and evaporated. The crude product was purified by FCC (hexane/ethyl acetate, gradient elution; TLC hexane/ethyl acetate 1:1 R_f = 0.3) to give methyl 4-(1-ethyl-1*H*-pyrazol-3-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-19b** (570.0 mg, 2.44 mmol, 32.4% yield).

[00698] Step B: Methyl 1-amino-4-(1-ethyl-1*H*-pyrazol-3-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **19c**.

[00699] Methyl 4-(1-ethyl-1*H*-pyrazol-3-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **Int-19b** (600.36 mg, 2.57 mmol) was dissolved in DMF and the mixture was cooled to 0°C. Sodium hydride (80.29 mg, 3.35 mmol) was added in portions and the mixture was stirred at RT until the evolution of gas stopped (20 min), then it was cooled again and the solution of O-(2,4-dinitrophenyl)hydroxylamine (666.22 mg, 3.35 mmol) in DMF was added dropwise at 0-+5°C. The mixture was stirred at RT overnight, then poured into a saturated solution of ammonium chloride, extracted with ethyl acetate, washed with water, brine and evaporated to give methyl 1-amino-4-(1-ethyl-1*H*-pyrazol-3-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **19c** (650.0 mg, 85.0%

purity, 2.23 mmol, 86.5% yield). The product was used without purification.

[00700] Step C: 6-(1-Ethyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-19d**.

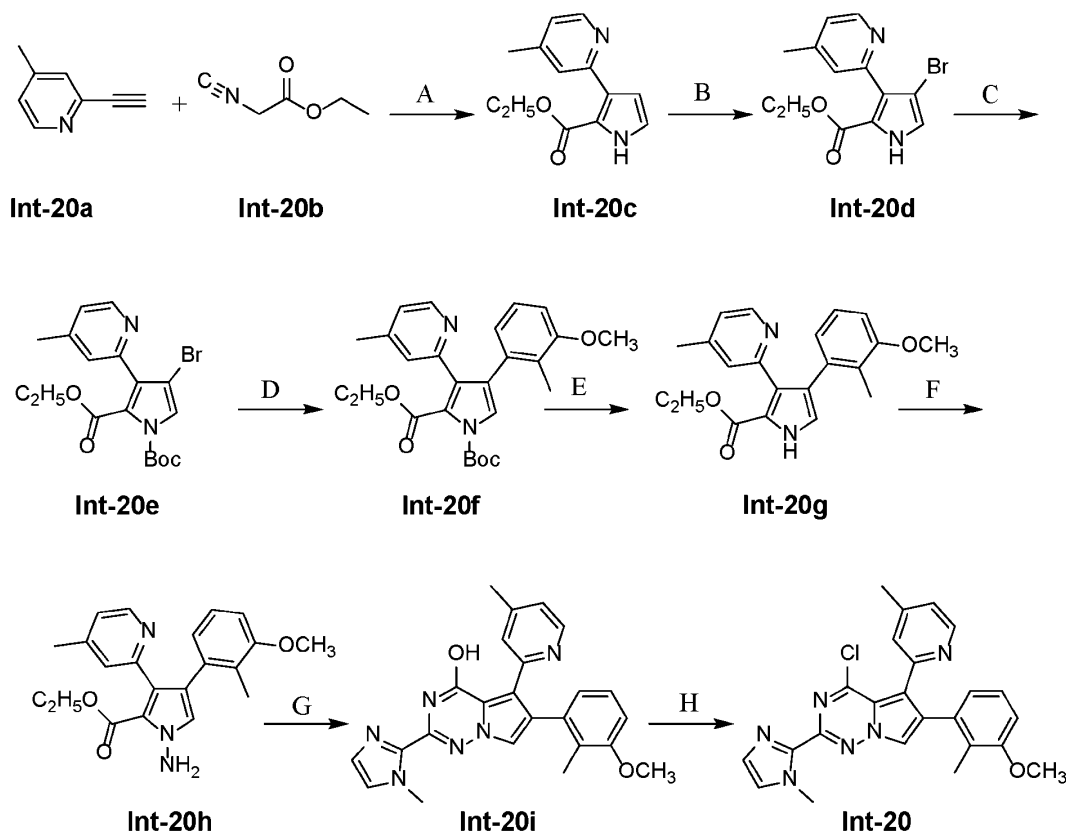
[00701] Methyl 1-amino-4-(1-ethyl-1*H*-pyrazol-3-yl)-3-methyl-1*H*-pyrrole-2-carboxylate **19c** (650.36 mg, 2.62 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (336.69 mg, 3.14 mmol) were dissolved in dioxane. Sodium hydride (138.29 mg, 5.76 mmol) was added in portions and the mixture was heated at 80°C overnight. The crude product was purified by FCC (chloroform/methanol, gradient elution (TLC 20:1 R_f =0.6, first flake)) to give 6-(1-ethyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-19d** (426.0 mg, 75.0% purity, 988.09 μ mol, 37.7% yield).

[00702] Step D: 4-Chloro-6-(1-ethyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-19**.

[00703] 6-(1-Ethyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-19d** (500.0 mg, 1.55 mmol) was dissolved in phosphoryl trichloride (4.03 g, 26.31 mmol, 2.45 mL, 17.0 equiv) (5 mL for 1 g) and the mixture was refluxed for 30 min. Then the mixture was poured into ice, neutralized with Na₂CO₃ solution, extracted with chloroform, dried over Na₂SO₄ and evaporated to give 4-chloro-6-(1-ethyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-19** (500.0 mg, 61.0% purity, 892.34 μ mol, 57.7% yield). The product was used without purification.

[00704] Example Int-20: Synthesis of Intermediate Int-20

[00705] Scheme 20: The Synthesis of Intermediate **Int-20**



[00706] **Step A:** Ethyl 3-(4-methylpyridin-2-yl)-1H-pyrrole-2-carboxylate **Int-20c**.

[00707] A mixture of 2-ethynyl-4-methylpyridine **Int-20a** (6.0 g, 51.27 mmol) and silver carbonate (1.4 g, 5.13 mmol) in dioxane was heated to 90°C and ethyl 2-isocyanoacetate ethyl 2-isocyanoacetate **Int-20b** (5.8 g, 51.27 mmol, 5.6 ml, 1.0 equiv) was added dropwise under an argon atmosphere. The reaction mixture was stirred at 100°C for 2 h then cooled and filtered through SiO₂. The filtrate was evaporated and crude material purified by flash chromatography to give ethyl 3-(4-methylpyridin-2-yl)-1H-pyrrole-2-carboxylate **Int-20c** (7.3 g, 91% purity, 56.9% yield).

[00708] **Step B:** Ethyl 4-bromo-3-(4-methylpyridin-2-yl)-1H-pyrrole-2-carboxylate **Int-20d**.

[00709] To a solution of ethyl 3-(4-methylpyridin-2-yl)-1H-pyrrole-2-carboxylate **Int-20c** (7.3 g, 31.7 mmol) in DMF (250 mL), N-bromosuccinimide (5.05 g, 28.53 mmol) was added under cooling with ice. The reaction mixture was stirred at RT overnight, then poured into water and extracted ethyl acetate (3x70 mL). The combined ethyl acetate was washed with water (5x50

mL), dried with Na₂SO₄ and evaporated. The crude material was purified by flash chromatography to give ethyl 4-bromo-3-(4-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-20d** (2.4 g, 95% purity, 24.5% yield).

[00710] Step C: 1-(*tert*-Butyl) 2-ethyl 4-bromo-3-(4-methylpyridin-2-yl)-1*H*-pyrrole-1,2-dicarboxylate **Int-20e**.

[00711] To the mixture of ethyl 4-bromo-3-(4-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-20d** (2.41 g, 7.78 mmol), triethylamine (2.36 g, 23.35 mmol) and *N,N*-dimethylpyridin-4-amine (95.0 mg, 778.15 μ mol, 100.0 μ L, 0.1 equiv) in dichloromethane (50 mL), di-*tert*-butyl dicarbonate (2.55 g, 11.67 mmol, 2.68 mL, 1.5 equiv) was added under cooling with ice. The reaction mixture was stirred at RT overnight and then washed with water (3x20 mL). The organic layer was dried with Na₂SO₄ and evaporated to give 1-(*tert*-butyl) 2-ethyl 4-bromo-3-(4-methylpyridin-2-yl)-1*H*-pyrrole-1,2-dicarboxylate **Int-20e** (3.5g, 97% purity, 99% yield).

[00712] Step D: 1-(*tert*-Butyl) 2-ethyl 4-(3-methoxy-2-methylphenyl)-3-(4-methylpyridin-2-yl)-1*H*-pyrrole-1,2-dicarboxylate **Int-20f**.

[00713] A mixture of 1-(*tert*-butyl) 2-ethyl 4-bromo-3-(4-methylpyridin-2-yl)-1*H*-pyrrole-1,2-dicarboxylate **Int-20e** (3.5 g, 8.55 mmol), (3-methoxy-2-methylphenyl)boronic acid (1.42 g, 8.55 mmol), tripotassium phosphate (3.62 g, 17.1 mmol), dicyclohexyl[2',4',6'-tris(propan-2-yl)-[1,1'-biphenyl]-2-yl]phosphane (814.78 mg, 1.71 mmol) and palladium(2+) diacetate (191.51 mg, 855.22 μ mol) in dioxane/H₂O (60 mL/3 mL) was stirred at 80°C under an argon atmosphere overnight then cooled to RT and filtered through SiO₂. The filtrate was evaporated and crude material was purified by flash chromatography to give 1-(*tert*-butyl) 2-ethyl 4-(3-methoxy-2-methylphenyl)-3-(4-methylpyridin-2-yl)-1*H*-pyrrole-1,2-dicarboxylate **Int-20f** (0.2 g, 54% purity, 2.6% yield).

[00714] Step E: Ethyl 4-(3-methoxy-2-methylphenyl)-3-(4-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-20g**.

[00715] To a solution of 1-(*tert*-butyl) 2-ethyl 4-(3-methoxy-2-methylphenyl)-3-(4-methylpyridin-2-yl)-1*H*-pyrrole-1,2-dicarboxylate **Int-20f** (201.86 mg, 448.05 μ mol) in dichloromethane (5 mL), trifluoroacetic acid (768.04 mg, 6.74 mmol, 520.0 μ L, 15.0 equiv) was added dropwise under cooling with ice. The reaction mixture was stirred at RT overnight and then poured into an aqueous solution of NaHCO₃. The organic layer was separated and washed with water and evaporated to give ethyl 4-(3-methoxy-2-methylphenyl)-3-(4-methylpyridin-2-

yl)-1*H*-pyrrole-2-carboxylate **Int-20g** (0.24 g, 51% purity, 80% yield).

[00716] Step F: Ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(4-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-20h**.

[00717] To solution of ethyl 4-(3-methoxy-2-methylphenyl)-3-(4-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-20g** (239.73 mg, 684.13 μ mol) in DMF (10 mL), sodium hydride (35.57 mg, 60.0% purity, 889.37 μ mol) was added at 0°C. After 1 h, O-(2,4-dinitrophenyl)hydroxylamine (177.01 mg, 889.37 μ mol) was added portionwise at 0°C. The reaction mixture was stirred at RT overnight. An aqueous solution of NH₄Cl was added to reaction mixture, extracted with ethyl acetate (3*20 mL), and the combined ethyl acetate was washed with water (7*5 mL), dried and evaporated under reduce pressure to give ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(4-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-20h** (0.27 g, 36% purity, 39% yield).

[00718] Step G: 6-(3-Methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(4-methylpyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-20i**.

[00719] To a mixture of ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(4-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-20h** (269.91 mg, 738.62 μ mol) and 1-methyl-1*H*-imidazole-2-carbonitrile (79.07 mg, 738.62 μ mol) in dioxane (30 mL), sodium hydride (88.63 mg, 60.0% purity, 2.22 mmol) was added under cooling with ice. The reaction mixture was stirred at 100°C overnight. An aqueous solution of NH₄Cl was added to reaction mixture, which was extracted with ethyl acetate (3*15 mL), dried and evaporated under reduce pressure to give 6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(4-methylpyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-20i** (0.3 g, 25% purity, 25% yield).

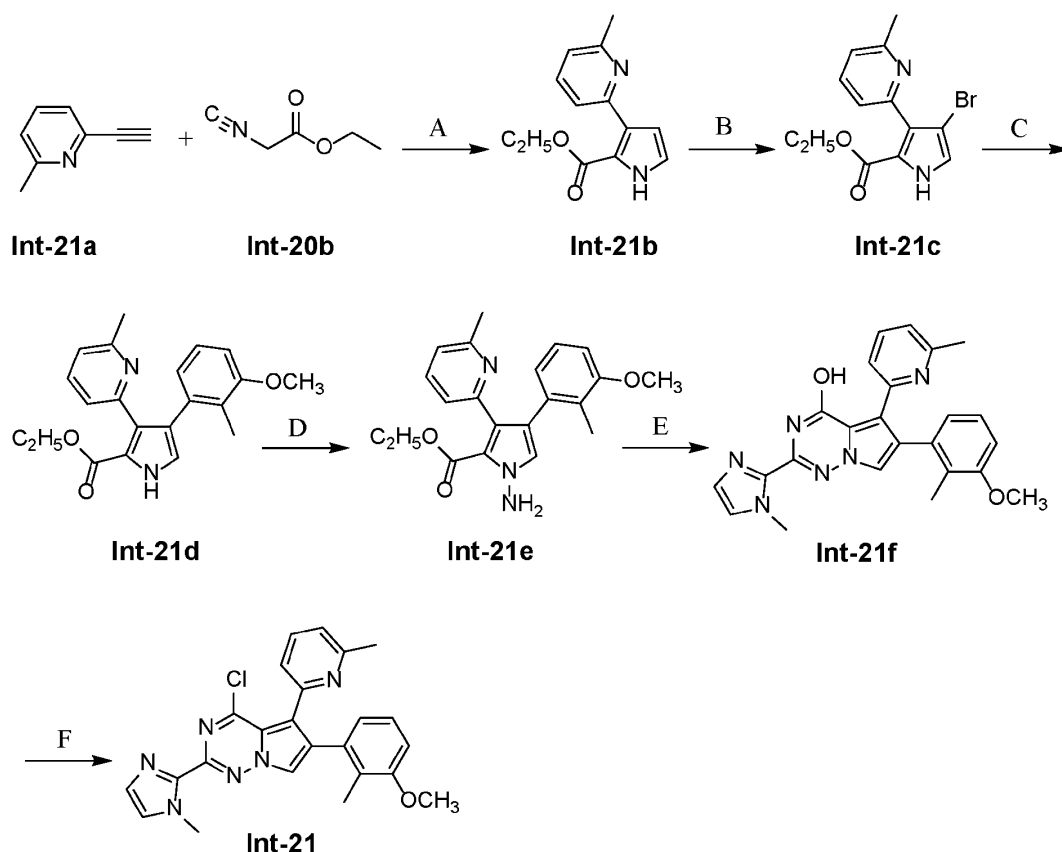
[00720] Step H: 4-chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(4-methylpyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Into-20**.

[00721] The starting material 6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(4-methylpyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-20i** (300.02 mg, 703.5 μ mol) was suspended in phosphoryl trichloride (1.07 g, 7.04 mmol, 650.0 μ l, 10.0 equiv) and the reaction mixture was heated at 100°C overnight. The solution was cooled to RT, evaporated under reduced pressure, poured into an aqueous solution of NaHCO₃ and the product was extracted with chloroform (3*20 mL) and evaporated to give 4-chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(4-methylpyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Into-20** (0.34

g, 16% purity, 17% yield).

[00722] Example Int-21: Synthesis of Intermediate Int-21

[00723] Scheme 21: The Synthesis of Intermediate Int-21



[00724] Step A: Ethyl 3-(6-methylpyridin-2-yl)-1H-pyrrole-2-carboxylate **Int-21b**.

[00725] A mixture of 2-ethynyl-6-methylpyridine **Int-21a** (3.0 g, 25.63 mmol) and silver carbonate (701.66 mg, 2.56 mmol) in dioxane (50 mL) was heated to 90°C and ethyl 2-isocyanoacetate **Int-21b** (3.48 g, 30.75 mmol) was added dropwise under an argon atmosphere. The reaction mixture was stirred at 100°C for 2 h and then cooled and filtered through SiO₂. The filtrate was evaporated and crude material was purified by flash chromatography to give ethyl 3-(6-methylpyridin-2-yl)-1H-pyrrole-2-carboxylate **Int-21b** (2.9 g, 82% purity, 40% yield).

[00726] Step B: Ethyl 4-bromo-3-(6-methylpyridin-2-yl)-1H-pyrrole-2-carboxylate **Int-21c**.

[00727] To a solution of ethyl 3-(6-methylpyridin-2-yl)-1H-pyrrole-2-carboxylate **Int-21b** (2.9 g, 12.59 mmol) in DMF (50 mL), N-bromosuccinimide (2.01 g, 11.34 mmol) was added

under cooling with ice. The reaction mixture was stirred at RT overnight, then poured into water and extracted with ethyl acetate (3x30 mL). The combined ethyl acetate layers was washed with water (5x20 mL), dried over Na₂SO₄ and evaporated. The crude material was purified by flash chromatography to give ethyl 4-bromo-3-(6-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-21c** (1.2 g, 95% purity, 31% yield).

[00728] **Step C:** Ethyl 4-(3-methoxy-2-methylphenyl)-3-(6-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-21d**.

[00729] A mixture of ethyl 4-bromo-3-(6-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-21c** (1.2 g, 3.88 mmol), (3-methoxy-2-methylphenyl)boronic acid (644.58 mg, 3.88 mmol), cesium (I) carbonate (2.53 g, 7.76 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (315.89 mg, 388.12 μmol) in dioxane/H₂O (25 mL/2 mL) was stirred at 100°C under an argon atmosphere overnight then cooled to RT and filtered through SiO₂. The filtrate was evaporated and crude material was purified by flash chromatography to give ethyl 4-(3-methoxy-2-methylphenyl)-3-(6-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-21d** (0.41 g, 70% purity, 21% yield).

[00730] **Step D:** Ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(6-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-21e**.

[00731] To a solution of ethyl 4-(3-methoxy-2-methylphenyl)-3-(6-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-21d** (410.41 mg, 1.17 mmol) in DMF (10 mL), O-(2,4-dinitrophenyl)hydroxylamine (303.03 mg, 1.52 mmol) was added at 0°C. After 1 h sodium hydride (60.9 mg, 60.0% purity, 1.52 mmol) was added portionwise at 0°C. The reaction mixture was stirred at RT overnight. An aqueous solution of NH₄Cl was added to reaction mixture, which was extracted with ethyl acetate (3*20 mL), and the combined EtOAc was washed with water (7*5 mL), dried and evaporated under reduce pressure to give ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(6-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-21e** (0.4 g, 68% purity, 65% yield).

[00732] **Step E:** 6-(3-Methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(6-methylpyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-21f**.

[00733] To a mixture of ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(6-methylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-21e** (400.15 mg, 1.1 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (117.22 mg, 1.1 mmol) in dioxane (30 mL), sodium hydride (87.59 mg, 60.0%

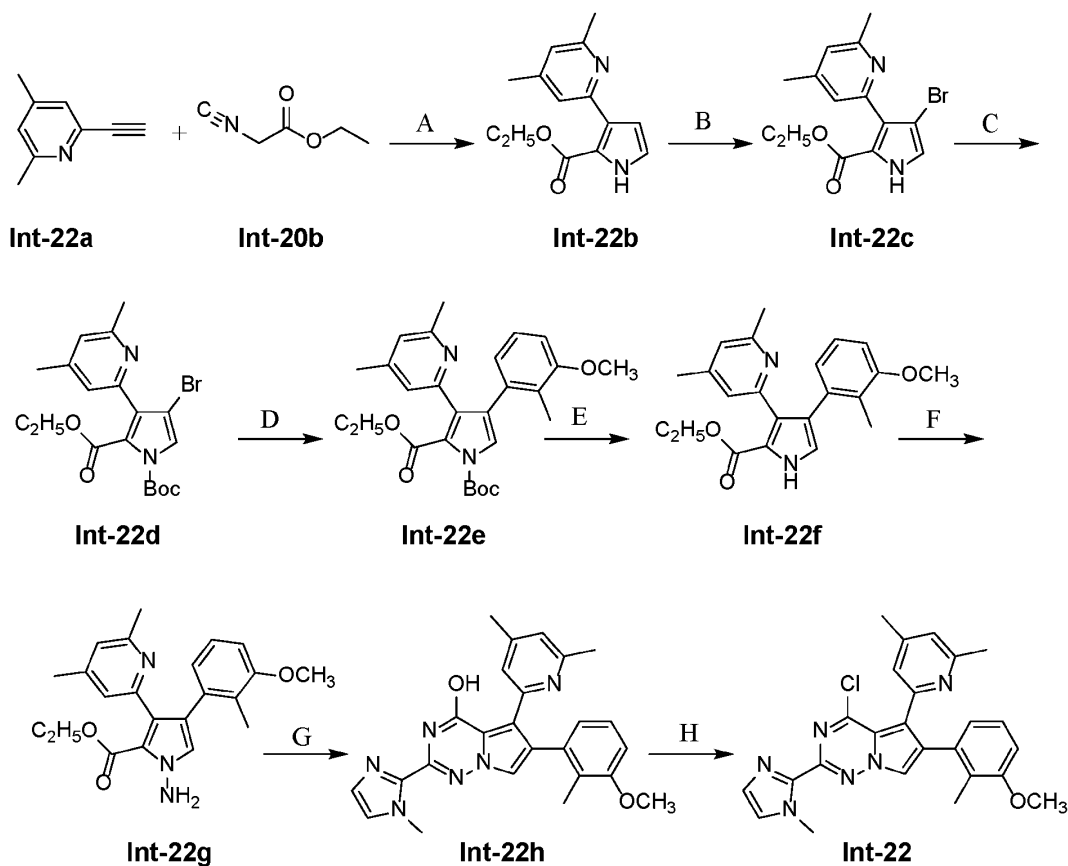
purity, 2.19 mmol) was added under cooling with ice. The reaction mixture was stirred at 100°C overnight. An aqueous solution of NH₄Cl was added to reaction mixture, which was extracted with ethyl acetate (3*20 mL), dried and evaporated under reduce pressure to give 6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(6-methylpyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-21f** (0.47 g, 43% purity, 44% yield).

[00734] Step F: 4-chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(6-methylpyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-21**.

[00735] The starting material 6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(6-methylpyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-21f** (470.0 mg, 1.1 mmol) was suspended in phosphoryl trichloride (1.67 g, 11.01 mmol) and the reaction mixture was heated at 100°C overnight. The solution was cooled to RT, evaporated under reduced pressure, poured into an aqueous solution of NaHCO₃ and the product was extracted with chloroform (3*50 mL. The chloroform layer was evaporated to give 4-chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(6-methylpyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-21** (0.53 g, 53% purity, 60% yield).

[00736] Example Int-22: Synthesis of Intermediate Int-22

[00737] Scheme 22: The Synthesis of Intermediate **Int-22**



[00738] **Step A:** Ethyl 3-(4,6-dimethylpyridin-2-yl)-1H-pyrrole-2-carboxylate **Int-22b**.

[00739] A mixture of 2-ethynyl-4,6-dimethylpyridine **Int-22a** (4.5 g, 34.33 mmol) and silver carbonate (940.0 mg, 3.43 mmol) in dioxane was heated to 90°C and ethyl 2-isocyanoacetate **Int-22b** (3.88 g, 34.33 mmol, 3.75 ml, 1.0 equiv) was added dropwise under an argon atmosphere. The reaction mixture was stirred at 100°C for 2 h then cooled and filtered through SiO₂. The filtrate was evaporated and crude material was purified by flash chromatography to give ethyl 3-(4,6-dimethylpyridin-2-yl)-1H-pyrrole-2-carboxylate **Int-22b** (5 g, 88% purity, 53% yield).

[00740] **Step B:** Ethyl 4-bromo-3-(4,6-dimethylpyridin-2-yl)-1H-pyrrole-2-carboxylate **Int-22c**.

[00741] To a solution of ethyl 3-(4,6-dimethylpyridin-2-yl)-1H-pyrrole-2-carboxylate **Int-22b** (5.0 g, 20.47 mmol) in DMF (150 mL), N-bromosuccinimide (3.26 g, 18.42 mmol) was added

under cooling with ice. The reaction mixture was stirred at RT overnight, and then poured into water and extracted with ethyl acetate (3x70 mL). The combined ethyl acetate layers were washed with water (5x30 mL), dried over Na₂SO₄ and evaporated. The crude material was purified by flash chromatography to give ethyl 4-bromo-3-(4,6-dimethylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-22c** (1.6 g, 5% purity, 27% yield).

[00742] Step C: 1-(*tert*-Butyl) 2-ethyl 4-bromo-3-(4,6-dimethylpyridin-2-yl)-1*H*-pyrrole-1,2-dicarboxylate **Int-22d**.

[00743] To a mixture of ethyl 4-bromo-3-(4,6-dimethylpyridin-2-yl)-1*H*-pyrrole-2-carboxylate **Int-22c** (1.6 g, 4.95 mmol), N,N-dimethylpyridin-4-amine (60.48 mg, 495.39 μ mol) and triethylamine (1.5 g, 14.86 mmol, 2.07 ml, 3.0 equiv) in dichloromethane (50 mL), di-*tert*-butyl dicarbonate (1.62 g, 7.43 mmol) was added under cooling with ice. The reaction mixture was stirred at RT overnight and then washed with water (3x20 mL). The organic layer was dried over Na₂SO₄ and evaporated to give 1-(*tert*-butyl) 2-ethyl 4-bromo-3-(4,6-dimethylpyridin-2-yl)-1*H*-pyrrole-1,2-dicarboxylate **Int-22d** (1.8 g, 93% purity, 84% yield).

[00744] Step D: 1-(*tert*-Butyl) 2-ethyl 3-(4,6-dimethylpyridin-2-yl)-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-1,2-dicarboxylate **Int-22e**.

[00745] A mixture of 1-(*tert*-butyl) 2-ethyl 4-bromo-3-(4,6-dimethylpyridin-2-yl)-1*H*-pyrrole-1,2-dicarboxylate **Int-22d** (1.8 g, 4.25 mmol), (3-methoxy-2-methylphenyl)boronic acid (706.07 mg, 4.25 mmol), cesium (I) carbonate (2.77 g, 8.5 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (346.02 mg, 425.14 μ mol) in dioxane/H₂O (20 mL/2 mL) was stirred at 80°C under an argon atmosphere overnight then cooled to RT and filtered through SiO₂. The filtrate was evaporated and crude material was purified by flash chromatography to give 1-(*tert*-butyl) 2-ethyl 3-(4,6-dimethylpyridin-2-yl)-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-1,2-dicarboxylate **Int-22e** (2.3 g, 75% purity, 91% yield).

[00746] Step E: Ethyl 3-(4,6-dimethylpyridin-2-yl)-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-22f**.

[00747] To solution of 1-(*tert*-butyl) 2-ethyl 3-(4,6-dimethylpyridin-2-yl)-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-1,2-dicarboxylate **Int-22e** (2.3 g, 4.95 mmol) in dichloromethane (5 mL) trifluoroacetic acid (8.46 g, 74.24 mmol, 5.73 ml, 15.0 equiv) was added dropwise under cooling with ice. The reaction mixture was stirred at RT overnight and then poured into an

aqueous solution of NaHCO₃. The organic layer was separated and washed with water and then evaporated. The crude material was purified by flash chromatography to give ethyl 3-(4,6-dimethylpyridin-2-yl)-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-22f** (1 g, 95% purity, 56% yield).

[00748] Step F: Ethyl 1-amino-3-(4,6-dimethylpyridin-2-yl)-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-22g**.

[00749] To a solution of ethyl 3-(4,6-dimethylpyridin-2-yl)-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-22f** (999.81 mg, 2.74 mmol) in DMF (10 mL), sodium hydride (142.64 mg, 60.0% purity, 3.57 mmol) was added at 0°C. After 1 h, O-(2,4-dinitrophenyl)hydroxylamine (709.81 mg, 3.57 mmol) was added portionwise at 0°C. The reaction mixture was stirred at RT overnight. An aqueous solution of NH₄Cl was added to reaction mixture, which was then extracted with ethyl acetate (3*30 mL), and the combined ethyl acetate layers were washed with water (7*10 mL), dried and evaporated under reduce pressure to give ethyl 1-amino-3-(4,6-dimethylpyridin-2-yl)-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-22g** (0.5 g, 71% purity, 37% yield).

[00750] Step G: 5-(4,6-Dimethylpyridin-2-yl)-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-22h**.

[00751] To a mixture of ethyl 1-amino-3-(4,6-dimethylpyridin-2-yl)-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-22g** (499.62 mg, 1.32 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (140.95 mg, 1.32 mmol) in dioxane (20 mL), sodium hydride (157.99 mg, 60.0% purity, 3.95 mmol) was added under cooling with ice. The reaction mixture was stirred at 100°C overnight. An aqueous solution of NH₄Cl was added to reaction mixture, which was then extracted with ethyl acetate (3*20 mL), dried and evaporated under reduce pressure to give 5-(4,6-dimethylpyridin-2-yl)-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-22h** (0.76 g, 63% purity, 82% yield).

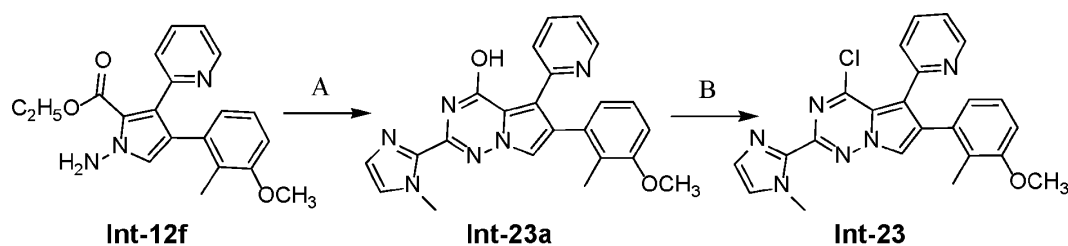
[00752] Step H: 4-Chloro-5-(4,6-dimethylpyridin-2-yl)-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-22**.

[00753] The starting material 5-(4,6-dimethylpyridin-2-yl)-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-22h** (760.0 mg, 1.73 mmol) was suspended in phosphoryl trichloride (2.62 g, 17.26 mmol) and the reaction mixture was heated at 100°C overnight. The solution was cooled to RT, evaporated under reduced pressure, poured into

an aqueous solution of NaHCO_3 and the product was extracted with chloroform (3*50 mL), and chloroform evaporated to give 4-chloro-5-(4,6-dimethylpyridin-2-yl)-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-22** (0.62 g, 38% purity, 30% yield).

[00754] Example Int-23: Synthesis of Intermediate Int-23

[00755] Scheme 23: The Synthesis of Intermediate Int-23



[00756] Step A: 6-(3-Methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-23a**.

[00757] Sodium hydride (0.2 g, 5.1 mmol) (60% in mineral oil) was added portionwise to the solution of ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(pyridin-2-yl)-1*H*-pyrrole-2-carboxylate **12f** (prepared as described herein) (900.0 mg, 2.56 mmol) and 1-methyl-1*H*-imidazole-4-carbonitrile (411.12 mg, 3.84 mmol) in dry dioxane (16 mL) at RT. Then the reaction mixture was heated to 80°C and stirred at this temperature for 16 h. After the mixture was cooled to room temperature, it was poured into ice water, neutralized with acetic acid and extracted with ethyl acetate (3*100 mL). The combined organic phases was washed with water, brine, dried over Na_2SO_4 , concentrated *in vacuo* and purified by FCC (Interchim; 40 g SiO_2 , chloroform/acetonitrile/methanol with methanol from 0~30%, flow rate = 85 mL/min, $R_v = 30 - 35$ CV) to give 6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-23a** (400.0 mg, 95.0% purity, 921.34 μmol , 36% yield).

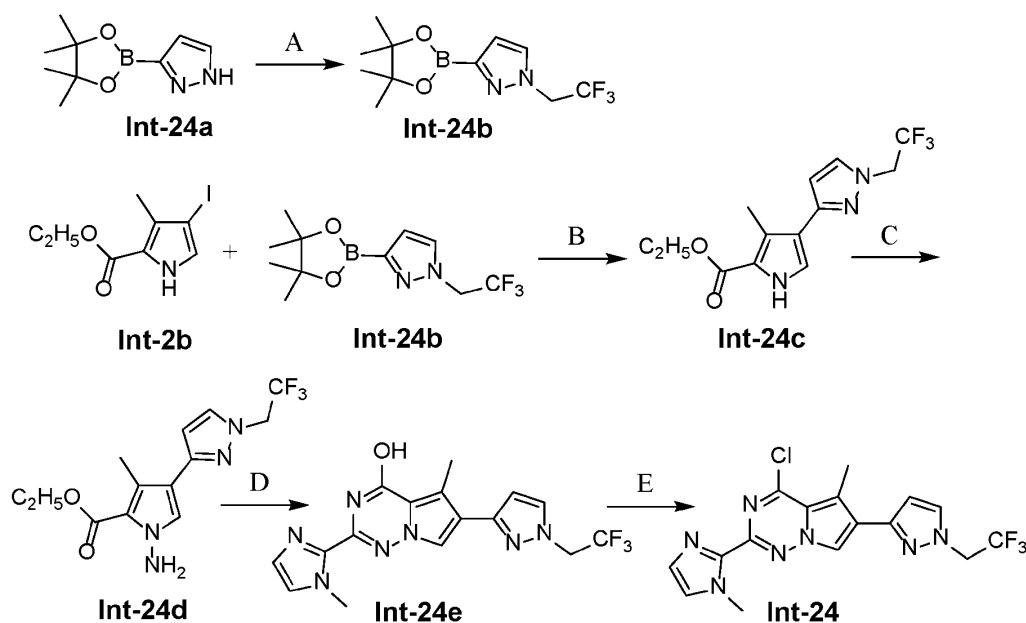
[00758] Step B: 4-Chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-23**.

[00759] To a solution of 6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-23a** (400.0 mg, 969.83 μmol) in acetonitrile (15 mL), phosphoryl trichloride (11.79 g, 77.61 mmol) was added dropwise. The mixture was heated to 100°C in a sealed tube and stirred at this temperature for 16 h then concentrated *in*

vacuo, dissolved in ethyl acetate/acetonitrile 10 mL/10 mL, washed with ice cold aq NaHCO₃, brine, dried over Na₂SO₄, and concentrated *in vacuo*, to give 4-chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-23** (360.0 mg, 90.0% purity, 751.93 μmol, 77% yield).

[00760] Example Int-24: Synthesis of Intermediate Int-24

[00761] Scheme 24: The Synthesis of Intermediate Int-24



[00762] Step A: 3-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole **Int-24b**.

[00763] To a solution of 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1*H*-pyrazole **Int-24a** (30.0 g, 0.155 mol) in *N,N*-dimethylformamide (10 mL) and tetrahydrofuran (10 mL) were added 2,2,2-trifluoroethyl trifluoromethanesulfonate (107.5 g, 0.46 mol) and potassium *t*-butoxide (34.63 g, 0.31 mol) at 25°C. The resultant mixture was stirred at room temperature for 1 h. Then 30 mL of water was added to the mixture and it was extracted with ethyl acetate (20 mL*3). The organic layer was dried over sodium sulfate, and concentrated to afford 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole **Int-24b**. (5.8 g, 11.7%).

[00764] Step B: Ethyl 3-methyl-4-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate **Int-24c**.

[00765] Ethyl 4-iodo-3-methyl-1*H*-pyrrole-2-carboxylate **Int-2b** (prepared as described in

herein) (9.68 g, 34.71 mmol), 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1-(2,2,2-trifluoroethyl)-1*H*-pyrazole **Int-24b** (11.5 g, 41.65 mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) dichloromethane complex (2.82 g, 3.47 mmol), cesium (I) carbonate (22.61 g, 69.41 mmol), bis(adamantan-1-yl)(butyl)phosphane (2.8 g, 7.81 mmol) were dissolved in degassed dioxane (180 ml) under Ar. Then 9.8 mL of water was added *via* syringe. The reaction mixture was heated to 80°C and stirred at this temperature for 16 h. The mixture was cooled to room temperature, filtered through celite and concentrated. The residue was purified by column chromatography (eluted with hexane:ethyl acetate 20:1 to 1:1). Ethyl 3-methyl-4-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate **Int-24c** (8.2 g, 27.22 mmol, 78.4% yield) was obtained as light-yellow powder.

[00766] Step C: Ethyl 1-amino-3-methyl-4-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate **Int-24d**.

[00767] Sodium hydride (483.32 mg, 60.0% purity, 12.08 mmol) (60% in mineral oil) was added portion wise to a solution of ethyl 3-methyl-4-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate **Int-24c** (2.8 g, 9.29 mmol) in DMF (10 mL) at 0°C. The mixture was stirred for 1 h at room temperature. Then the mixture was cooled to 0°C and *O*-(2,4-dinitrophenyl)hydroxylamine (2.41 g, 12.08 mmol) was added portionwise. The mixture was stirred for 16 h at room temperature. Then the mixture poured in ice water, diluted with ethyl acetate (10 mL), washed with water (5*5 mL), dried *in vacuo* and purified by flash chromatography. Ethyl 1-amino-3-methyl-4-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate **Int-24d** (350.0 mg, 1.11 mmol, 11.9% yield) was obtained.

[00768] Step D: 5-Methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-24e**.

[00769] Sodium hydride (88.62 mg, 60.0% purity, 2.22 mmol) (60% in mineral oil) was added portion wise (during 3 min) to the solution of ethyl 1-amino-3-methyl-4-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl)-1*H*-pyrrole-2-carboxylate **Int-24d** (350.0 mg, 1.11 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (142.31 mg, 1.33 mmol) in dioxane (20 mL). The reaction mixture was heated to reflux and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured into ice water and neutralized by acetic acid. The formed precipitate was collected by filtration, washed with water (2*10 mL), concentrated and purified by flash chromatography. 5-Methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-(2,2,2-trifluoroethyl)-1*H*-

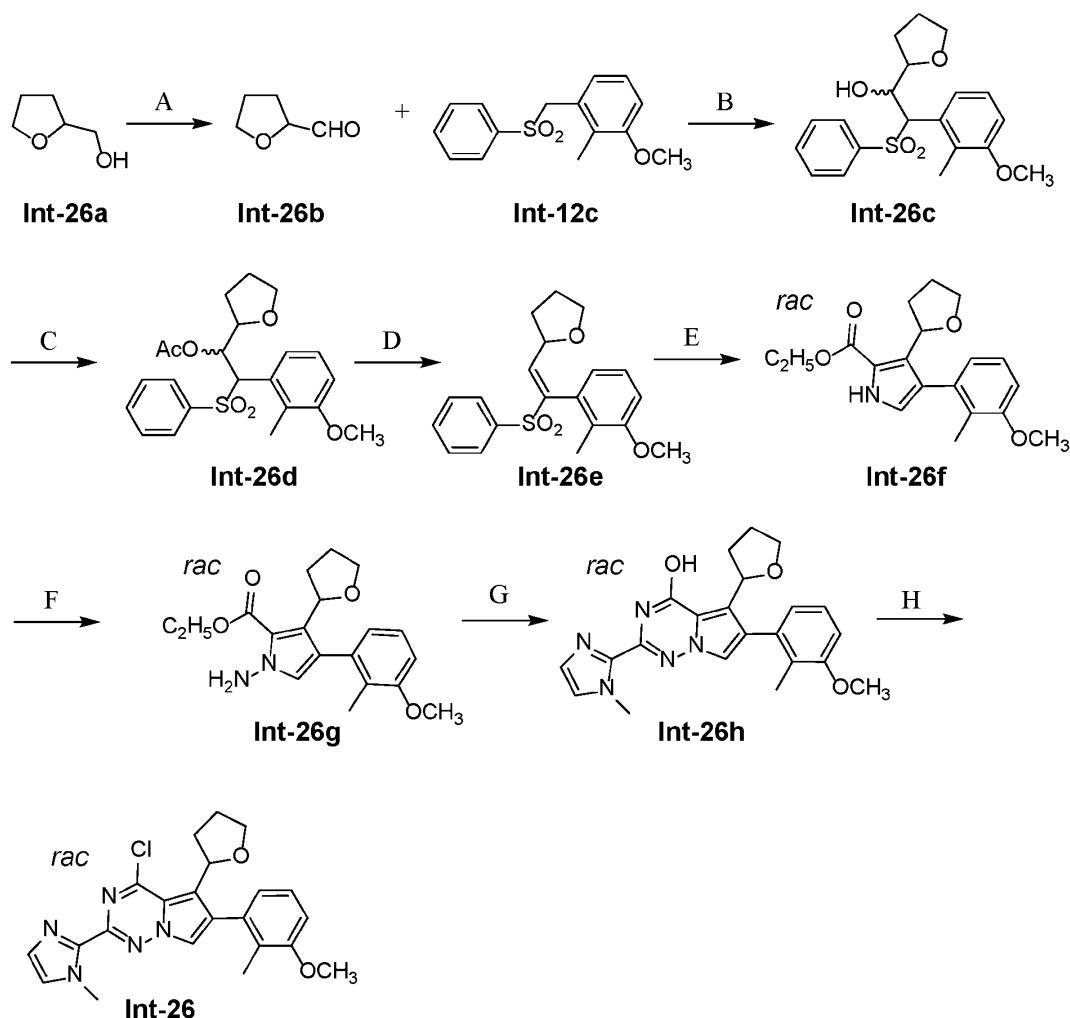
pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-24e** (70.0 mg, 185.52 μ mol, 16.7% yield) was obtained.

[00770] **Step E:** 4-Chloro-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-24**.

[00771] 5-Methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-24e** (349.9 mg, 927.31 μ mol) was dissolved in phosphoryl trichloride (2.81 g, 18.52 mmol, 1.71 mL, 20.0 equiv). The mixture was heated to 100°C and stirred at this temperature for 16 h. The reaction mixture was concentrated *in vacuo*, poured into ice water (5 mL) and neutralized with K₂CO₃. The formed precipitate was collected by filtration, washed with water (2*5 mL), evaporated and used in next step without further purification. 4-Chloro-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-24** (300.0 mg, 88.0% purity, 667.05 μ mol, 71.9% yield) was obtained.

[00772] **Example Int-26: Synthesis of Intermediate Int-26**

[00773] Scheme 26: The Synthesis of **Int-26**



[00774] **Step A:** Tetrahydrofuran-2-carbaldehyde **Int-26b**.

[00775] Dimethyl sulfoxide (14.9 g, 191.0 mmol) was added dropwise to a solution of oxalyl chloride (22.2 g, 176.3 mmol, 14.92 mL, 1.2 equiv) in methylene chloride (225 mL) at -78°C. The mixture was stirred for 15 min, then (tetrahydrofuran-2-yl)methanol **Int-26a** (15.0 g, 146.92 mmol) was added dropwise. After stirring for 15 min, triethylamine (37.14 g, 367.3 mmol) was added over 15 min. The reaction mixture was warmed to room temperature then stirred for 30 min. H₂O (100 mL) was added and the mixture was extracted with methylene chloride (1x80 mL). The combined organic extracts were washed with 1N HCl, brine, dried over MgSO₄ and the solvent evaporated to give tetrahydrofuran-2-carbaldehyde **Int-26b** (2.6 g, 90.0% purity, 23.37

mmol, 15% yield) and was used in the next step without further purification.

[00776] Step B: 2-(3-Methoxy-2-methylphenyl)-2-(phenylsulfonyl)-1-(tetrahydrofuran-2-yl)ethan-1-ol **Int-26c**.

[00777] To 1-methoxy-2-methyl-3-((phenylsulfonyl)methyl)benzene **Int-12c** (prepared as described herein) (7.17 g, 25.95 mmol) in THF (200 mL) was added LiHMDS (1.1 M in THF/ethylbenzene, 26 mL), at -78°C and the mixture was stirred for 1 h. To the resulting mixture was added tetrahydrofuran-2-carbaldehyde **Int-26b** (2.86 g, 28.54 mmol), and followed by tetrachlorotitanium (5.36 g, 28.54 mmol). The mixture was stirred for 1 h at -78°C, and then to ambient temperature overnight. The resulting mixture was poured into saturated aq. NH₄Cl (150 mL) and extracted with ethyl acetate (3*100 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (OK. Interchim, 330 g SiO₂, hexane/ethyl acetate (0-100%), flow rate = 127 ml/min, 11-16,3 CV.) to 2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)-1-(tetrahydrofuran-2-yl)ethan-1-ol **Int-26c** (4.61 g, 60.0% purity, 7.35 mmol, 28% yield).

[00778] Step C: 2-(3-Methoxy-2-methylphenyl)-2-(phenylsulfonyl)-1-(tetrahydrofuran-2-yl)ethyl acetate **Int-26d**.

[00779] Acetic anhydride (475.78 mg, 4.66 mmol) was added dropwise at RT to a stirred solution of 2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)-1-(tetrahydrofuran-2-yl)ethan-1-ol **Int-26c** (1.95 g, 5.18 mmol) in pyridine (40 mL). The mixture was stirred at RT overnight. Then the reaction mixture was concentrated *in vacuo*, diluted with ethyl acetate, washed with 1N HCl (20 mL), water, brine, dried over Na₂SO₄ and concentrated *in vacuo* to give 2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)-1-(tetrahydrofuran-2-yl)ethyl acetate **Int-26d** (2.0 g, 60.0% purity, 2.87 mmol, 92% yield).

[00780] Step D: (*E*)-2-(2-(3-Methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)tetrahydrofuran **Int-26e**.

[00781] Diazabicyclo[5.4.0]undec-7-ene (DBU) (519.18 mg, 3.41 mmol, 510.0 µL, 1.2 equiv) was added dropwise at RT to a stirred solution of 2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)-1-(tetrahydrofuran-2-yl)ethyl acetate **Int-26d** (1.98 g, 4.74 mmol) in methylene chloride (25 mL). The mixture was stirred at 45°C overnight. Then reaction mixture was washed with 1N HCl (20 mL), water, brine, dried over Na₂SO₄ and concentrated *in vacuo* to give (*E*)-2-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)tetrahydrofuran **Int-26e** (1.56 g, 50.0%

purity, 2.18 mmol, 76% yield).

[00782] **Step E:** *rac* Ethyl 4-(3-methoxy-2-methylphenyl)-3-(tetrahydrofuran-2-yl)-1*H*-pyrrole-2-carboxylate **Int-26f**.

[00783] Potassium *t*-butoxide (365.79 mg, 3.27 mmol) was added portionwise to the solution of (*E*)-2-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)tetrahydrofuran **Int-26e** (1.56 g, 4.35 mmol) and ethyl 2-isocyanoacetate (369.11 mg, 3.27 mmol) in dry THF (60 mL) at (-10°C), and stirred at room temperature overnight. Then reaction mixture was diluted with ice water (40 mL) and extracted 3 times with ethyl acetate (3*40 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give *rac* ethyl 4-(3-methoxy-2-methylphenyl)-3-(tetrahydrofuran-2-yl)-1*H*-pyrrole-2-carboxylate **Int-26f** (1.49 g, 45.0% purity, 2.04 mmol, 93% yield) and used for the next step without further purification.

[00784] **Step F:** *rac* Ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(tetrahydrofuran-2-yl)-1*H*-pyrrole-2-carboxylate **Int-26g**.

[00785] Sodium hydride (0.328g, 8.2 mmol) (60% in mineral oil), was added portionwise to a solution of *rac* ethyl 4-(3-methoxy-2-methylphenyl)-3-(tetrahydrofuran-2-yl)-1*H*-pyrrole-2-carboxylate **Int-26f** (1.49 g, 4.52 mmol) in DMF (15 mL) at 0°C. The mixture was stirred for 1 h at room temperature. Then the mixture was cooled to 0°C and *O*-(2,4-dinitrophenyl)hydroxylamine (810.18 mg, 4.07 mmol) was added portionwise. The mixture was stirred for 16 h at room temperature. Then the mixture was poured into ice water and extracted with ethyl acetate (3*30 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give *rac* ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(tetrahydrofuran-2-yl)-1*H*-pyrrole-2-carboxylate **Int-26g** (2.0 g, 30.0% purity, 1.74 mmol, 85% yield) and used for the next step without further purification.

[00786] **Step G:** *rac* 6-(3-Methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(tetrahydrofuran-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-26h**.

[00787] Sodium hydride (1 g, 25 mmol) (60% in mineral oil) was added portionwise to the solution of *rac* ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(tetrahydrofuran-2-yl)-1*H*-pyrrole-2-carboxylate **Int-26g** (2.0 g, 5.81 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (279.6 mg, 2.61 mmol) in dry dioxane (24 mL). Then the reaction mixture was heated to 80°C and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured into ice water, neutralized with acetic acid and extracted with ethyl acetate (3*30 mL).

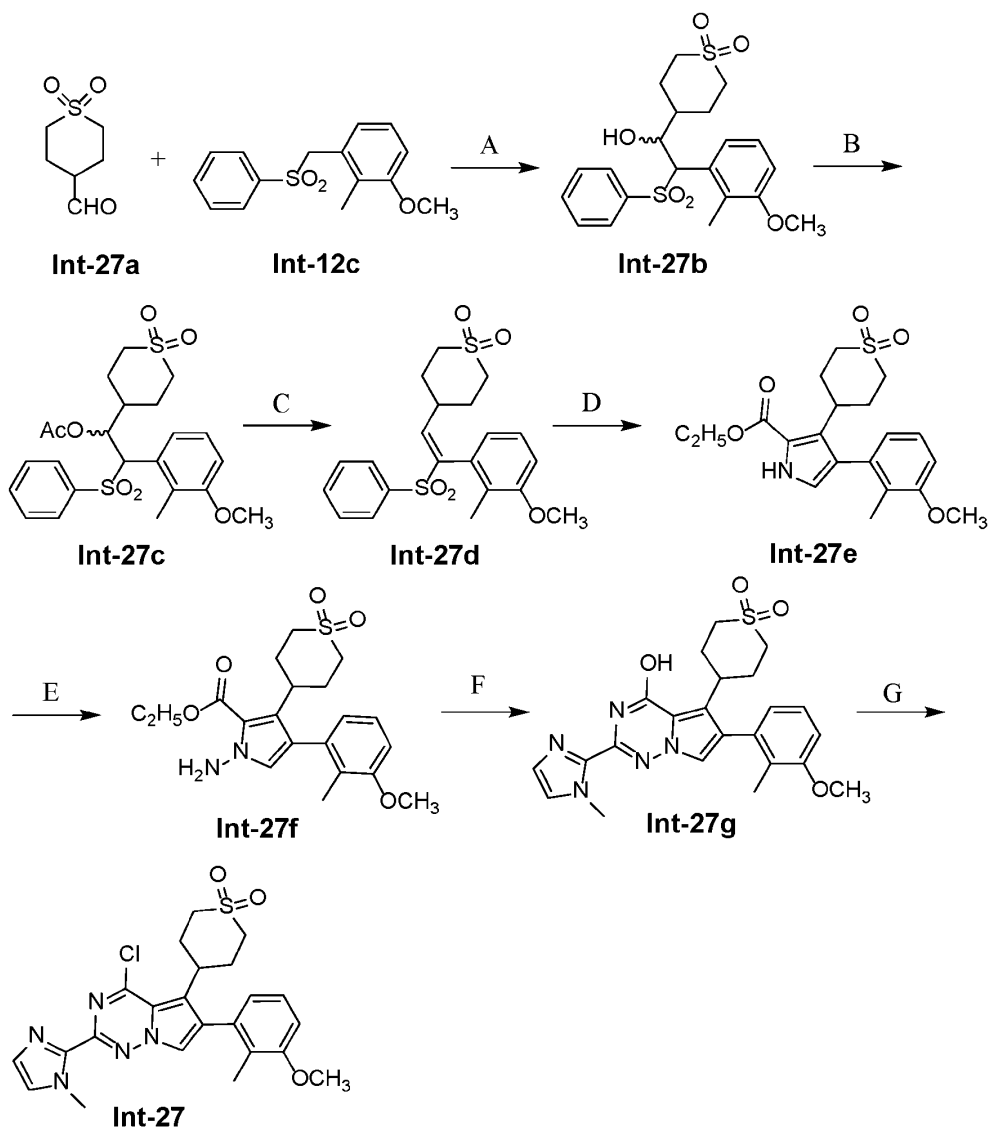
The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (2d Interchim, 40g SiO₂, methyl *t*-butyl ether/methanol with methanol from 0~50%, flow rate =40 mL/min, Rv = 7-8CV;) to give *rac* 6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(tetrahydrofuran-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-26h** (70.0 mg, 95.0% purity, 164.02 μmol, 9% yield).

[00788] Step H: *rac* (*R*)-4-Chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(tetrahydrofuran-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-26**.

[00789] To the solution of *rac* 6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(tetrahydrofuran-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-26h** (70.0 mg, 172.65 μmol) in acetonitrile (1.5 mL), phosphoryl trichloride (1.05 g, 6.91 mmol) was added dropwise. The mixture was heated to 80°C and stirred at this temperature for 16 h and then concentrated *in vacuo*, dissolved in ethyl acetate/acetonitrile 10 mL/10 mL, washed with ice cold aq NaHCO₃, brine, dried over Na₂SO₄, and concentrated *in vacuo*, to give *rac* (*R*)-4-chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(tetrahydrofuran-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-26** (90.0 mg, 67.0% purity, 142.25 μmol, 82% yield).

[00790] Example Int-27: Synthesis of Intermediate Int-27

[00791] Scheme 27: The Synthesis of **Int-27**



[00792] **Step A:** 4-(1-Hydroxy-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethyl)tetrahydro-2H-thiopyran 1,1-dioxide **Int-27b**.

[00793] To 1-methoxy-2-methyl-3-((phenylsulfonyl)methyl)benzene **Int-12c** (prepared as described herein) (6.81 g, 24.64 mmol) in THF (150 mL) was added LiHMDS (1.1 M in THF/ethylbenzene, 25 mL), at -78°C and the mixture was stirred for 1 h. To the resulting mixture was added tetrahydro-2H-thiopyran-4-carbaldehyde 1,1-dioxide **Int-27a** (4.39 g, 27.11 mmol), and followed by tetrachlorotitanium (5.09 g, 27.11 mmol). The mixture was stirred for 1

h at -78°C, and then to ambient temperature overnight. The resulting mixture was poured into saturated aq. NH₄Cl (150 mL) and extracted with ethyl acetate (3*100 mL). The organic phase washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (OK. Interchim, 220 g SiO₂, chloroform/acetonitrile (0-40%), flow rate = 100 mL/min, 9,8-12,5 CV) to 4-(1-hydroxy-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethyl)tetrahydro-2H-thiopyran 1,1-dioxide **Int-27b** (6.0 g, 92.0% purity, 12.59 mmol, 51% yield).

[00794] Step B: 1-(1,1-Dioxidotetrahydro-2H-thiopyran-4-yl)-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethyl acetate **Int-27c**.

[00795] Acetic anhydride (1.93 g, 18.88 mmol) was added dropwise at RT to a stirred solution of 4-(1-hydroxy-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethyl)tetrahydro-2H-thiopyran 1,1-dioxide **Int-27b** (6.0 g, 13.68 mmol) in pyridine (60 mL). The mixture was stirred at RT overnight. Then the reaction mixture was concentrated *in vacuo*, diluted with ethyl acetate, washed with 1N HCl (20 mL), water, brine, dried over Na₂SO₄ and concentrated *in vacuo* to give 1-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethyl acetate **Int-27c** (9.33 g, 60.0% purity, 11.65 mmol, 92% yield).

[00796] Step C: (E)-4-(2-(3-Methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)tetrahydro-2H-thiopyran 1,1-dioxide **Int-27d**.

[00797] Diazabicyclo[5.4.0]undec-7-ene (DBU) (2.13 g, 13.98 mmol) was added dropwise at RT to a stirred solution of 1-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)ethyl acetate **Int-27c** (9.33 g, 19.41 mmol) in methylene chloride (60 mL). The mixture was stirred at 45°C overnight. Then the reaction mixture was washed with 1N HCl (30 mL), water, brine, dried over Na₂SO₄ and concentrated *in vacuo* to give (E)-4-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)tetrahydro-2H-thiopyran 1,1-dioxide **Int-27d** (9.0 g, 50.0% purity, 10.7 mmol, 91% yield).

[00798] Step D: Ethyl 3-(1,1-dioxidotetrahydro-2H-thiopyran-4-yl)-4-(3-methoxy-2-methylphenyl)-1H-pyrrole-2-carboxylate **Int-27e**.

[00799] Potassium *t*-butoxide (1.8 g, 16.05 mmol) was added portion wise to a solution of (E)-4-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)tetrahydro-2H-thiopyran 1,1-dioxide **Int-27d** (9.0 g, 21.4 mmol) and ethyl 2-isocynoacetate (1.81 g, 16.05 mmol) in dry THF (120 mL) at (-10°C), and stirred at room temperature overnight. Then the reaction mixture was diluted with ice water (80 mL) and extracted 3 times with ethyl acetate (3*60 mL). The

organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim, 220 g SiO₂, chloroform/acetonitrile (0-40%), flow rate = 100 mL/min, 9,8-12,5 CV.) to give ethyl 3-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-27e** (250.0 mg, 99.0% purity, 632.21 μmol, 6% yield).

[00800] Step E: Ethyl 1-amino-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-27f**.

[00801] Sodium hydride (0.04g, 1 mmol) (60% in mineral oil), was added portionwise to a solution of ethyl 3-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-27e** (250.0 mg, 638.6 μmol) in DMF (5 mL) at 0°C. The mixture was stirred for 1 h at room temperature. Then the mixture was cooled to 0°C and *O*-(2,4-dinitrophenyl)hydroxylamine (190.95 mg, 959.42 μmol) was added portionwise. The mixture was stirred for 16 h at room temperature. Then the mixture was poured into ice water and extracted with ethyl acetate (3*10 mL). The combined organic phases were washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give ethyl 1-amino-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-27f** (500.0 mg, 50.0% purity, 615.01 μmol, 96% yield) and used for the next step without further purification.

[00802] Step F: 4-(4-Hydroxy-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)tetrahydro-2*H*-thiopyran 1,1-dioxide **Int-27g**.

[00803] Sodium hydride (0.118 g, 2.95 mmol) (60% in mineral oil) was added portion wise to the solution of ethyl 1-amino-3-(1,1-dioxidotetrahydro-2*H*-thiopyran-4-yl)-4-(3-methoxy-2-methylphenyl)-1*H*-pyrrole-2-carboxylate **Int-27f** (500.0 mg, 1.23 mmol) and 1-methyl-1*H*-imidazole-2-carbonitrile (98.91 mg, 923.98 μmol) in dry dioxane (4 mL). Then the reaction mixture was heated to 80°C and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured into ice water, neutralized with acetic acid and extracted with ethyl acetate (3*10 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by HPLC (column: CHROMATOREX C18 100*19mm, 5 μm ((SYSTEM 0-2-8 min 23-30-45% H₂O/ACN/0.1%FA, 30 mL/min (loading pump 4 mL acetonitrile))) to give 4-(4-hydroxy-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)tetrahydro-2*H*-thiopyran 1,1-dioxide **Int-27g** (5.6 mg, 79.0%

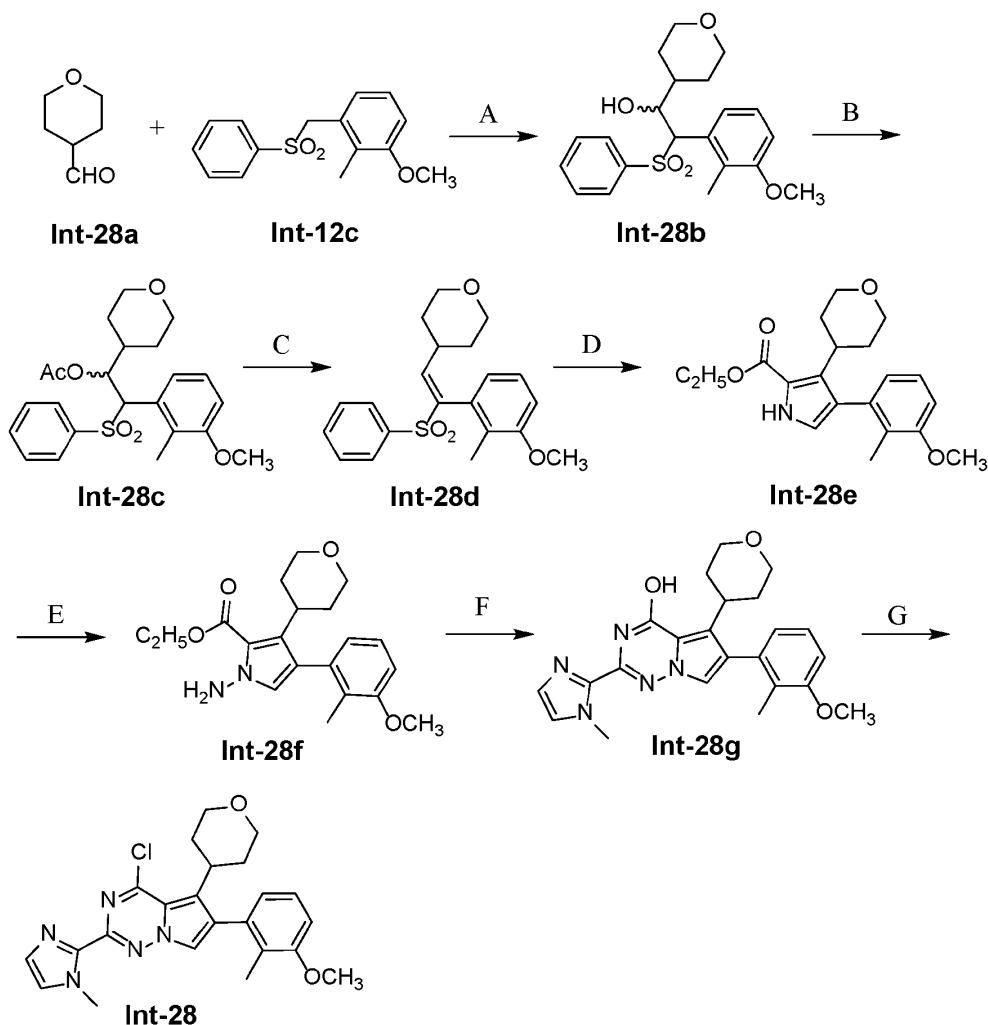
purity, 9.46 μmol , 1.5% yield).

[00804] Step G: 4-(4-Chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)tetrahydro-2*H*-thiopyran 1,1-dioxide **Int-27**.

[00805] To the solution of 4-(4-hydroxy-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)tetrahydro-2*H*-thiopyran 1,1-dioxide **Int-27g** (5.6 mg, 11.98 μmol) in acetonitrile (1.5 mL), phosphoryl trichloride (57.5 mg, 378.61 μmol) was added dropwise. The mixture was heated to 80°C and stirred at this temperature for 16 h and then concentrated *in vacuo*, dissolved in ethyl acetate/acetonitrile 5 mL/5 mL, washed with ice cold NaHCO_3 , brine, dried over Na_2SO_4 , and concentrated *in vacuo* to give 4-(4-chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-5-yl)tetrahydro-2*H*-thiopyran 1,1-dioxide **Int-27** (6.0 mg, 75.0% purity, 9.26 μmol , 97% yield).

[00806] Example Int-28: Synthesis of Intermediate Int-28

[00807] Scheme 28: The Synthesis of **Int-28**



[00808] **Step A:** 2-(3-Methoxy-2-methylphenyl)-2-(phenylsulfonyl)-1-(tetrahydro-2H-pyran-4-yl)ethan-1-ol **Int-28b**.

[00809] To 1-methoxy-2-methyl-3-((phenylsulfonyl)methyl)benzene **Int-12c** (prepared as described herein) (3.57 g, 12.92 mmol) in THF (200 mL) was added LiHMDS (1.1 M in THF/ethylbenzene, 12.9 mL), at -78°C and the mixture was stirred for 1 h. To the resulting mixture was added tetrahydro-2H-pyran-4-carbaldehyde **Int-28a** (1.62 g, 14.21 mmol), then followed by tetrachlorotitanium (2.67 g, 14.21 mmol). The mixture was stirred for 1 h at -78°C, and then to ambient temperature overnight. The resulting mixture was poured into saturated aq NH₄Cl (150 mL) and extracted with ethyl acetate (3*100 mL). The combined organic phases

were washed with water, brine, dried over Na₂SO₄ and concentrated *in vacuo* to give 2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-yl)ethan-1-ol **Int-28b** (5.6 g, 70.0% purity, 10.04 mmol, 77% yield).

[00810] Step B: 2-(3-Methoxy-2-methylphenyl)-2-(phenylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-yl)ethyl acetate **Int-28c**.

[00811] Acetic anhydride (2.19 g, 21.51 mmol) was added dropwise at RT to a stirred solution of 2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-yl)ethan-1-ol **Int-28b** (4.0 g, 10.24 mmol) in pyridine (40 mL). The mixture was stirred at RT overnight. Then the reaction mixture was concentrated *in vacuo*, diluted with ethyl acetate, washed with 1N HCl (20 mL), water, brine, dried over Na₂SO₄ and concentrated *in vacuo* to give 2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-yl)ethyl acetate **Int-28c** (4.52 g, 65.0% purity, 6.79 mmol, 94% yield).

[00812] Step C: (*E*)-4-(2-(3-Methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)tetrahydro-2*H*-pyran **Int-28d**.

[00813] Diazabicyclo[5.4.0]undec-7-ene (DBU) (1.23 g, 8.12 mmol) was added dropwise at RT to a stirred solution of 2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)-1-(tetrahydro-2*H*-pyran-4-yl)ethyl acetate **Int-28c** (4.5 g, 10.4 mmol) in methylene chloride (25 mL). The mixture was stirred at 45°C overnight. Then the reaction mixture was washed with 1N HCl (20 mL), water, brine, dried over Na₂SO₄ and concentrated *in vacuo* to give (*E*)-4-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)tetrahydro-2*H*-pyran **Int-28d** (2.87 g, 70.0% purity, 5.39 mmol, 79% yield).

[00814] Step D: Ethyl 4-(3-methoxy-2-methylphenyl)-3-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrrole-2-carboxylate **Int-28e**.

[00815] Potassium *t*-butoxide (1.21 g, 10.79 mmol) was added portionwise to the solution of (*E*)-4-(2-(3-methoxy-2-methylphenyl)-2-(phenylsulfonyl)vinyl)tetrahydro-2*H*-pyran **Int-28d** (2.87 g, 7.71 mmol) and ethyl 2-isocyanoacetate (1.22 g, 10.79 mmol) in dry THF (60 mL) at (-10°C), and stirred at room temperature overnight. Then the reaction mixture was diluted with ice water (40 mL) and extracted 3 times with ethyl acetate (3*40 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim, 80 g SiO₂, hexane/methyl *t*-butyl ether (0-50%), flow rate = 65 mL/min, 9-10 CV.) to give ethyl 4-(3-methoxy-2-methylphenyl)-3-(tetrahydro-2*H*-pyran-4-yl)-1*H*-pyrrole-2-

carboxylate **Int-28e** (1.3 g, 80.0% purity, 3.03 mmol, 56% yield).

[00816] Step E: Ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrrole-2-carboxylate **Int-28f**.

[00817] Sodium hydride (0.328g, 8.2 mmol) (60% in mineral oil), was added portionwise to a solution of ethyl 4-(3-methoxy-2-methylphenyl)-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrrole-2-carboxylate **Int-28e** (1.3 g, 3.79 mmol) in DMF (15 mL) at 0°C. The mixture was stirred for 1 h at room temperature. Then the mixture was cooled to 0°C and *O*-(2,4-dinitrophenyl)hydroxylamine (1.2 g, 6.05 mmol) was added portionwise. The mixture was stirred for 16 h at room temperature. Then the mixture was poured into ice water and extracted with ethyl acetate (3*30 mL). The combined organic phases were washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrrole-2-carboxylate **Int-28f** (2.0 g, 50.0% purity, 2.79 mmol, 92% yield) and used for the next step without further purification.

[00818] Step F: 6-(3-Methoxy-2-methylphenyl)-2-(1-methyl-1H-imidazol-2-yl)-5-(tetrahydro-2H-pyran-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-28g**.

[00819] Sodium hydride (0.44 g, 11 mmol) (60% in mineral oil) was added portionwise to a solution of ethyl 1-amino-4-(3-methoxy-2-methylphenyl)-3-(tetrahydro-2H-pyran-4-yl)-1H-pyrrole-2-carboxylate **Int-28f** (2.0 g, 5.58 mmol) and 1-methyl-1H-imidazole-2-carbonitrile (597.16 mg, 5.58 mmol) in dry dioxane (24 mL). Then the reaction mixture was heated to 80°C and stirred at this temperature for 16 h. Then the mixture was cooled to room temperature, poured into ice water, neutralized with acetic acid and extracted with ethyl acetate (3*30 mL). The combined organic phases were washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim; 80 g SiO₂, methyl *t*-butyl ether/methanol with methanol from 0~10%, flow rate =65 mL/min, R_v = 5,3-6,3 CV) to give 6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1H-imidazol-2-yl)-5-(tetrahydro-2H-pyran-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-28g** (610.0 mg, 95.0% purity, 1.38 mmol, 49% yield).

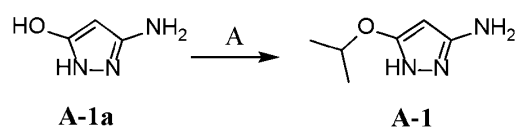
[00820] Step G: 4-Chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1H-imidazol-2-yl)-5-(tetrahydro-2H-pyran-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-28**.

[00821] To a solution of give 6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1H-imidazol-2-yl)-5-(tetrahydro-2H-pyran-4-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-ol **Int-28g** (610.17 mg, 1.45 mmol) in acetonitrile (10 mL), phosphoryl trichloride (8.84 g, 58.18 mmol, 5.37 mL, 40.0 equiv) was

added dropwise. The mixture was heated to 80°C and stirred at this temperature for 16 h and then concentrated *in vacuo*, dissolved in ethyl acetate/acetonitrile 30 mL/30 mL, washed with ice cold NaHCO₃, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give 4-chloro-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(tetrahydro-2*H*-pyran-4-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-28** (500.0 mg, 80.0% purity, 913.4 μmol, 62% yield).

[00822] Example A1: Synthesis of Amine A-1

[00823] Scheme 29: The Synthesis of Amine A-1.

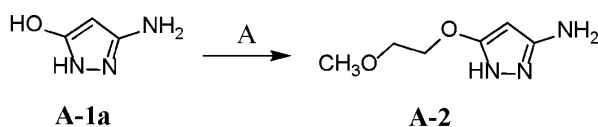


[00824] Step A 5-Isopropoxy-1*H*-pyrazol-3-amine **A-1**.

[00825] Diisopropyl azodicarboxylate (6.67 g, 33.02 mmol) was added portion wise to a solution of triphenylphosphine (8.65 g, 33.02 mmol) in CH₂Cl₂ (110 mL) at 0-5 °C and stirred at this temperature over 20 min. After this time, 3-amino-1*H*-pyrazol-5-ol **A-1a** (3.0 g, 30.29 mmol) and propan-2-ol (1.98 g, 33.02 mmol) in dry CH₂Cl₂ (20 mL) was added dropwise and the mixture was left to stirred overnight. The resulting mixture was evaporated to dryness and purified by FCC (column Interchim; 33 0g SiO₂, chloroform/acetonitrile (0-100%), further acetonitrile/methanol (0-100%) flow rate = 127 mL/min, RV = 10,6-13,3 CV) to give 5-isopropoxy-1*H*-pyrazol-3-amine **A-1** (250.0 mg, 90.0% purity, 1.59 mmol, 5.3% yield) as white solid.

[00826] Example A2: Synthesis of Amine A-2

[00827] Scheme 30: The Synthesis of Amine A-2.



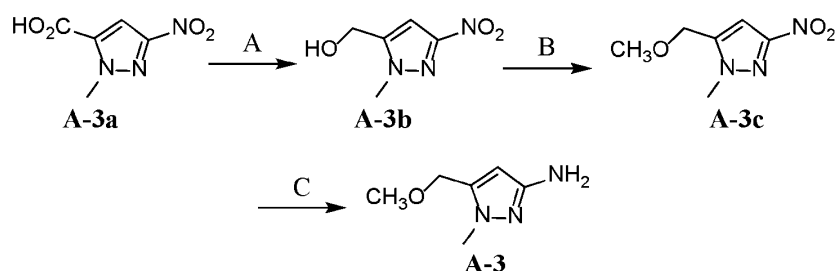
[00828] Step A: 5-(2-Methoxyethoxy)-1*H*-pyrazol-3-amine **A-2**.

[00829] Diisopropyl azodicarboxylate (6.67 g, 33.02 mmol) was added portion wise to a solution of triphenylphosphine (8.65 g, 33.02 mmol) in CH₂Cl₂ (110 mL) at 0-5 °C and stirred at this temperature over 20 min. After this time 3-amino-1*H*-pyrazol-5-ol **A-1a** (3.0 g, 30.29 mmol) and 2-methoxyethan-1-ol (2.51 g, 33.02 mmol) in dry CH₂Cl₂ (20 mL) was added dropwise and the mixture was left to stir overnight. The resulting mixture was evaporated to dryness and

purified by FCC (column Interchim, 330 g SiO₂, acetonitrile/methanol with methanol from 0~10%, flow rate = 135 mL/min, Rv = 5-6 CV) to give 5-(2-methoxyethoxy)-1*H*-pyrazol-3-amine **A-2** (150.0 mg, 95.0% purity, 906.66 μmol, 3% yield) as a yellow solid.

[00830] Example A3: Synthesis of Amine A-3

[00831] Scheme 31: The Synthesis of Amine **A-3**.



[00832] Step A: (1-Methyl-3-nitro-1*H*-pyrazol-5-yl)methanol **A-3b**.

[00833] Borane dimethyl sulfide complex ((CH₃)₂S BH₃) (1.33 g, 17.55 mmol) was added dropwise to a stirred solution of 1-methyl-3-nitro-1*H*-pyrazole-5-carboxylic acid **A-3a** (1.0 g, 5.85 mmol) in THF (30 mL) at 20-60°C. The mixture was stirred at 62°C overnight and then cooled to room temperature and carefully quenched by methanol (10 mL). Then the reaction mixture was concentrated *in vacuo*, and evaporated with methanol 2 times (20 mL). The residue was dissolved in methylene chloride (30 mL), washed with water, brine, dried over sodium sulfate and concentrated *in vacuo* to give (1-methyl-3-nitro-1*H*-pyrazol-5-yl)methanol **A-3b** (1.0 g, 90.0% purity, 5.73 mmol, 97% yield).

[00834] Step B: 5-(Methoxymethyl)-1-methyl-3-nitro-1*H*-pyrazole **A-3c**.

[00835] Sodium hydride (0.38g, 9.5 mmol)(60% on mineral oil), was added portion wise to a solution of (1-methyl-3-nitro-1*H*-pyrazol-5-yl)methanol **A-3b** (1.0 g, 6.37 mmol) in THF (10 mL) at 0°C. The mixture was stirred for 10 min. Then iodomethane (1.23 g, 8.65 mmol) was added in one portion at 0°C. The mixture was stirred for 16 h at room temperature. Afterwards the mixture was poured in ice water (25 mL), extracted with ethyl acetate (3*15 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated *in vacuo* to give 5-(methoxymethyl)-1-methyl-3-nitro-1*H*-pyrazole **A-3c** (1.0 g, 90.0% purity, 5.26 mmol, 91% yield).

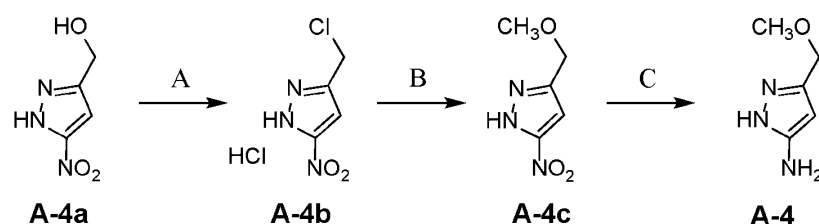
[00836] Step C: 5-(Methoxymethyl)-1-methyl-1*H*-pyrazol-3-amine **A-3**.

[00837] A 150-mL single-neck round-bottomed flask equipped with a magnetic stirrer was

charged with Pd/C (0.1 g) and methanol (50 mL). The mixture was hydrogenated (1 atm) at room temperature for 15 h. It was then filtered and the filtrate was concentrated under reduced pressure to afford 5-(methoxymethyl)-1-methyl-1*H*-pyrazol-3-amine **A-3** (750.0 mg, 90.0% purity, 4.78 mmol, 90% yield), which was used in the next step without further purification.

[00838] Example A4: Synthesis of Amine A-4

[00839] Scheme 32: The Synthesis of Amine A-4



[00840] Step A: 3-(Chloromethyl)-5-nitro-1*H*-pyrazole hydrochloride salt **A-4b.**

[00841] To a solution of (5-nitro-1*H*-pyrazol-3-yl)methanol **A-4a** (8.7 g, 60.83 mmol) in dichloromethane (130 mL), sulfuryl dichloride (71.72 g, 608.31 mmol, 43.73 mL, 10.0 equiv) was added dropwise at 0°C and stirred overnight. After this the reaction mixture was evaporated to dryness and reevaporated with dichloromethane (2x100 mL) to give 3-(chloromethyl)-5-nitro-1*H*-pyrazole hydrochloride salt **A-4b** (11.5 g, 30.0% purity, 17.42 mmol, 28% yield) which was used without further purification.

[00842] Step B: 3-(Methoxymethyl)-5-nitro-1*H*-pyrazole **A-4c.**

[00843] To a mixture of 3-(chloromethyl)-5-nitro-1*H*-pyrazole hydrochloride salt **A-4b** (11.5 g, 40.0% purity, 23.23 mmol) in methanol (240 mL) NaHCO₃ (70 mL 30% aq. solution) was added dropwise at +10°C and stirred over 1 h. Afterwards the resulting mixture was extracted with ethyl acetate (3*200 mL). The organic phase was washed with water, brine, dried over Na₂SO₄, concentrated *in vacuo* and purified by FCC (Interchim, 120 g SiO₂, chloroform/acetonitrile (0-20%), flow rate = 80 mL/min, 7,2-9,7 CV.) to give 3-(methoxymethyl)-5-nitro-1*H*-pyrazole **A-4c** (3.5 g, 95.0% purity, 21.16 mmol, 91% yield).

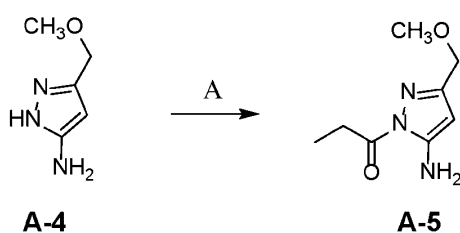
[00844] Step C: 3-(Methoxymethyl)-1*H*-pyrazol-5-amine **A-4.**

[00845] A 150-mL single-neck round-bottomed flask equipped with a magnetic stirrer was charged with 3-(methoxymethyl)-5-nitro-1*H*-pyrazole **A-4c** (2.8 g, 17.83 mmol), Pd/C (0.28 g) and methanol (60 mL). The mixture was hydrogenated (1atm) at room temperature for 15 h. The reaction mixture was then filtered, and the filtrate was concentrated under reduced pressure to

afford : 3-(methoxymethyl)-1*H*-pyrazol-5-amine **A-4** (2.1 g, 90.0% purity, 14.86 mmol, 83% yield), which was used without further purification.

[00846] Example A5: Synthesis of Amine A-5

[00847] Scheme 33: The Synthesis of Amine **A-5**

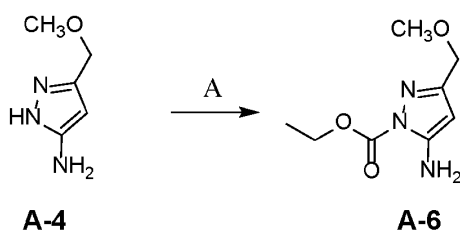


[00848] Step A: 1-(5-amino-3-(methoxymethyl)-1*H*-pyrazol-1-yl)propan-1-one **A-5**.

[00849] To a solution of compound 3-(methoxymethyl)-1*H*-pyrazol-5-amine **A-4** (prepared as described herein) (450.0 mg, 3.54 mmol) in dichloromethane (15 mL) was added *N,N*-dimethylpyridin-4-amine (21.62 mg, 177.12 μ mol) and triethylamine (429.85 mg, 4.25 mmol) at room temperature. The reaction mixture was cooled to 0° and propanoyl propanoate (460.74 mg, 3.54 mmol) was added dropwise and left to stir overnight at RT. Afterwards the resulting solution was washed with H₂O, brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure and purified by FCC (Interchim; 40 g SiO₂, hexane/methyl *t*-butyl ether with methyl *t*-butyl ether from 0~30%, flow rate =40 mL/min, R_v = 12-15 CV) to give 1-(5-amino-3-(methoxymethyl)-1*H*-pyrazol-1-yl)propan-1-one **A-5** (200.0 mg, 95.0% purity, 1.04 mmol, 29% yield).

[00850] Example A6: Synthesis of Amine A-6

[00851] Scheme 34: The Synthesis of Amine **A-6**



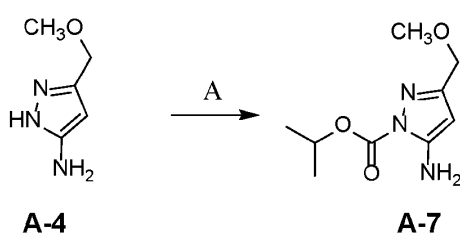
[00852] Step A: Ethyl 5-amino-3-(methoxymethyl)-1*H*-pyrazole-1-carboxylate **A-6**.

[00853] To a solution of compound 3-(methoxymethyl)-1*H*-pyrazol-5-amine **A-4** (prepared as described herein) (801.2 mg, 6.3 mmol) in THF (15 mL) was added diisopropyl ethyl amine

(895.73 mg, 6.94 mmol) at room temperature. The reaction mixture was cooled to 0° and ethyl chloroformate (681.0 mg, 6.31 mmol, 600.0 μ l, 1.0 equiv) was added dropwise and left to stir overnight at RT. Afterwards the resulting solution was filtered, concentrated under reduced pressure and purified by FCC (Interchim; 40 g SiO₂, chloroform/acetonitrile with acetonitrile from 0~15%, flow rate =40 mL/min, Rv = 8-11 CV) to give ethyl 5-amino-3-(methoxymethyl)-1*H*-pyrazole-1-carboxylate **A-6** (300.0 mg, 95.0% purity, 1.43 mmol, 22% yield).

[00854] Example A7: Synthesis of Amine A-7

[00855] Scheme 35: The Synthesis of Amine A-7



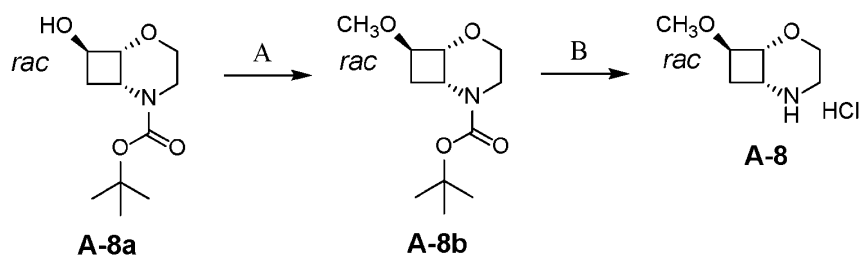
[00856] Step A: isopropyl 5-amino-3-(methoxymethyl)-1*H*-pyrazole-1-carboxylate **A-7**.

[00857] Method 2 was implemented with 3-(methoxymethyl)-1*H*-pyrazol-5-amine (150.0 mg, 1.18 mmol), propan-2-yl chloroformate (144.2 mg, 1.18 mmol), ethylbis(propan-2-yl)amine (183.16 mg, 1.42 mmol) in THF (15 mL). Purified by FCC (Interchim; 12g SiO₂, chloroform/acetonitrile with acetonitrile from 0~20%, flow rate =15 mL/min, Rv = 9,3-11CV) to give propan-2-yl 5-amino-3-(methoxymethyl)-1*H*-pyrazole-1-carboxylate.

[00858] Yield: 130.0 mg, 95.0% purity, 579.18 μ mol, 49% yield.

[00859] Example A8: Synthesis of Amine A-8

[00860] Scheme 36: The Synthesis of Amine A-8



[00861] Step A: *rac tert*-butyl (1*R*,6*R*,8*R*)-8-methoxy-2-oxa-5-azabicyclo[4.2.0]octane-5-carboxylate **A-8b**.

[00862] To the suspension of sodium hydride (0.052g (60% in mineral oil)) in THF, *rac tert*-

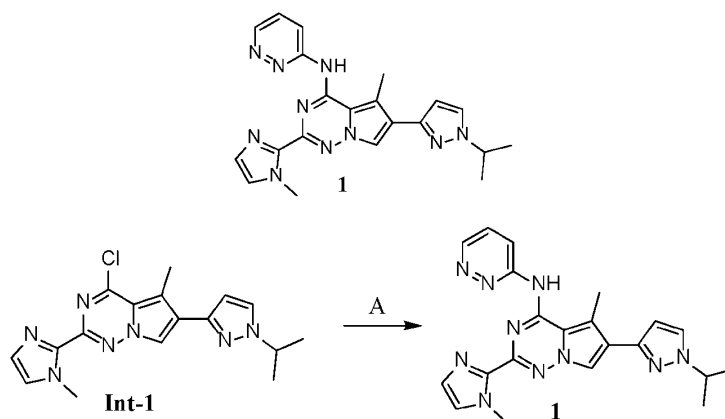
butyl (1*R*,6*R*,8*R*)-8-hydroxy-2-oxa-5-azabicyclo[4.2.0]octane-5-carboxylate **A-8a** (200.0 mg, 872.86 μ mol) was added at RT, and after 15 min iodomethane (191.69 mg, 1.35 mmol) was added and the reaction mixture was left to stir overnight. Then the mixture was poured into ice cold NH_4Cl solution and extracted with ethyl acetate (3*20 mL). The combined organic phases were washed with water, brine, dried over Na_2SO_4 , and concentrated *in vacuo* to give *rac tert*-butyl (1*R*,6*R*,8*R*)-8-methoxy-2-oxa-5-azabicyclo[4.2.0]octane-5-carboxylate **A-8b** (200.0 mg, 95.0% purity, 780.93 μ mol, 89% yield).

[00863] Step B: *rac* (1*R*,6*R*,8*R*)-8-methoxy-2-oxa-5-azabicyclo[4.2.0]octane hydrochloride salt **A-8**.

[00864] To a stirred solution of *rac tert*-butyl (1*R*,6*R*,8*R*)-8-methoxy-2-oxa-5-azabicyclo[4.2.0]octane-5-carboxylate **A-8b** (200.0 mg, 822.03 μ mol) in dioxane (5 mL) was added dioxane*HCl 6N (5 mL) and the solution was stirred at room temperature for 3 h. The solvent was removed under reduced pressure to give *rac* (1*R*,6*R*,8*R*)-8-methoxy-2-oxa-5-azabicyclo[4.2.0]octane hydrochloride salt **A-8** (110.0 mg, 90.0% purity, 551.09 μ mol, 66.9% yield) and used for the next step without further purification.

[00865] **Example 1: Synthesis of Compound 1**

[00866] Scheme 37: The Synthesis of **Compound 1**.



[00867] Representative Procedure for Method 1 Amination

[00868] **Step A:** 6-(1-Isopropyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-*N*-(pyridazin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine **1**.

[00869] Sodium hydride (24.63 mg, 1.03 mmol) (60% in mineral oil) was added portion-wise to the solution of pyridazin-3-amine (53.23 mg, 560.08 μ mol) in DMF (2 mL). The mixture was

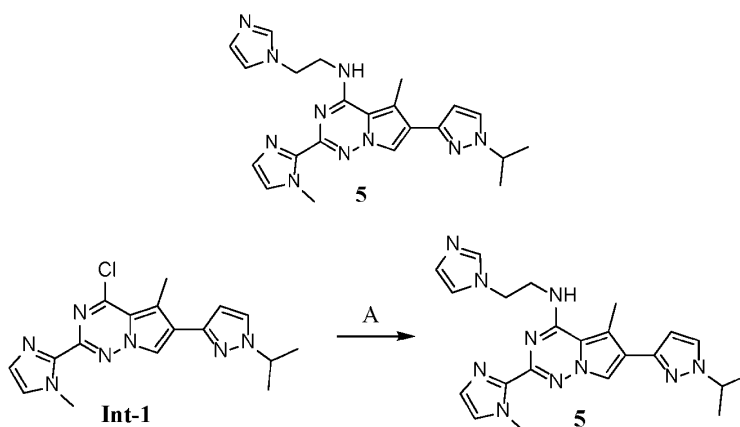
stirred for 30 min at room temperature, then 4-chloro-6-(1-isopropyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-1** (100.0 mg, 281.59 μ mol) was added in one portion. The mixture was stirred at room temperature for 16 h. The mixture was quenched by concentrated aq. NH_4Cl and purified by HPLC (2-10 min 30-70% water-MeOH+HCl; flow 30 mL/min ((loading pump 4 mL MeOH+HCl); column: YMC-ACTUS TRIART C18 100*20 5 μm). 6-(1-Isopropyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-*N*-(pyridazin-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine **1**. Yield and analytical data are shown in Table A.

[00870] Example 2 – Example 4: Synthesis of Compound 2 – Compound 4

[00871] Compound 2 – Compound 4 in Table A were prepared using the Representative Procedure for Method 1 Amination (as detailed in Example 1).

[00872] Example 5: Synthesis of Compound 5

[00873] Scheme 38: The Synthesis of **Compound 5**.



[00874] Representative Procedure for Method 2 Amination

[00875] Step A: *N*-(2-(1*H*-Imidazol-1-yl)ethyl)-6-(1-isopropyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine **5**.

[00876] 2-(1*H*-Imidazol-1-yl)ethan-1-amine (61.44 mg, 553.16 μ mol) was added in one portion to the solution of 4-chloro-6-(1-isopropyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-1** (98.36 mg, 276.96 μ mol) and diisopropylethylamine (178.08 mg, 1.38 mmol, 240.0 μL , 5.0 equiv) in DMF (1 mL). The mixture was heated to 100°C and stirred at this temperature for 16 h. The mixture was purified by HPLC (SunFire C18 column, 2-10 min 45-65% water-MeOH+ NH_4OH , flow 30 mL/min). *N*-

(2-(1*H*-Imidazol-1-yl)ethyl)-6-(1-isopropyl-1*H*-pyrazol-3-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine **5** was obtained. Yield and analytical data are shown in Table A.

[00877] Example 5 – Example 29: Synthesis of Compound 5 – Compound 29

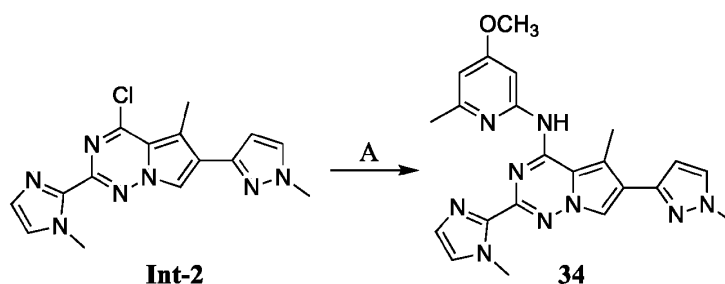
[00878] Table A provides the structures, final step conditions, yield, and analytical data, for the preparation of Compound 5 – Compound 29.

[00879] Example 30 – Example 33: Compound 30 – Compound 33

[00880] Table B provides the structures of of Compound 30 – Compound 33 which can be prepared according to the procedures described herein.

[00881] Example 34: Synthesis of Compound 34

[00882] Scheme 39: The Synthesis of Compound 34.



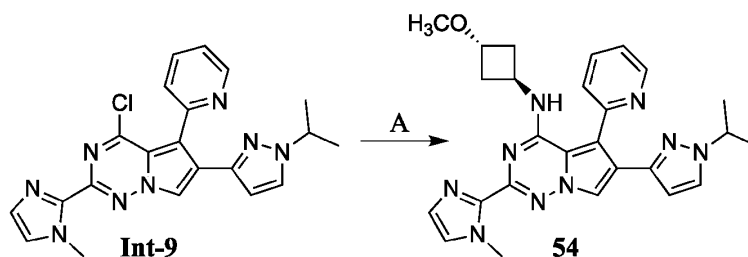
[00883] Representative Procedure for Method 3 Amination

[00884] Step A: *N*-(4-Methoxy-6-methylpyridin-2-yl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine **34**.

[00885] Sodium hydride (26.84 mg, 60.0% purity, 671.05 μ mol) was added in one portion to the solution of 4-methoxy-6-methylpyridin-2-amine (84.23 mg, 610.04 μ mol) in DMF (1ml). The mixture was stirred at ambient temperature for 0.5h. 2-[4-Chloro-5-methyl-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-2-yl]-1-methyl-1*H*-imidazole (100.0 mg, 305.72 μ mol) in DMF was added in one portion and stirred 16h. The mixture was quenched with conc. NH_4Cl and purified by HPLC. 4-Methoxy-6-methyl-*N*-[5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl]pyridin-2-amine (23.0 mg, 95.0% purity, 50.88 μ mol, 16.7% yield) was obtained.

[00886] Example 35 – Example 53: Compound 35 – Compound 53

[00887] Table B provides the structures of of Compound 35 – Compound 53 which can be prepared according to the procedures described herein.

[00888] **Example 54: Synthesis of Compound 54**[00889] Scheme 40: The Synthesis of **Compound 54**.

[00890] Representative Procedure for Method 4 Amination

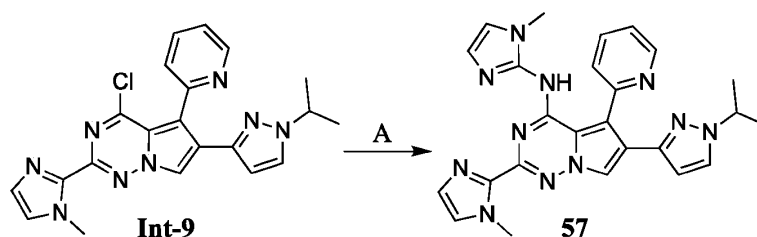
[00891] **Step A:** 6-(1-Isopropyl-1*H*-pyrazol-3-yl)-*N*-((1*r*,3*r*)-3-methoxycyclobutyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine **54**.

[00892] Diisopropyl ethyl amine (26.98 mg, 208.86 μ mol) was added in one portion to the solution of 4-chloro-6-(1-isopropyl-1*H*-pyrazol-3-yl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-9** (prepared as described herein) (35.0 mg, 83.56 μ mol) and *rac* (1*r*,3*r*)-3-methoxycyclobutan-1-amine hydrochloride salt (13.74 mg, 100.25 μ mol) in acetonitrile (5 mL) at RT. The mixture was heated to 80°C and stirred at this temperature for 3 h. It was then diluted with water and extracted with ethyl acetate (3x25 mL). The organic phases were combined, washed with H₂O, brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure and purified by HPLC (SYSTEM 23-30-50% 0-2-7 min H₂O/acetonitrile/0.1NH₄OH flow 30 ml/min ((loading pump 4 ml ACN) column: XBridge BEH C18 100*19 mm,5 microM))) to give 6-(1-isopropyl-1*H*-pyrazol-3-yl)-*N*-((1*r*,3*r*)-3-methoxycyclobutyl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine **54** (31.5 mg, 65.14 μ mol, 78% yield).

[00893] **Example 55 – Example 56: Compound 55 – Compound 56**

[00894] Table B provides the structures of of Compound 55 – Compound 56 which can be prepared according to the procedures described herein.

[00895] **Example 57: Synthesis of Compound 57**[00896] Scheme 41: The Synthesis of **Compound 57**.



[00897] Representative Procedure for Method 5 Amination

[00898] **Step A:** 6-(1-Isopropyl-1*H*-pyrazol-3-yl)-*N*,2-bis(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine **57**.

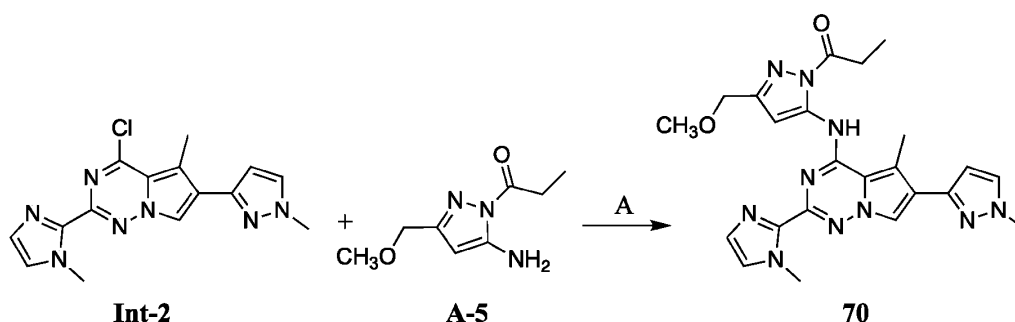
[00899] Sodium hydride (14mg, 0.35 mmol) (60% in mineral oil) was added in portionwise to the solution of 1-methyl-1*H*-imidazol-2-amine (27.69 mg, 285.27 μ mol) in DMF (1.5 mL). The mixture was stirred at room temperature for 30 min, then 4-chloro-6-(1-isopropyl-1*H*-pyrazol-3-yl)-2-(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-9** (100.0 mg, 238.73 μ mol) was added in one portion and stirred at 40°C overnight. After this time the resulting mixture was quenched with methanol, concentrated *in vacuo* and purified by HPLC (SYSTEM 33-40-75% 0-2-9 min H₂O/CAN/0.1NH₄OH, flow 30 mL/min ((loading pump 4 mL CAN) column: Xbridge BEH C18 100*19 mm,5 microM))) to give 6-(1-isopropyl-1*H*-pyrazol-3-yl)-*N*,2-bis(1-methyl-1*H*-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine **57** (35.3 mg, 95.0% purity, 69.93 μ mol, 29% yield).

[00900] **Example 58 – Example 69: Compound 58 – Compound 69**

[00901] Table B provides the structures of of Compound 58 – Compound 69 which can be prepared according to the procedures described herein.

[00902] **Example 70: Synthesis of Compound 70**

[00903] Scheme 42: The Synthesis of **Compound 70**.



[00904] Representative Procedure for Method 6 Amination

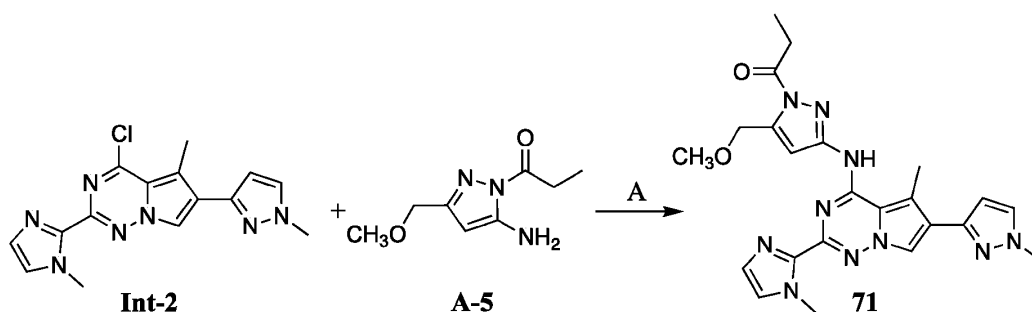
[00905] Step A: 1-(3-(Methoxymethyl)-5-((5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)-1*H*-pyrazol-1-yl)propan-1-one **70**.

[00906] Sodium hydride (13mg, (60% in mineral oil) was added in portionwise to the solution of 1-(5-amino-3-(methoxymethyl)-1*H*-pyrazol-1-yl)propan-1-one **A-5** (prepared as described herein) (47.33 mg, 258.35 μ mol) in DMF (1.5 mL). The mixture was stirred at room temperature for 30 min, then 4-chloro-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-2** (prepared as described herein) (65.0 mg, 198.72 μ mol) was added in one portion, and stirred at RT overnight. After this time resulting mixture was diluted with water and extracted with ethyl acetate (3x15 mL). The organic phases were combined, washed with H₂O, brine, dried over anhydrous sodium sulfate, and concentrated under reduced pressure and purified by HPLC (SYSTEM 13-20-65% 0-2-9 min H₂O/acetonitrile/0.1 NH₄HCO₃, flow 30 mL/min ((loading pump 4 mL acetonitrile) column: Chromatorex C18 SMB100-5T 100*19 mm, 5 microM))) to give 1-(3-(methoxymethyl)-5-((5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)-1*H*-pyrazol-1-yl)propan-1-one **70** (7.6 mg, 95.0% purity, 15.22 μ mol, 7% yield).

[00907] ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm) 11.40 (s, 1H), 8.55 (s, 1H), 7.77 (t, *J* = 2.0 Hz, 1H), 7.40 (s, 1H), 7.09 (s, 1H), 6.78 (d, *J* = 1.6 Hz, 1H), 6.66 (d, *J* = 1.9 Hz, 1H), 4.44 (d, *J* = 1.6 Hz, 2H), 4.03 (d, *J* = 1.6 Hz, 3H), 3.90 (d, *J* = 1.5 Hz, 3H), 3.30 (s, 3H), 2.55 (s, 3H), 2.46 – 2.40 (m, 2H), 1.10 – 1.03 (m, 3H). LCMS(ESI): [M+H]⁺ *m/z*: calc 474.2; found 475.2; Rt = 0.836 min.

[00908] Example 71: Synthesis of Compound 71

[00909] Scheme 43: The Synthesis of Compound 71.



[00910] Acyl migration in final product **71** relative to amine **A-5**.

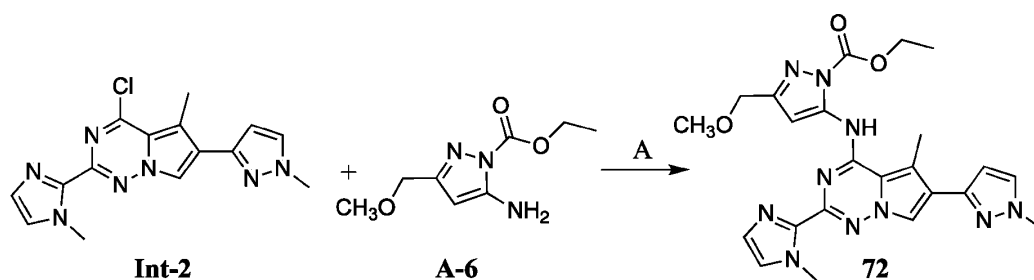
[00911] Step A: 1-(5-(Methoxymethyl)-3-((5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)-1*H*-pyrazol-1-yl)propan-1-one **71**.

[00912] The procedure described for the synthesis of Compound **70** in Example 70 was implemented with sodium hydride (83 mg, (60% in mineral oil), 1-(5-amino-3-(methoxymethyl)-1*H*-pyrazol-1-yl)propan-1-one **A-5** (prepared as described herein) (320.0 mg, 80.0% purity, and 1.4 mmol), 4-chloro-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-2** (prepared as described herein) (457.03 mg, 1.4 mmol) in DMF (10 mL). The product was purified by HPLC (SYSTEM15-30% 0-2-7 min H₂O/acetonitrile/0.1 NaHCO₃ flow 30 mL/min ((loading pump 4 mL acetonitrile) column: XBridge BEH C18 100*19 mm, 5 microM). After HPLC isomerization has been observed to give 1-(5-(methoxymethyl)-3-((5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)-1*H*-pyrazol-1-yl)propan-1-one **71** (456.1 mg, 95.0% purity, 65% yield).

[00913] ¹H NMR (500 MHz, DMSO-*d*₆) δ (ppm) 10.68 (s, 1H), 8.55 (s, 1H), 7.78 (d, *J* = 2.3 Hz, 1H), 7.38 (d, *J* = 1.1 Hz, 1H), 7.08 (d, *J* = 1.0 Hz, 1H), 6.96 (s, 1H), 6.65 (d, *J* = 2.2 Hz, 1H), 4.81 (s, 2H), 3.99 (s, 3H), 3.90 (s, 3H), 3.19 (s, 3H), 2.39 (s, 3H), 2.35 (d, *J* = 7.6 Hz, 2H), 1.07 (t, *J* = 7.5 Hz, 3H). LCMS(ESI): [M+H]⁺ *m/z*: calc 474.2; found 475.2; Rt = 1.823 min.

[00914] Example 72: Synthesis of Compound 72

[00915] Scheme 44: The Synthesis of Compound **72**.



[00916] Representative Procedure for Method 7 Amination

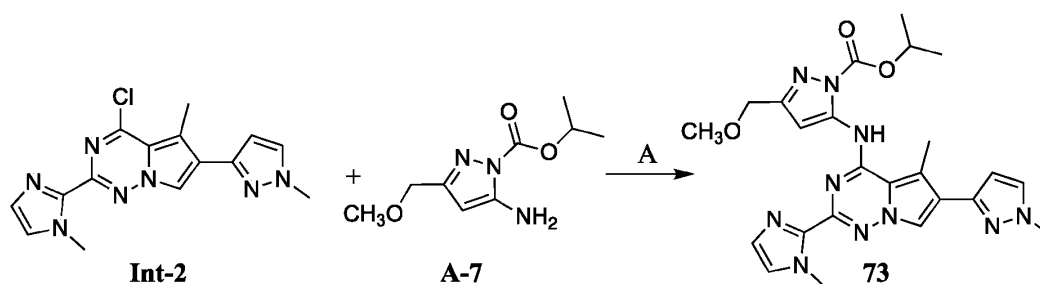
[00917] Step A: Ethyl 3-(methoxymethyl)-5-((5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)-1*H*-pyrazole-1-carboxylate **72**.

[00918] Sodium hydride (75 mg, (60% in mineral oil)) was added in portionwise to a solution of ethyl 5-amino-3-(methoxymethyl)-1*H*-pyrazole-1-carboxylate **A-6** (prepared as described

herein) (300.0 mg, 1.51 mmol) in DMF (6 mL). The mixture was stirred at room temperature for 30 min, then 4-chloro-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-2** (prepared as described herein) (492.8 mg, 1.51 mmol) was added in one portion, and stirred at RT overnight. After this time resulting mixture was diluted with water and extracted with ethyl acetate (3x10 mL). The organic phases were combined, washed with H₂O, brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by HPLC (SYSTEM 8-15-50% 0-2-7 min H₂O/acetonitrile/0.1 NH₄HCO₃, flow 30 mL/min ((loading pump 4 mL acetonitrile) column: Chromatorex C18 SMB100-5T 100*19 mm, 5 microM))) to give ethyl 3-(methoxymethyl)-5-((5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)-1*H*-pyrazole-1-carboxylate **72** (480.0 mg, 95.0% purity, 929.63 μ mol, 61% yield). LCMS(ESI): [M+H]⁺ m/z: calc 490.2; found 491.4.

[00919] **Example 73: Synthesis of Compound 73**

[00920] Scheme 45: The Synthesis of **Compound 73**.



[00921] Following the Representative Procedure for Method 7 Amination

[00922] **Step A:** Isopropyl 3-(methoxymethyl)-5-((5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)-1*H*-pyrazole-1-carboxylate **73**.

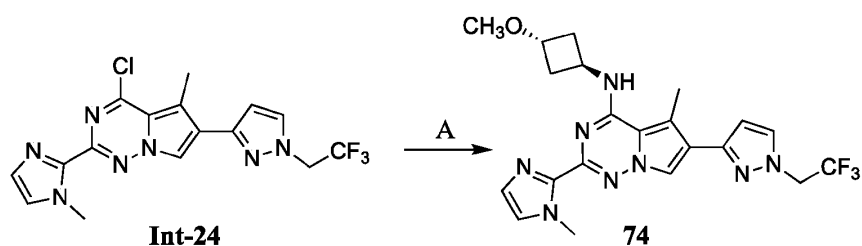
[00923] The procedure described for the synthesis of Compound **72** in Example 72 was implemented with sodium hydride (30 mg, (60% in mineral oil)), 4-chloro-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-2** (prepared as described herein) (199.68 mg, 610.45 μ mol) and isopropyl 5-amino-3-(methoxymethyl)-1*H*-pyrazole-1-carboxylate **A-7** (prepared as described herein) (130.0 mg, 609.66 μ mol) in DMF. The product was purified by HPLC (SYSTEM 23-30-55% 0-2-8 min H₂O/acetonitrile/0.1 NH₄HCO₃, flow 30 mL/min ((loading pump 4 mL acetonitrile) column:

XBridge BEH C18 100*19 mm, 5 micro M))) to give isopropyl 3-(methoxymethyl)-5-((5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)-1*H*-pyrazole-1-carboxylate **73** (135.0 mg, 95.0% purity, 254.19 μ mol, 41% yield).

LCMS(ESI): [M+H]⁺ m/z: calc 504.2; found 505.2.

[00924] Example 74: Synthesis of Compound 74

[00925] Scheme 46: The Synthesis of Compound 74.



[00926] Representative Procedure for Method 8 Amination

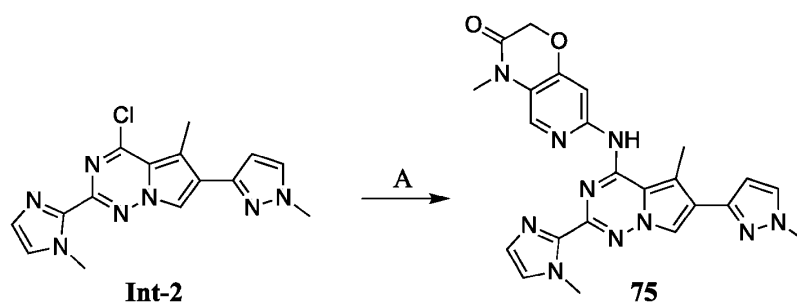
[00927] Step A: *N*-((1*r*,3*r*)-3-Methoxycyclobutyl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine **74**.

[00928] Diisopropyl ethyl amine (162.68 mg, 1.26 mmol) was added in one portion to the solution of (1*r*,3*r*)-3-methoxycyclobutan-1-amine hydrochloride salt (69.06 mg, 503.85 μ mol) in DMF (1 mL). The mixture was stirred at ambient temperature for 0.5 h. 4-chloro-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-24** (prepared as described herein) (100.0 mg, 252.67 μ mol) in DMF was added in one portion and stirred 16 h. The mixture was quenched with conc. NH₄Cl and purified by HPLC. *N*-((1*r*,3*r*)-3-methoxycyclobutyl)-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-(2,2,2-trifluoroethyl)-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-amine **74** (3.1 mg, 95.0% purity, 6.4 μ mol, 2.5% yield) was obtained. ¹H NMR (600 MHz, DMSO-*d*₆) δ (ppm) 7.97 (s, 1H), 7.87 (d, *J* = 2.4 Hz, 1H), 7.26 (s, 1H), 7.12 (d, *J* = 6.5 Hz, 1H), 6.96 (s, 1H), 6.73 – 6.66 (m, 1H), 5.16 (q, *J* = 9.1 Hz, 2H), 4.77 (q, *J* = 7.3 Hz, 1H), 4.04 (td, *J* = 6.7, 3.3 Hz, 1H), 3.93 (s, 3H), 3.16 (s, 3H), 2.74 (s, 3H), 2.47 – 2.40 (m, 2H), 2.33 (ddt, *J* = 11.2, 8.2, 3.3 Hz, 2H).

LCMS(ESI): [M+H]⁺ m/z: calcd 474.2; found 475.2.

[00929] Example 75: Synthesis of Compound 75

[00930] Scheme 47: The Synthesis of Compound 75.



[00931] Representative Procedure for Method 9 Amination

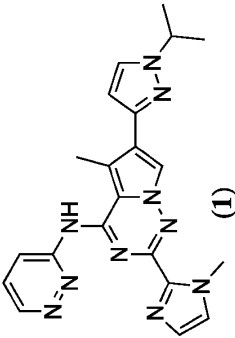
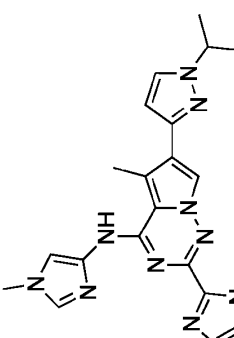
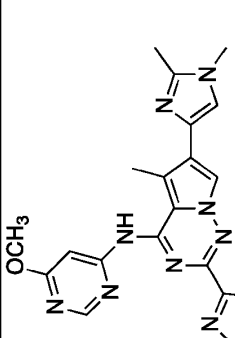
[00932] **Step A:** 4-Methyl-7-((5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)-2*H*-pyrido[4,3-*b*][1,4]oxazin-3(4*H*)-one **75**.

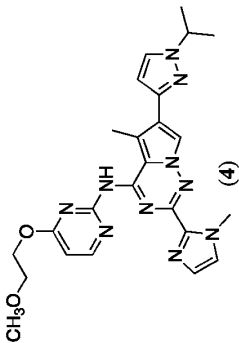
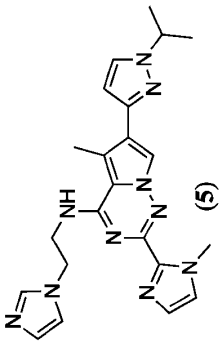
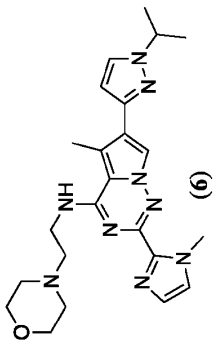
[00933] Trifluoroacetic acid (69.78 mg, 612.13 μmol) was added in one portion to the solution of 7-amino-4-methyl-2*H*-pyrido[4,3-*b*][1,4]oxazin-3(4*H*)-one hydrochloride salt (144.8 mg, 673.34 μmol) and 4-chloro-5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazine **Int-2** (prepared as described herein) (100.0 mg, 305.72 μmol) in butan-1-ol (1 mL). The mixture was heated to 100°C and stirred at this temperature for 16 h. The mixture was evaporated to dryness and purified by HPLC. 4-Methyl-7-((5-methyl-2-(1-methyl-1*H*-imidazol-2-yl)-6-(1-methyl-1*H*-pyrazol-3-yl)pyrrolo[2,1-*f*][1,2,4]triazin-4-yl)amino)-2*H*-pyrido[4,3-*b*][1,4]oxazin-3(4*H*)-one **75** (6.1 mg, 95.0% purity, 12.32 μmol , 4% yield) was obtained. LCMS(ESI): $[\text{M}+\text{H}]^+$ m/z : calcd 470.2; found 471.2.

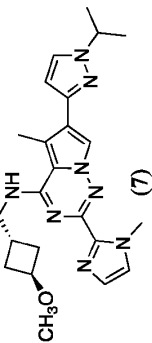
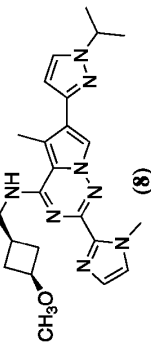
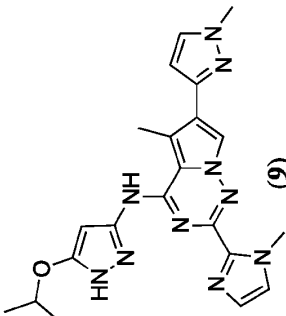
[00934] **Example 76 – Example 96: Compound 76 – Compound 94**

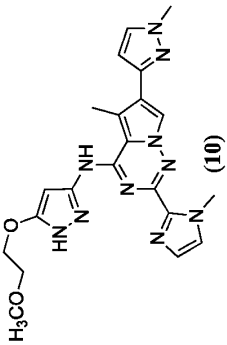
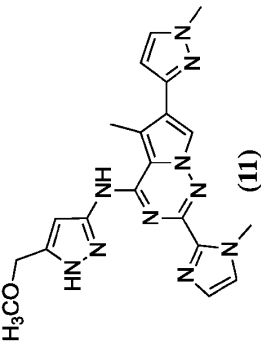
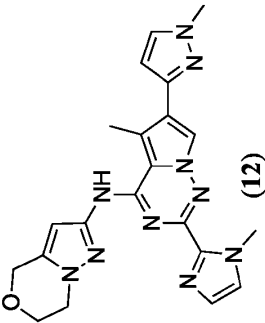
[00935] Table C provides the structures of of Compound 76 – Compound 94 which can be prepared according to the procedures described herein.

Table A

Example	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
1		6-(1-(1-Isopropyl-1H-pyrazol-3-yl)-5-methyl-2-(1-methyl-1H-imidazol-2-yl)-N-(pyridazin-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-1 Method 1	4.9 mg 4.2% 99%	415.2	415.2	
2		6-(1-(1-Isopropyl-1H-pyrazol-3-yl)-5-methyl-2-(1-methyl-1H-imidazol-2-yl)-N-(1-methyl-1H-imidazol-4-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-1 Method 1	14.7 mg 12.6% 95%	417.2	417.2	
3		6-(1,2-Dimethyl-1H-imidazol-4-yl)-N-(6-methoxypyrimidin-4-yl)-5-methyl-2-(1-methyl-1H-imidazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-3 Method 1	1.7 mg 7.1% 97%	431.2	431.2	

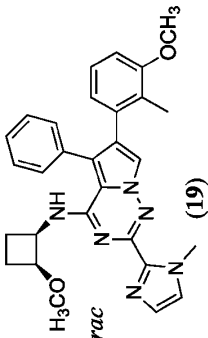
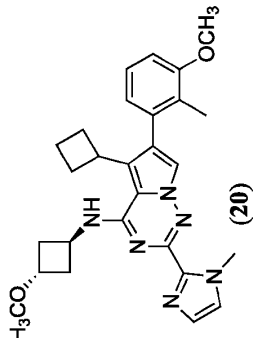
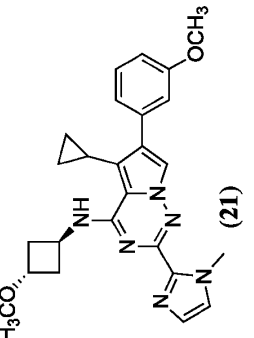
Example	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
4		6-(1-Isopropyl-1H-pyrazol-3-yl)-N-(4-(2-methoxyethoxy)pyrimidin-2-yl)-5-methyl-2-(1-methyl-1H-imidazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-1 Method 1	15.7 mg 11.5% 98%	489.2	489.2	
5		N-(2-(1H-Imidazol-1-yl)ethyl)-6-(1-isopropyl-1H-pyrazol-3-yl)-5-methyl-2-(1-methyl-1H-imidazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-1 Method 2	37.3 mg 31.3% 100%	431.5	431.1	(400 MHz, DMSO-d ₆) δ (ppm) 1.42 (m, 6H), 2.67 (s, 3H), 3.86 (m, 2H), 3.93 (s, 3H), 4.29 (t, 2H), 4.52 (sept, 1H), 6.53 (d, 1H), 6.87 (d, 1H), 6.97 (s, 1H), 7.26 (m, 3H), 7.65 (s, 1H), 7.79 (d, 1H), 7.91 (d, 1H).
6		6-(1-Isopropyl-1H-pyrazol-3-yl)-5-methyl-2-(1-methyl-1H-imidazol-2-yl)-N-(2-morpholinoethyl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-1 Method 2	35.7 mg 28.3% 100%	450.3	450.2	(400 MHz, DMSO-d ₆) δ (ppm) 1.41 (m, 6H), 2.62 (m, 4H), 2.68 (m, 2H), 2.72 (s, 3H), 3.52 (m, 4H), 3.63 (m, 2H), 3.96 (s, 3H), 4.52 (sept, 1H), 6.51 (d, 1H), 6.94 (d, 1H), 7.10 (m, 1H), 7.28 (s, 1H), 7.78 (d, 1H), 7.92 (d, 1H).

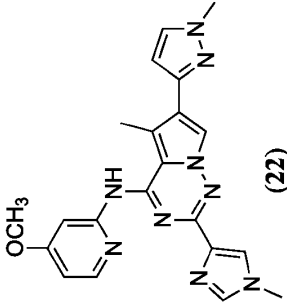
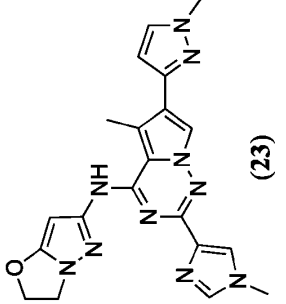
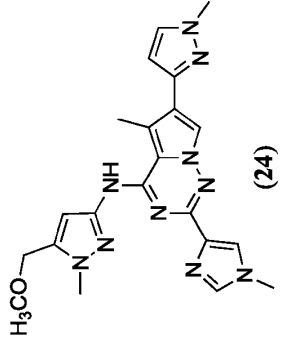
Example	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
7		6-(1-Isopropyl-1H-pyrazol-3-yl)-N-methoxycyclobutyl-methyl-5-methyl-2-(1-methyl-1H-imidazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-1 Method 2	45.5 mg 37.3% 100%	435.2	435.1	(400 MHz, DMSO- <i>d</i> ₆) δ (ppm) 1.41 (m, 6H), 1.92 (m, 2H), 2.10 (m, 2H), 2.56 (m, 1H), 2.69 (s, 3H), 3.08 (s, 3H), 3.62 (m, 2H), 3.93 (m, 4H), 4.49 (m, 1H), 6.49 (d, 1H), 6.95 (d, 1H), 7.27 (m, 2H), 7.76 (d, 1H), 7.87 (s, 1H).
8		6-(1-Isopropyl-1H-pyrazol-3-yl)-N-methoxycyclobutyl-methyl-5-methyl-2-(1-methyl-1H-imidazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-1 Method 2	24.0 mg 19.7% 100%	435.2	435.2	(400 MHz, DMSO- <i>d</i> ₆) δ (ppm) 1.40 (m, 6H), 1.60 (m, 2H), 2.23 (m, 2H), 2.53 (m, 2H), 2.70 (s, 3H), 3.07 (s, 3H), 3.62 (m, 2H), 3.91 (s, 3H), 4.51 (sept, 1H), 6.50 (d, 1H), 6.94 (d, 1H), 7.25 (m, 2H), 7.76 (d, 1H), 7.81 (s, 1H).
9		N-(5-Isopropoxy-1H-pyrazol-3-yl)-5-methyl-2-(1-methyl-1H-imidazol-2-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	A-1 Int-2 Method 1*	15.3 mg 7.4% 98%	433.2	433.2	

Example	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
10		<i>N</i> -(5-(2-Methoxyethoxy)-1 <i>H</i> -pyrazol-3-yl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	A-2 Int-2 Method 1*	14.0 mg 6.5% 99%	449.2	449.2	¹ H NMR (500 MHz, dmsol) δ 12.87 (s, 2H), 7.71 (d, <i>J</i> = 3.2 Hz, 1H), 7.68 (d, <i>J</i> = 2.2 Hz, 1H), 7.49 (s, 1H), 7.14 (s, 1H), 6.50 (d, <i>J</i> = 2.2 Hz, 1H), 6.10 (s, 1H), 4.39 (s, 2H), 4.04 (s, 3H), 3.86 (s, 3H), 3.26 (s, 3H), 2.77 (s, 3H).
11		<i>N</i> -(5-(5-Methoxymethyl)-1 <i>H</i> -pyrazol-3-yl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-2 Method 1*	19.2 mg 9.9% 100%	419.2	419.2	
12		<i>N</i> -(5-Methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-yl)-6,7-dihydro-4 <i>H</i> -pyrazolo[5,1- <i>c</i>][1,4]oxazin-2-amine	Int-2 Method 2**	0.528 g 43.0% 100%	431.2	431.2	

Example	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
13		<i>N</i> -(5-(Methoxymethyl)-1-methyl-1 <i>H</i> -pyrazol-3-yl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	A-3 Int-2 Method 1*	49.7 mg 9% 95%	433.2	433.2	(500 MHz, TFA/DMSO) δ (ppm) 2.85 (s, 3H), 3.74 (s, 3H), 4.22 (s, 3H), 4.36 (s, 3H), 4.40 (s, 3H), 4.88 (s, 2H), 6.93 (s, 1H), 7.01 (m, 1H), 7.57 (d, 1H), 7.64 (d, 1H), 8.15 (d, 1H), 8.34 (m, 1H).
14		5-(5-(Methoxymethyl)- <i>N</i> -(5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-yl)isoxazol-3-amine	Int-2 Method 1	30.0 mg 22.3% 100%	420.2	420.2	(500 MHz, DMSO-d6) δ 2.76 (dd, 3H), 3.28 (d, 2H), 3.77 (m, 3H), 3.89 (d, 3H), 4.19 (m, 3H), 6.62 (m, 2H), 7.16 (s, 1H), 7.48 (s, 1H), 7.74 (m, 1H), 8.16 (dd, 1H)
15		<i>N</i> -(5-Methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-yl)-[1,3]dioxolo[4,5- <i>c</i>]pyridin-4-amine	Int-2 Method 1	11.3 mg 8.6% 100%	430.2	430.2	(500 MHz, DMSO-d6) δ 2.82 (d, 3H), 3.29 (s, 2H), 3.87 (d, 3H), 3.96 (d, 3H), 6.17 (d, 2H), 6.54 (dd, 1H), 6.72 (d, 1H), 7.09 (d, 1H), 7.35 (dd, 1H), 7.49 (s, 1H), 7.69 (d, 1H), 7.74 (m, 1H), 13.35 (s, 1H)

Example	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
16		<i>N</i> -(6-Methoxypyrimidin-4-yl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5,6-di(pyridin-4-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-4 Method 1	28.7 mg 22.2% 100%	477.2	477.2	(500 MHz, DMSO- <i>d</i> ₆) δ (ppm) 3.82 (s, 3H), 4.02 (s, 3H), 7.10 (m, 3H), 7.28 (m, 4H), 8.28 (m, 6H).
17		<i>N</i> -((1 <i>r</i> ,3 <i>r</i>)-3-Methoxycyclobutyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5,6-di(pyridin-4-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-4 Method 2	34.5 mg 28.0% 97%	453.2	453.2	(500 MHz, DMSO- <i>d</i> ₆) δ (ppm) 2.00 (m, 2H), 2.20 (m, 2H), 3.06 (s, 3H), 3.81 (m, 1H), 3.91 (s, 3H), 4.50 (m, 1H), 5.91 (d, 1H), 6.91 (d, 1H), 7.06 (m, 2H), 7.28 (d, 1H), 7.43 (m, 2H), 8.30 (s, 1H), 8.40 (d, 2H), 8.68 (d, 2H).
18		<i>N</i> -(4-Methoxypyridin-2-yl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5,6-di(pyridin-4-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-4 Method 1	13.0 mg 50.5% 100%	476.2	476.2	

Example	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
19		<i>rac</i> 6-(3-Methoxy-2-methylphenyl)- <i>N</i> -(1 <i>R</i> ,2 <i>S</i>)-2-methoxycyclobutyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5-phenylpyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine (19)	Int-5 Method 2	52 mg 19.5% 100%	495.2	495.2	(500 MHz, DMSO- <i>d</i> ₆) δ (ppm) 1.69 (m, 2H), 1.80 (s, 3H), 1.98 (m, 2H), 2.89 (s, 3H), 3.68 (s, 3H), 3.92 (m, 4H), 4.53 (m, 1H), 6.28 (d, 1H), 6.63 (d, 1H), 6.80 (d, 1H), 6.91 (s, 1H), 7.02 (dd, 1H), 7.20 (m, 3H), 7.34 (m, 3H), 7.80 (s, 1H).
20		5-Cyclobutyl-6-(3-methoxy-2-methylphenyl)- <i>N</i> -(1 <i>r</i> ,3 <i>r</i>)-3-methoxycyclobutyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine (20)	Int-6 Method 2***	2.3 mg 43.3% 99%	473.3	473.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ (ppm) 1.45 (m, 1H), 1.75 (m, 3H), 1.96 (s, 3H), 2.10 (m, 1H), 2.36 (m, 4H), 3.12 (s, 3H), 3.65 (s, 3H), 3.89 (s, 3H), 4.00 (m, 1H), 4.10 (m, 1H), 4.70 (m, 1H), 6.76 (m, 2H), 6.90 (m, 2H), 7.12 (dd, 1H), 7.20 (m, 1H), 7.51 (s, 1H).
21		5-Cyclopropyl- <i>N</i> -(1 <i>r</i> ,3 <i>r</i>)-3-methoxycyclobutyl)-6-(3-methoxyphenyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine (21)	Int-7 Method 2***	37.0 mg 66.7% 100%	445.2	445.2	

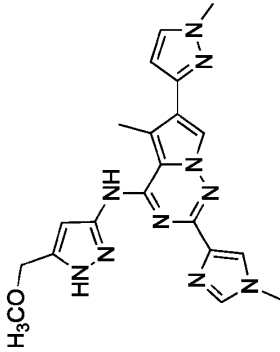
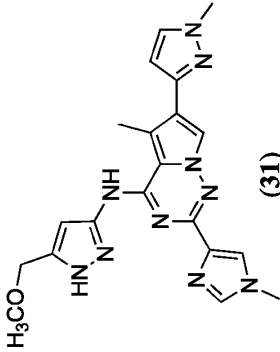
Example	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
22		<i>N</i> -(4-Methoxyphenyl)-2-methyl-2-(1-methyl-1 <i>H</i> -imidazol-4-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine (22)	Int-11 Method 1	Purity =100%	416.2	416.2	
23		<i>N</i> -(5-Methyl-2-(1-methyl-1 <i>H</i> -imidazol-4-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-yl)-2,3-dihydropyrazolo[5,1- <i>b</i>]oxazol-6-amine (23)	Int-11 Method 1	Purity =100%	417.2	417.2	
24		<i>N</i> -(5-(Methoxymethyl)-1-methyl-1 <i>H</i> -pyrazol-3-yl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-4-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine (24)	Int-11 Method 1	Purity =90%	433.2	433.4	

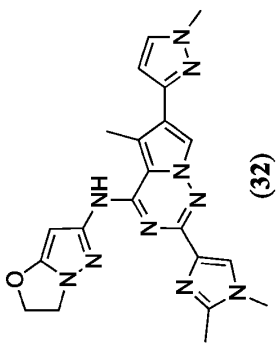
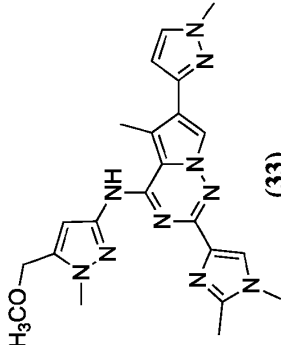
Example	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
25		<i>N</i> -(4,6-Dimethoxypyrimidin-2-yl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-2 Method 1	200 mg 93% 100%	446.2	446.2	
26		<i>N</i> -(4,6-Dimethoxypyrimidin-2-yl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-2 Method 1	31 mg 13.9% 92%	447.2	447.2	
27		<i>N</i> -(5-Methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-yl)-2,3-dihydro-[1,4]dioxino[2,3- <i>c</i>]pyridin-7-amine	Int-2 Method 1	30 mg 14% 100%	444.1	444.0	

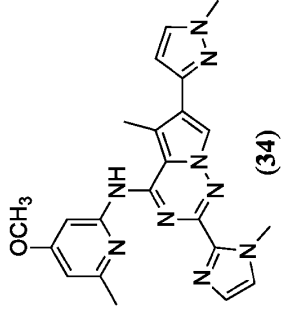
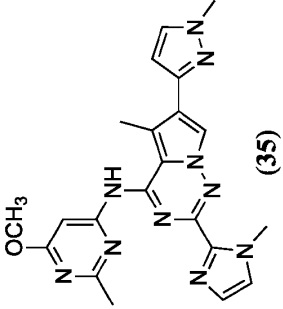
Example	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
28		5-Methyl-2-(1-methyl-1H-imidazol-2-yl)-N,6-bis(1-methyl-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-1 Method 2	25 mg 13.3% 100%	389.2	389.0	
29		6-(3-Methoxy-2-methylphenyl)-3-methoxycyclobutyl)-5-(4-methoxypyridin-2-yl)-2-(1-methyl-1H-imidazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-1 Method 2	154.7 mg 57.2% 100%	526.2	526.2	

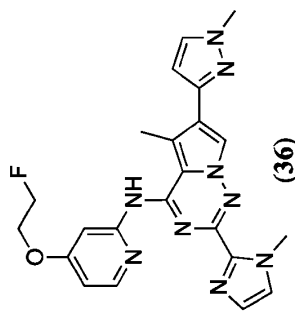
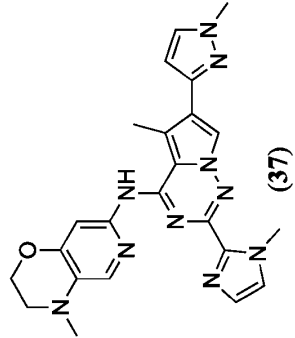
Table note: *Stirred overnight at 40°C, **Stirred at 60°C, ***Stirred at 80°C, 3 h.

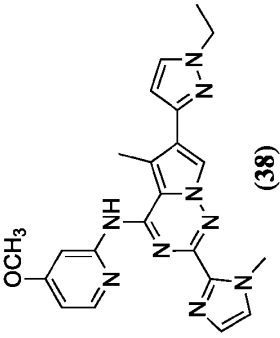
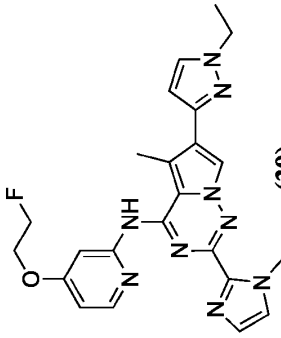
Table B

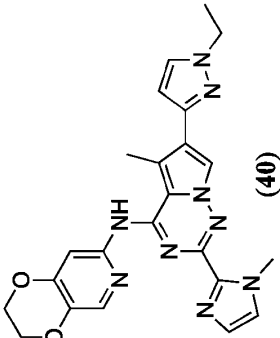
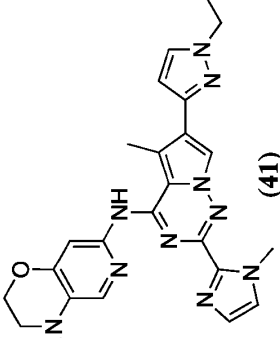
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
30		<i>N</i> -(5-(Methoxymethyl)-1 <i>H</i> -pyrazol-3-yl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-4-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine					
31		2-(1,2-Dimethyl-1 <i>H</i> -imidazol-4-yl)- <i>N</i> -(4-methoxypyridin-2-yl)-5-methyl-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-11 Method 3	27.6 mg 21% 100%	430.2	430.2	(600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 14.94 (s, 1H), 8.22 (d, <i>J</i> = 5.6 Hz, 1H), 7.77 – 7.58 (m, 3H), 6.74 – 6.66 (m, 2H), 6.51 (dd, <i>J</i> = 3.1, 7.2 Hz, 1H), 3.86 (s, 6H), 3.62 (d, <i>J</i> = 19.4 Hz, 3H), 2.83 (d, <i>J</i> = 8.2 Hz, 3H), 2.39 (s, 3H).

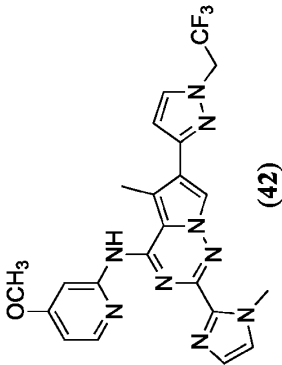
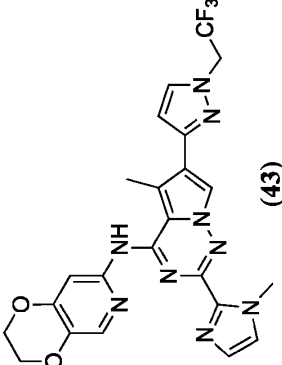
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
32		<i>N</i> -(2-(1,2-Dimethyl-1 <i>H</i> -imidazol-4-yl)-5-methyl-6-(1H-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-yl)-2,3-dihydropyrazolo[5,1- <i>b</i>]oxazol-6-amine	Int-18 Method 7	18.7 mg 12% 100%	431.2	431.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 12.74 (s, 1H), 7.74 (s, 1H), 7.72 – 7.62 (m, 1H), 7.59 (s, 1H), 6.48 (dd, <i>J</i> = 30.4, 2.2 Hz, 1H), 5.30 (s, 1H), 5.02 (q, <i>J</i> = 8.0 Hz, 2H), 4.34 – 4.19 (m, 2H), 3.85 (s, 3H), 3.63 (s, 3H), 2.72 (s, 3H), 2.37 (s, 3H)
33		2-(1,2-Dimethyl-1 <i>H</i> -imidazol-4-yl)- <i>N</i> -(5-(methoxymethyl)-1-methyl-1 <i>H</i> -pyrazol-3-yl)-5-methyl-6-(1H-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-18 Method 3	3.0 mg 2% 97%	447.2	447.2	

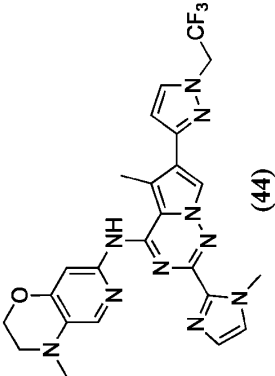
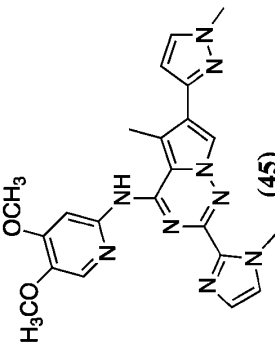
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
34		<i>N</i> -(4-Methoxy-6-methylpyridin-2-yl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-2 Method 3	23.0 mg 17% 95%	430.2	430.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 15.27 (s, 1H), 7.92 (s, 1H), 7.71 (s, 1H), 7.51 (s, 1H), 7.18 (s, 1H), 6.55 (s, 1H), 6.29 (s, 1H), 4.04 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 2.84 (s, 3H), 1.16 (s, 3H).
35		<i>N</i> -(6-Methoxy-2-methylpyrimidin-4-yl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-6-(1-methyl-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-2 Method 3	140 mg 68% 95%	431.2	431.2	

Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
36		<i>N</i> -(4-(2-Fluoroethoxy)pyridin-2-yl)-5-methyl-1,2-(1H-methyl-1H-imidazol-2-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-2 Method 3	29 mg 20% 95%	448.2	448.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 14.97 (s, 1H), 8.20 (d, <i>J</i> = 5.8 Hz, 1H), 7.83 (s, 1H), 7.70 (s, 1H), 7.42 (d, <i>J</i> = 83.9 Hz, 1H), 7.13 (d, <i>J</i> = 46.2 Hz, 1H), 6.73 (d, <i>J</i> = 17.7 Hz, 2H), 6.54 (s, 1H), 4.76 (d, <i>J</i> = 47.7 Hz, 2H), 4.39 (d, <i>J</i> = 30.5 Hz, 2H), 4.04 (s, 3H), 3.87 (s, 3H), 2.85 (s, 3H).
37		4-Methyl- <i>N</i> -(5-methyl-2-(1-methyl-1H-imidazol-2-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-yl)-3,4-dihydro-2H-pyrido[4,3- <i>b</i>][1,4]oxazin-7-amine	Int-2 Method 3	100 mg 6.4% 90%	457.2	457.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 14.70 (s, 1H), 7.74 – 7.67 (m, 3H), 7.48 (s, 1H), 7.18 (s, 1H), 6.57 – 6.48 (m, 2H), 4.35 (t, <i>J</i> = 4.3 Hz, 2H), 4.03 (d, <i>J</i> = 5.6 Hz, 3H), 3.86 (d, <i>J</i> = 4.8 Hz, 3H), 3.23 (s, 2H), 2.88 (d, <i>J</i> = 13.5 Hz, 3H), 2.78 (s, 3H).

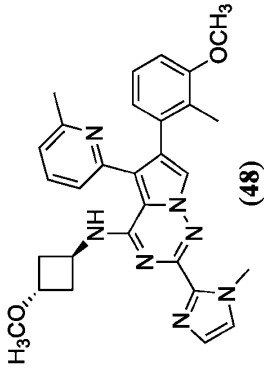
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
38		6-(1-Ethyl-1H-pyrazol-3-yl)-N-(4-methoxypyridin-2-yl)-5-methyl-2-(1-methyl-1H-imidazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-19 Method 3	8.2 mg 6.9% 95%	430.2	430.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 8.49 (s, 1H), 8.43 (d, <i>J</i> = 7.0 Hz, 1H), 7.90 (d, <i>J</i> = 1.7 Hz, 1H), 7.82 (d, <i>J</i> = 1.8 Hz, 1H), 7.78 (d, <i>J</i> = 2.3 Hz, 2H), 7.59 (d, <i>J</i> = 2.6 Hz, 1H), 7.19 (dd, <i>J</i> = 7.2, 2.6 Hz, 1H), 6.67 (d, <i>J</i> = 2.3 Hz, 1H), 4.21 – 4.14 (m, 2H), 4.14 (s, 3H), 4.04 (s, 3H), 2.87 (s, 3H), 1.41 (t, <i>J</i> = 7.3 Hz, 3H).
39		6-(1-Ethyl-1H-pyrazol-3-yl)-N-(4-(2-fluoroethoxy)pyridin-2-yl)-5-methyl-2-(1-methyl-1H-imidazol-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-19 Method 3	7.3 mg 5.1% 95%	462.2	462.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 14.96 (s, 1H), 8.20 (d, <i>J</i> = 5.8 Hz, 1H), 7.83 (s, 1H), 7.75 (s, 1H), 7.50 (s, 1H), 7.19 (s, 1H), 6.73 (s, 2H), 6.54 (s, 1H), 4.81 (s, 1H), 4.73 (s, 1H), 4.42 (s, 2H), 4.16 (q, <i>J</i> = 7.3 Hz, 2H), 4.04 (s, 3H), 2.86 (s, 3H), 1.41 (t, <i>J</i> = 7.3 Hz, 3H).

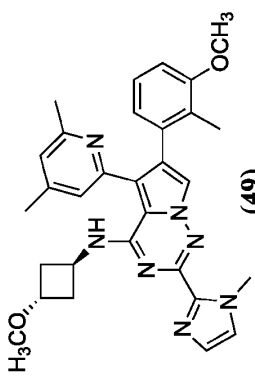
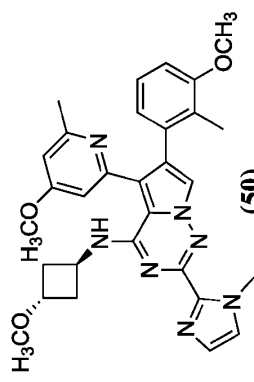
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
40	 (40)	<i>N</i> -(6-(1-Ethyl-1 <i>H</i> -pyrazol-3-yl)-5-methyl-2-(1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-yl)-2,3-dihydro-[1,4]dioxino[2,3- <i>c</i>]pyridin-7-amine	Int-19 Method 3	10.0 mg 7.1% 95%	458.2	458.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 8.37 (d, <i>J</i> = 3.4 Hz, 2H), 7.88 (s, 1H), 7.80 (s, 1H), 7.78 (d, <i>J</i> = 2.3 Hz, 1H), 7.65 (s, 1H), 6.65 (d, <i>J</i> = 2.3 Hz, 1H), 4.57 (t, <i>J</i> = 4.1 Hz, 2H), 4.43 (t, <i>J</i> = 4.1 Hz, 2H), 4.18 (q, <i>J</i> = 7.3 Hz, 2H), 4.09 (s, 3H), 2.87 (s, 3H), 1.41 (t, <i>J</i> = 7.3 Hz, 3H).
41	 (41)	<i>N</i> -(6-(1-Ethyl-1 <i>H</i> -pyrazol-3-yl)-5-methyl-2-(1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-yl)-4-methyl-3,4-dihydro-2 <i>H</i> -pyrido[4,3- <i>b</i>][1,4]oxazin-7-amine					

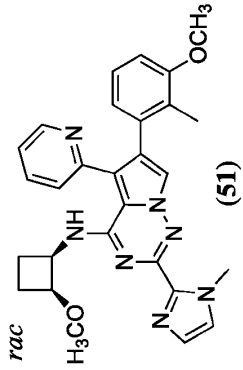
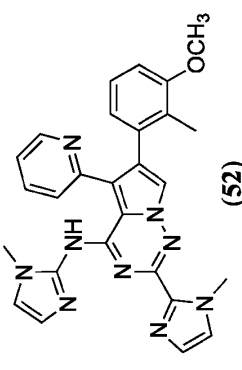
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
42		<i>N</i> -(4-Methoxyphenyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-6-(1-(2,2,2-trifluoroethyl)-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine					
43		<i>N</i> -(5-Methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-6-(1-(2,2,2-trifluoroethyl)-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-yl)-2,3-dihydro-[1,4]dioxino[2,3- <i>c</i>]pyridin-7-amine					

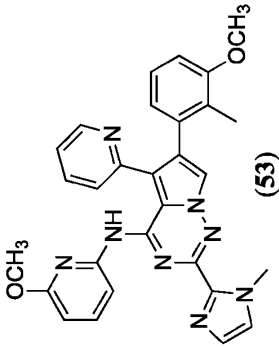
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
44		4-Methyl-N-(5-methyl-2-(1-methyl-1H-imidazol-2-yl)-6-(1-(2,2,2-trifluoroethyl)-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-yl)-3,4-dihydro-2H-pyrido[4,3-b][1,4]oxazin-7-amine					
45		N-(4,5-Dimethoxypyridin-2-yl)-5-methyl-2-(1-methyl-1H-imidazol-2-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine					

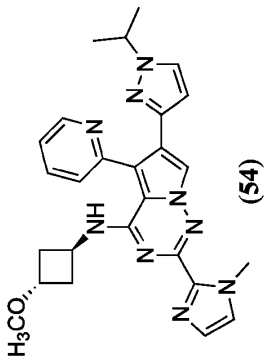
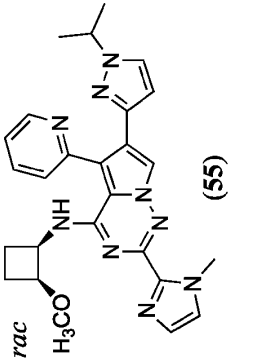
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
46		6-(3-Methoxy-2-methylphenyl)-N-((1r,3r)-3-methoxycyclobutyl)-2-(1-methyl-1H-imidazol-2-yl)-5-phenethylpyrrolo[2,1-f][1,2,4]triazin-4-amine					
47		6-(3-Methoxy-2-methylphenyl)-N-((1r,3r)-3-methoxycyclobutyl)-2-(1-methyl-1H-imidazol-2-yl)-5-(4-methylpyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-20 Method 4	7.1 mg 1.8% 95%	510.2	510.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.94 (d, <i>J</i> = 5.9 Hz, 1H), 8.53 (d, <i>J</i> = 5.1 Hz, 1H), 7.76 (s, 1H), 7.33 – 7.23 (m, 2H), 7.10 (d, <i>J</i> = 5.1 Hz, 1H), 7.03 (d, <i>J</i> = 8.2 Hz, 1H), 6.98 (d, <i>J</i> = 1.1 Hz, 1H), 6.85 (d, <i>J</i> = 7.5 Hz, 1H), 6.63 (s, 1H), 4.64 – 4.52 (m, 1H), 4.08 (ddd, <i>J</i> = 11.7, 6.9, 5.0 Hz, 1H), 3.97 (s, 3H), 3.80 (s, 3H), 3.17 (s, 3H), 2.41 (ddd, <i>J</i> = 12.9, 8.0, 4.8 Hz, 2H), 2.29 (ddd, <i>J</i> = 12.6, 6.8, 4.6 Hz, 2H),

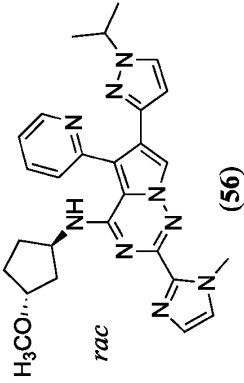
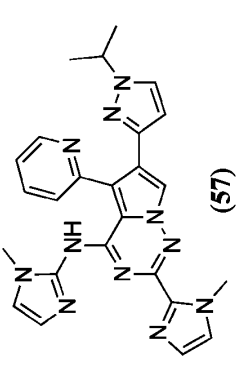
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
							1.95 (s, 3H), 1.78 (s, 3H).
48		6-(3-Methoxy-2-methylphenyl)-N-methoxy-N-methyl-1H-imidazo[2,1-b]pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-21 Method 4	28.6 mg 4.4% 93%	510.2	510.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 10.98 (d, <i>J</i> = 6.2 Hz, 1H), 7.77 (s, 1H), 7.45 (t, <i>J</i> = 7.9 Hz, 1H), 7.29 (s, 1H), 7.21 (t, <i>J</i> = 7.9 Hz, 1H), 7.12 (d, <i>J</i> = 7.7 Hz, 1H), 7.02 – 6.94 (m, 2H), 6.81 (d, <i>J</i> = 7.6 Hz, 1H), 6.68 (d, <i>J</i> = 8.0 Hz, 1H), 4.73 (p, <i>J</i> = 7.0 Hz, 1H), 4.08 (tt, <i>J</i> = 6.8, 4.0 Hz, 1H), 3.98 (s, 3H), 3.78 (s, 3H), 3.17 (s, 3H), 2.64 (s, 3H), 2.43 (td, <i>J</i> = 8.4, 3.9 Hz, 2H), 2.30 (ddd, <i>J</i> = 15.9, 7.8, 4.7 Hz, 2H), 1.78 (s, 3H).

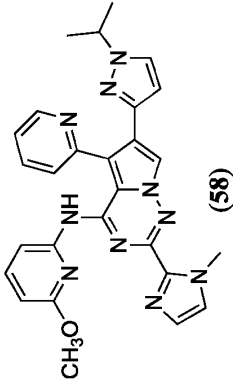
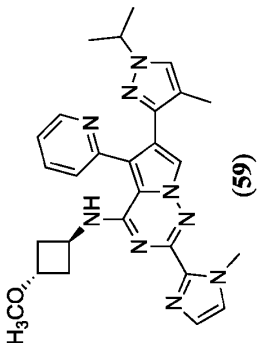
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
49	 (49)	5-(4,6-Dimethylpyridin-2-yl)-6-(3-methoxy-2-methylphenyl)-N-((1 <i>r</i> ,3 <i>r</i>)-3-methoxycyclobutyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-22 Method 4	18.1 mg 5.2% 96%	524.3	734.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.13 (d, <i>J</i> = 6.2 Hz, 1H), 7.77 (s, 1H), 7.29 (s, 1H), 7.23 (t, <i>J</i> = 7.9 Hz, 1H), 7.02 – 6.97 (m, 2H), 6.96 (s, 1H), 6.82 (d, <i>J</i> = 7.6 Hz, 1H), 6.45 (s, 1H), 4.72 (h, <i>J</i> = 6.6 Hz, 1H), 4.07 (td, <i>J</i> = 6.8, 3.5 Hz, 1H), 3.98 (s, 3H), 3.78 (s, 3H), 3.17 (s, 3H), 2.59 (s, 3H), 2.43 (ddd, <i>J</i> = 12.5, 7.9, 3.9 Hz, 2H), 2.32 – 2.25 (m, 2H), 1.90 (s, 3H), 1.75 (s, 3H).
50	 (50)	6-(3-Methoxy-2-methylphenyl)-5-(4-methoxy-6-methylpyridin-2-yl)-N-((1 <i>r</i> ,3 <i>r</i>)-3-methoxycyclobutyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine					

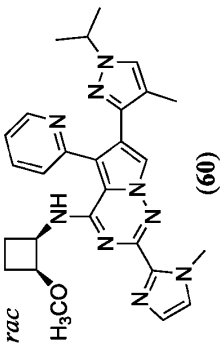
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
51		<i>rac</i> 6-(3-Methoxy-2-methylphenyl)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-2-methoxycyclobutyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5-(pyridin-2-yl)pyrrolol[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-23 Method 6	59.9 mg 43.7% 100%	496.2	496.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.81 (d, <i>J</i> = 6.3 Hz, 1H), 8.64 – 8.59 (m, 1H), 7.75 (s, 1H), 7.55 (td, <i>J</i> = 7.8, 1.9 Hz, 1H), 7.30 – 7.27 (m, 1H), 7.26 – 7.20 (m, 1H), 7.02 – 6.97 (m, 2H), 6.84 (dd, <i>J</i> = 8.0, 4.0 Hz, 2H), 4.78 (t, <i>J</i> = 6.7 Hz, 1H), 4.18 – 4.12 (m, 1H), 3.98 (s, 3H), 3.80 (s, 3H), 3.22 (s, 3H), 2.21 – 2.12 (m, 2H), 2.00 (dp, <i>J</i> = 11.6, 6.5 Hz, 1H), 1.87 (dq, <i>J</i> = 10.7, 5.7 Hz, 1H), 1.82 (s, 3H).
52		6-(3-Methoxy-2-methylphenyl)- <i>N</i> ,2-bis(1-methyl-1 <i>H</i> -imidazol-2-yl)-5-(pyridin-2-yl)pyrrolol[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-23 Method 3	57.6 mg 33% 98%	492.2	492.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ (ppm) 13.87 (s, 1H), 8.38 (d, <i>J</i> = 4.8 Hz, 1H), 7.72 – 7.64 (m, 2H), 7.53 (d, <i>J</i> = 7.8 Hz, 1H), 7.48 (s, 1H), 7.20 – 7.13 (m, 2H), 7.00 (dd, <i>J</i> = 15.9, 8.0 Hz, 2H), 6.95 (s, 1H), 6.80 (d, <i>J</i> = 8.2

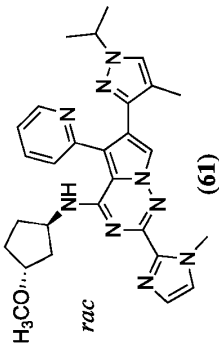
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
							Hz, 1H), 6.68 (d, <i>J</i> = 7.6 Hz, 1H), 4.07 (s, 3H), 3.72 (s, 3H), 3.06 (s, 3H), 1.87 (s, 3H).
53		6-(3-Methoxy-2-methylphenyl)-N-methoxypyridin-2-yl)-2-(1-methyl-1H-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-23 Method 3	37.8 mg 19% 95%	519.2	519.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ (ppm) 14.54 (s, 1H), 8.81 (d, <i>J</i> = 4.9 Hz, 1H), 8.46 (d, <i>J</i> = 7.9 Hz, 1H), 7.97 (d, <i>J</i> = 2.2 Hz, 1H), 7.78 (t, <i>J</i> = 8.0 Hz, 1H), 7.64 (t, <i>J</i> = 8.0 Hz, 1H), 7.39 – 7.31 (m, 2H), 7.27 (t, <i>J</i> = 8.0 Hz, 1H), 7.11 (s, 1H), 7.04 (d, <i>J</i> = 8.3 Hz, 1H), 6.91 (t, <i>J</i> = 8.0 Hz, 2H), 6.55 (d, <i>J</i> = 8.0 Hz, 1H), 4.02 (s, 3H), 3.96 (s, 3H), 3.81 (s, 3H), 1.84 (s, 3H).

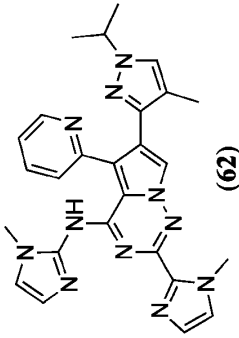
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
54		6-(1-Isopropyl-1H-pyrazol-3-yl)-N-((1r,3r)-3-methoxycyclobutyl)-2-(1-methyl-1H-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-9 Method 4	31.5 mg 78% 100%	484.2	484.2	
55		<i>rac</i> 6-(1-Isopropyl-1H-pyrazol-3-yl)-N-((1R,2S)-2-methoxycyclobutyl)-2-(1-methyl-1H-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-9 Method 4	8.7 mg 50% 95%	484.2	484.2	

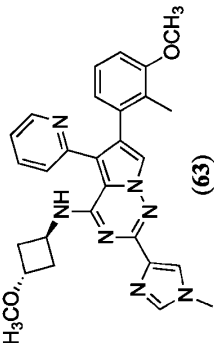
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
56	 rac 6-(1-Isopropyl-1H-pyrazol-3-yl)-N-methoxycyclopentyl-2-(1-methyl-1H-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	rac 6-(1-Isopropyl-1H-pyrazol-3-yl)-N-methoxycyclopentyl-2-(1-methyl-1H-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-9 Method 4	122 mg 63%	498.3	498.4	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 13.71 (s, 1H), 8.60 (d, <i>J</i> = 4.9 Hz, 1H), 7.87 (s, 1H), 7.81 (td, <i>J</i> = 7.7, 1.9 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.47 (s, 1H), 7.36 – 7.31 (m, 1H), 7.16 (s, 1H), 6.93 (dd, <i>J</i> = 17.1, 1.7 Hz, 2H), 5.60 (d, <i>J</i> = 2.3 Hz, 1H), 4.38 (h, <i>J</i> = 6.6 Hz, 1H), 4.08 (s, 3H), 2.94 (s, 3H), 1.34 (d, <i>J</i> = 6.6 Hz, 6H).
57	 6-(1-Isopropyl-1H-pyrazol-3-yl)-N,2-bis(1-methyl-1H-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	6-(1-Isopropyl-1H-pyrazol-3-yl)-N,2-bis(1-methyl-1H-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-9 Method 5	35.3 mg 29% 95%	480.2	480.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 13.71 (s, 1H), 8.60 (d, <i>J</i> = 4.9 Hz, 1H), 7.87 (s, 1H), 7.81 (td, <i>J</i> = 7.7, 1.9 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.47 (s, 1H), 7.36 – 7.31 (m, 1H), 7.16 (s, 1H), 6.93 (dd, <i>J</i> = 17.1, 1.7 Hz, 2H), 5.60 (d, <i>J</i> = 2.3 Hz, 1H), 4.38 (h, <i>J</i> = 6.6 Hz, 1H), 4.08 (s, 3H), 2.94 (s, 3H), 1.34 (d, <i>J</i> = 6.6 Hz, 6H).

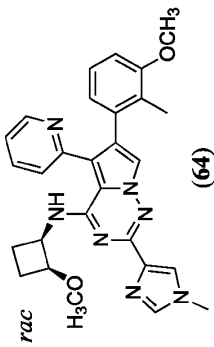
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
58		6-(1-Isopropyl-1 <i>H</i> -pyrazol-3-yl)- <i>N</i> -(6-methoxypyridin-2-yl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-9 Method 5	49.3 mg 40% 100%	507.2	507.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 13.99 (s, 1H), 8.84 – 8.80 (m, 1H), 8.45 (d, <i>J</i> = 7.9 Hz, 1H), 8.10 (s, 1H), 7.84 (d, <i>J</i> = 2.2 Hz, 1H), 7.80 – 7.71 (m, 2H), 7.42 – 7.36 (m, 3H), 7.11 (d, <i>J</i> = 1.1 Hz, 1H), 6.54 (d, <i>J</i> = 8.0 Hz, 1H), 6.34 (d, <i>J</i> = 2.2 Hz, 1H), 4.48 (h, <i>J</i> = 6.8 Hz, 1H), 4.02 (s, 3H), 3.95 (s, 3H), 1.39 (d, <i>J</i> = 6.7 Hz, 6H).
59		6-(1-Isopropyl-4-methyl-1 <i>H</i> -pyrazol-3-yl)- <i>N</i> -((1 <i>r</i> ,3 <i>r</i>)-3-methoxycyclobutyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-10 Method 4	17.8 mg 51% 100%	498.3	498.0	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.67 (d, <i>J</i> = 5.9 Hz, 1H), 8.68 (dd, <i>J</i> = 5.1, 1.8 Hz, 1H), 7.81 (s, 1H), 7.67 – 7.61 (m, 1H), 7.63 (s, 1H), 7.32 – 7.26 (m, 1H), 7.29 (s, 1H), 7.07 (d, <i>J</i> = 8.2 Hz, 1H), 6.99 (s, 1H), 4.59 (d, <i>J</i> = 9.2 Hz, 1H), 4.42 (hept, <i>J</i> = 6.8 Hz, 1H), 4.08 (h, <i>J</i> =

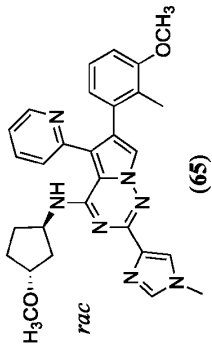
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
							5.1 Hz, 1H), 3.97 (s, 3H), 3.17 (s, 3H), 2.42 (ddd, <i>J</i> = 12.8, 8.0, 4.5 Hz, 2H), 2.33 – 2.26 (m, 2H), 1.74 (s, 3H), 1.37 (d, <i>J</i> = 6.7 Hz, 6H).
60	 (60)	<i>rac</i> 6-(1-Isopropyl-4-methyl-1 <i>H</i> -pyrazol-3-yl)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-2-methoxycyclobutyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-10 Method 4	16.7 mg 48% 100%	498.3	498.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.66 (d, <i>J</i> = 6.4 Hz, 1H), 8.61 (d, <i>J</i> = 4.9 Hz, 1H), 7.81 (s, 1H), 7.65 – 7.58 (m, 2H), 7.30 – 7.24 (m, 2H), 7.05 (d, <i>J</i> = 8.2 Hz, 1H), 6.98 (d, <i>J</i> = 1.1 Hz, 1H), 4.77 (s, 1H), 4.41 (p, <i>J</i> = 6.7 Hz, 1H), 4.17 – 4.11 (m, 1H), 3.97 (s, 3H), 3.21 (s, 3H), 2.15 (qd, <i>J</i> = 10.3, 6.3 Hz, 2H), 1.98 (dd, <i>J</i> = 11.0, 5.6 Hz, 1H), 1.86 (dd, <i>J</i> = 10.0, 5.1 Hz, 1H), 1.75 (s, 3H), 1.37 (d, <i>J</i> = 6.7

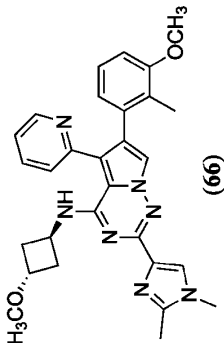
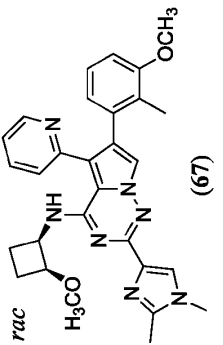
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
							Hz, 6H).
61		<i>rac</i> 6-(1-Isopropyl-4-methyl-1 <i>H</i> -pyrazol-3-yl)-3-methoxycyclopentyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-10 Method 4	10.6 mg 29% 100%	512.3	512.4	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.38 (d, <i>J</i> = 6.6 Hz, 1H), 8.65 – 8.55 (m, 1H), 7.79 (s, 1H), 7.65 – 7.59 (m, 2H), 7.29 – 7.25 (m, 2H), 7.05 (d, <i>J</i> = 8.2 Hz, 1H), 6.99 (d, <i>J</i> = 1.1 Hz, 1H), 4.57 (hept, <i>J</i> = 6.8 Hz, 1H), 4.40 (h, <i>J</i> = 6.8 Hz, 1H), 4.00 (s, 3H), 3.93 (dq, <i>J</i> = 6.2, 3.1 Hz, 1H), 3.19 (s, 3H), 2.17 (dt, <i>J</i> = 13.1, 6.8 Hz, 2H), 1.98 (dt, <i>J</i> = 14.8, 7.2 Hz, 1H), 1.78 (dt, <i>J</i> = 13.4, 6.5 Hz, 1H), 1.73 (s, 3H), 1.72 –

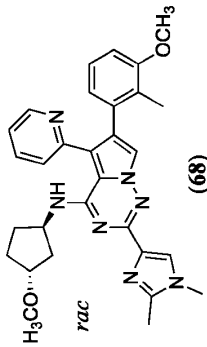
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
							1.65 (m, 1H), 1.60 (ddd, $J = 14.9, 12.5, 6.3$ Hz, 1H), 1.36 (d, $J = 6.6$ Hz, 6H).
62	 (62)	6-(1-Isopropyl-4-methyl-1H-pyrazol-3-yl)-N,2-bis(1-methyl-1H-imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-10 Method 5	24.2 mg 26% 100%	494.2	494.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 13.82 (s, 1H), 8.48 – 8.33 (m, 1H), 7.72 (d, $J = 6.1$ Hz, 2H), 7.56 (d, $J = 7.8$ Hz, 1H), 7.47 (s, 1H), 7.38 (s, 1H), 7.21 (dd, $J = 7.3, 5.1$ Hz, 1H), 7.17 (s, 1H), 6.94 (dd, $J = 12.1, 1.7$ Hz, 2H), 4.22 (p, $J = 6.6$ Hz, 1H), 4.08 (s, 3H), 3.03 (s, 3H), 1.71 (s, 3H), 1.22 (d, $J = 6.6$ Hz, 6H).

Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
63		6-(3-Methoxy-2-methylphenyl)-N-((1r,3r)-3-methoxycyclobutyl)-2-(1-methyl-1H-imidazol-4-yl)-5-(pyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-12 Method 6	45.9 mg 33% 100%	496.2	496.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.46 (d, <i>J</i> = 5.9 Hz, 1H), 8.66 (d, <i>J</i> = 4.8 Hz, 1H), 7.71 (d, <i>J</i> = 1.4 Hz, 1H), 7.64 (d, <i>J</i> = 5.4 Hz, 2H), 7.55 (td, <i>J</i> = 7.8, 1.8 Hz, 1H), 7.26 – 7.19 (m, 2H), 6.99 (d, <i>J</i> = 8.3 Hz, 1H), 6.83 (dd, <i>J</i> = 8.0, 3.6 Hz, 2H), 4.67 (q, <i>J</i> = 7.2 Hz, 1H), 4.07 (td, <i>J</i> = 6.7, 3.5 Hz, 1H), 3.79 (s, 3H), 3.71 (s, 3H), 3.19 (s, 3H), 2.45 (dd, <i>J</i> = 8.2, 4.3 Hz, 2H), 2.27 (dt, <i>J</i> = 12.7, 6.2 Hz, 2H), 1.81 (s, 3H).

Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
64		<i>rac</i> 6-(3-Methoxy-2-methylphenyl)- <i>N</i> -((1 <i>R</i> ,2 <i>S</i>)-2-methoxycyclobutyl)-2-(1-methyl-1 <i>H</i> -imidazol-4-yl)-5-(pyridin-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-12 Method 6	64.9 mg 47% 100%	496.2	496.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.51 (d, <i>J</i> = 6.7 Hz, 1H), 8.61 – 8.57 (m, 1H), 7.73 (d, <i>J</i> = 1.4 Hz, 1H), 7.66 – 7.62 (m, 2H), 7.53 (td, <i>J</i> = 7.8, 1.9 Hz, 1H), 7.25 – 7.18 (m, 2H), 6.99 (d, <i>J</i> = 8.3 Hz, 1H), 6.83 (dd, <i>J</i> = 7.9, 5.0 Hz, 2H), 4.90 – 4.84 (m, 1H), 4.14 (q, <i>J</i> = 5.4 Hz, 1H), 3.80 (s, 3H), 3.71 (s, 3H), 3.21 (s, 3H), 2.25 (tt, <i>J</i> = 12.5, 6.9 Hz, 1H), 2.17 – 2.09 (m, 1H), 1.98 (tt, <i>J</i> = 11.7, 6.1 Hz, 1H), 1.88 (tt, <i>J</i> = 10.7, 5.3 Hz, 1H), 1.82 (s, 3H).

Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
65		<i>rac</i> 6-(3-Methoxy-2-methylphenyl)- <i>N</i> '-((1 <i>R</i> ,3 <i>R</i>)-3-methoxycyclopentyl)-2-(1-methyl-1 <i>H</i> -imidazol-4-yl)-5-(pyridin-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-12 Method 6	61.7 mg 43% 100%	510.2	510.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.20 (d, <i>J</i> = 6.3 Hz, 1H), 8.61 – 8.57 (m, 1H), 7.71 (d, <i>J</i> = 1.3 Hz, 1H), 7.63 (d, <i>J</i> = 4.6 Hz, 2H), 7.53 (td, <i>J</i> = 7.8, 1.9 Hz, 1H), 7.24 – 7.19 (m, 2H), 6.98 (d, <i>J</i> = 8.3 Hz, 1H), 6.82 (d, <i>J</i> = 7.8 Hz, 2H), 4.61 (h, <i>J</i> = 6.9 Hz, 1H), 3.93 (tt, <i>J</i> = 6.3, 3.3 Hz, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.22 (s, 3H), 2.25 (dq, <i>J</i> = 14.2, 7.0 Hz, 2H), 1.97 (dq, <i>J</i> = 13.7, 6.7 Hz, 1H), 1.80 (s, 3H), 1.77 (dd, <i>J</i> = 13.7, 6.8 Hz, 2H), 1.56 (ddd, <i>J</i> = 15.0, 12.8, 6.8 Hz, 1H).

Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
66		2-(1,2-Dimethyl-1H-imidazol-4-yl)-6-(3-methoxy-2-methylphenyl)-N-((1R,3R)-3-methoxycyclobutyl)-5-(pyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-13 Method 8	7.4 mg 32% 100%	510.2	510.3	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.42 (d, <i>J</i> = 6.0 Hz, 1H), 8.66 (d, <i>J</i> = 4.8 Hz, 1H), 7.62 (d, <i>J</i> = 3.6 Hz, 2H), 7.54 (td, <i>J</i> = 7.8, 1.9 Hz, 1H), 7.25 – 7.19 (m, 2H), 6.99 (d, <i>J</i> = 8.3 Hz, 1H), 6.83 (d, <i>J</i> = 7.8 Hz, 2H), 4.66 (d, <i>J</i> = 6.1 Hz, 1H), 4.07 (dd, <i>J</i> = 7.9, 3.8 Hz, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 3.19 (s, 3H), 2.44 (dd, <i>J</i> = 8.3, 4.3 Hz, 23H), 2.31 (s, 3H), 2.26 (dt, <i>J</i> = 12.8, 6.3 Hz, 2H), 1.80 (s, 3H).
67		<i>rac</i> 2-(1,2-Dimethyl-1H-imidazol-4-yl)-6-(3-methoxy-2-methylphenyl)-N-((1R,2S)-2-methoxycyclobutyl)-5-(pyridin-2-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-13 Method 6	6.4 mg 27% 100%	510.2	510.3	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.47 (d, <i>J</i> = 6.8 Hz, 1H), 8.59 (d, <i>J</i> = 4.6 Hz, 1H), 7.62 (d, <i>J</i> = 12.7 Hz, 2H), 7.52 (td, <i>J</i> = 7.8, 1.9 Hz, 1H), 7.25 – 7.18 (m, 2H), 6.99 (d, <i>J</i> = 8.3 Hz, 1H), 6.82 (t, <i>J</i> = 7.5 Hz,

Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
		amine					2H), 4.86 (t, <i>J</i> = 6.1 Hz, 1H), 4.14 (q, <i>J</i> = 5.2 Hz, 1H), 3.79 (s, 3H), 3.60 (s, 3H), 3.21 (s, 3H), 2.31 (s, 3H), 2.24 (dq, <i>J</i> = 14.5, 7.6 Hz, 1H), 2.12 (dtd, <i>J</i> = 10.5, 7.4, 5.3 Hz, 1H), 1.97 (tt, <i>J</i> = 11.7, 6.2 Hz, 1H), 1.87 (tt, <i>J</i> = 10.7, 5.4 Hz, 1H), 1.81 (s, 3H).
68		<i>rac</i> 2-(1,2-Dimethyl-1 <i>H</i> -imidazol-4-yl)-6-(3-methoxy-2-methylphenyl)- <i>N</i> -((1 <i>R</i> ,3 <i>R</i>)-3-methoxycyclopentyl)-5-(pyridin-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-13 Method 6	9.2 mg 39% 100%	524.3	524.0	¹ H NMR (600 MHz DMSO- <i>d</i> ₆) δ (ppm) 11.16 (d, <i>J</i> = 6.3 Hz, 1H), 8.58 (dt, <i>J</i> = 4.9, 1.6 Hz, 1H), 7.61 (d, <i>J</i> = 12.5 Hz, 2H), 7.53 (td, <i>J</i> = 7.8, 1.9 Hz, 1H), 7.24 – 7.18 (m, 2H), 6.98 (d, <i>J</i> = 8.2 Hz, 1H), 6.84 – 6.80 (m, 2H), 4.60 (h, <i>J</i> = 6.9 Hz, 1H), 3.93 (tt, <i>J</i> = 6.3, 3.3 Hz, 1H), 3.79 (s, 3H), 3.61 (s, 3H), 3.21 (s, 3H), 2.31 (s, 3H), 2.28 – 2.18 (m, 2H), 1.97 (ddt, <i>J</i> =

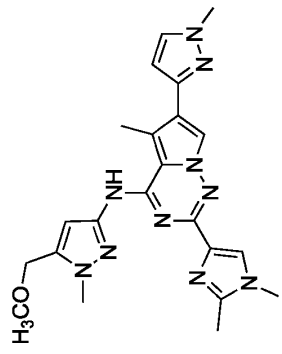
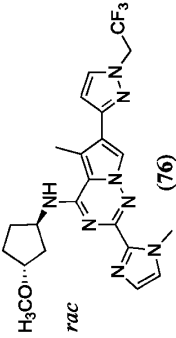
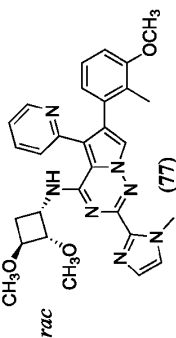
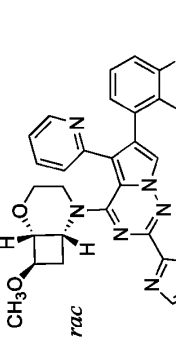
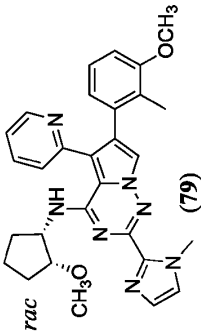
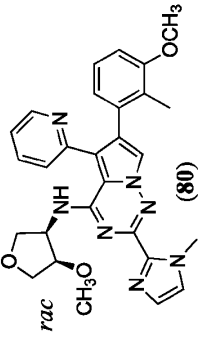
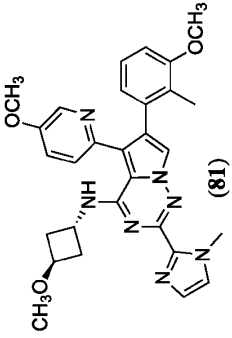
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
69		2-(1,2-Dimethyl-1H-imidazol-4-yl)-N-(5-(methoxymethyl)-1H-pyrazol-3-yl)-5-methyl-6-(1-methyl-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine					13.2, 8.8, 6.4 Hz, 1H), 1.79 (s, 4H), 1.75 – 1.66 (m, 1H), 1.55 (ddt, J = 12.8, 8.6, 6.3 Hz, 1H).

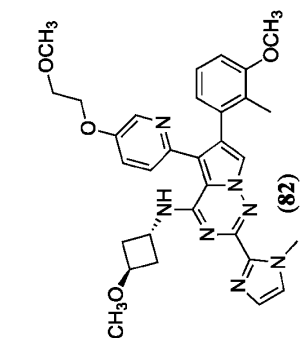
Table C

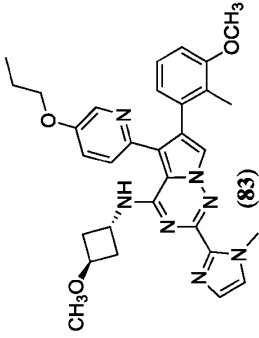
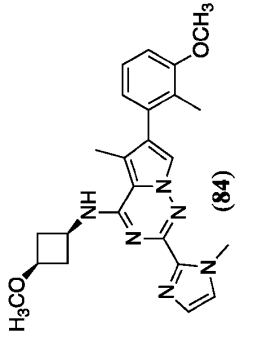
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
76		<i>rac</i> <i>N</i> -((1 <i>R</i> ,3 <i>R</i>)-3-Methoxycyclopentyl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-6-(1-(2,2,2-trifluoroethyl)-1 <i>H</i> -pyrazol-3-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-24 Method 8	100 mg 26% 100%	475.2	475.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 7.95 (s, 1H), 7.87 (d, <i>J</i> = 2.4 Hz, 1H), 7.25 (s, 1H), 6.96 (s, 1H), 6.76 (d, <i>J</i> = 7.6 Hz, 1H), 6.67 (d, <i>J</i> = 2.4 Hz, 1H), 5.15 (q, <i>J</i> = 9.1 Hz, 2H), 4.74 (h, <i>J</i> = 7.6 Hz, 1H), 3.94 (s, 3H), 3.89 (dt, <i>J</i> = 6.0, 2.8 Hz, 1H), 3.18 (s, 3H), 2.72 (s, 3H), 2.10 (dt, <i>J</i> = 12.9, 9.1 Hz, 2H), 2.06 – 1.97 (m, 1H), 1.85 (ddd, <i>J</i> = 14.0, 8.6, 6.0 Hz, 1H), 1.73 – 1.64 (m, 1H), 1.63 (s, 1H).

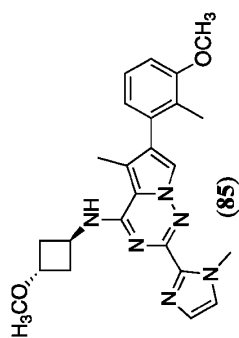
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
77		<i>rac</i> <i>N</i> -((1 <i>S</i> ,2 <i>S</i> ,3 <i>S</i>)-2,3-Dimethoxycyclobutyl)-6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-23 Method 4	53.9 mg 79% 100%	526.2	526.4	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.81 (d, <i>J</i> = 5.6 Hz, 1H), 8.63 (d, <i>J</i> = 5.0 Hz, 1H), 7.75 (s, 1H), 7.55 (td, <i>J</i> = 7.8, 1.9 Hz, 1H), 7.29 (s, 1H), 7.27 – 7.21 (m, 2H), 7.03 – 6.96 (m, 2H), 6.85 (dd, <i>J</i> = 10.3, 7.8 Hz, 2H), 4.62 (q, <i>J</i> = 6.4 Hz, 1H), 4.01 (t, <i>J</i> = 6.7 Hz, 1H), 3.98 (s, 3H), 3.92 (q, <i>J</i> = 7.9 Hz, 1H), 3.80 (s, 3H), 3.29 (s, 3H), 3.22 (s, 3H), 2.14 (dd, <i>J</i> = 12.3, 8.3 Hz, 1H), 1.88 – 1.80 (m, 1H), 1.83 (s, 3H).
78		<i>rac</i> (1 <i>R</i> ,6 <i>R</i> ,8 <i>R</i>)-8-Methoxy-5-(6-(3-methoxy-2-methylphenyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-yl)-2-oxa-5-azabicyclo[4.2.0]octane	Int-23 A-8 Method 4	39.7 mg 56% 100%	538.1	538.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 8.63 – 8.59 (m, 1H), 7.98 (s, 1H), 7.75 (td, <i>J</i> = 7.7, 1.8 Hz, 1H), 7.34 – 7.27 (m, 2H), 7.18 (d, <i>J</i> = 7.8 Hz, 1H), 7.07 – 7.00 (m, 2H), 6.85 (d, <i>J</i> = 8.2 Hz, 1H), 6.61 (d, <i>J</i> = 7.6 Hz, 1H), 4.22 (q, <i>J</i> = 7.3 Hz, 1H), 4.17 (t, <i>J</i> = 6.5 Hz, 1H), 4.02 (t, <i>J</i> = 6.5 Hz, 1H), 4.02 (t, <i>J</i> = 6.5 Hz, 1H).

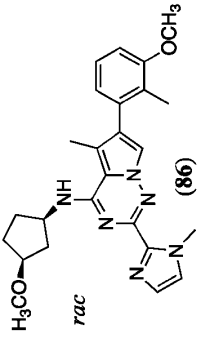
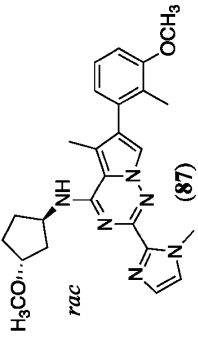
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
							= 6.7 Hz, 1H), 3.97 (s, 3H), 3.73 (s, 3H), 3.22 (s, 3H), 3.18 – 3.13 (m, 1H), 3.03 – 2.98 (m, 1H), 2.79 (t, <i>J</i> = 11.7 Hz, 1H), 2.67 (t, <i>J</i> = 10.8 Hz, 1H), 2.22 (dd, <i>J</i> = 11.9, 7.7 Hz, 1H), 1.76 (s, 3H), 1.61 (dt, <i>J</i> = 12.8, 6.7 Hz, 1H).
79		<i>rac</i> 6-(3-Methoxy-2-methylphenyl)- <i>N</i> -((1 <i>S</i> ,2 <i>R</i>)-2-methoxycyclopentyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-23 Method 4	37.9 56% 100%	510.2	510.0	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.36 (d, <i>J</i> = 7.2 Hz, 1H), 8.58 – 8.51 (m, 1H), 7.74 (s, 1H), 7.54 (td, <i>J</i> = 7.8, 1.9 Hz, 1H), 7.28 (s, 1H), 7.22 (td, <i>J</i> = 6.7, 1.8 Hz, 2H), 6.99 (d, <i>J</i> = 8.9 Hz, 2H), 6.83 (d, <i>J</i> = 7.8 Hz, 2H), 4.64 – 4.53 (m, 1H), 3.97 (s, 3H), 3.81 (d, <i>J</i> = 4.6 Hz, 1H), 3.79 (s, 3H), 3.24 (s, 3H), 2.09 – 2.03 (m, 1H), 1.85 – 1.78 (m, 5H), 1.72 (ddt, <i>J</i> = 13.0, 8.6, 4.8 Hz, 1H), 1.62 (ddq, <i>J</i> = 27.3, 12.3, 7.5 Hz, 2H).

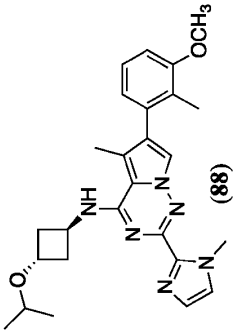
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
80		<i>rac</i> 6-(3-Methoxy-2-methylphenyl)- <i>N</i> -((3 <i>R</i> ,4 <i>R</i>)-4-methoxytetrahydrofuran-3-yl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5-(pyridin-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-23 Method 4	39.2 mg 57% 100%	512.2	512.2	¹ H NMR (600 MHz DMSO- <i>d</i> ₆) δ (ppm) 11.59 (d, <i>J</i> = 6.9 Hz, 1H), 8.58 – 8.54 (m, 1H), 7.78 (s, 1H), 7.55 (td, <i>J</i> = 7.8, 1.9 Hz, 1H), 7.31 – 7.28 (m, 1H), 7.26 – 7.20 (m, 2H), 7.00 (d, <i>J</i> = 9.0 Hz, 2H), 6.86 – 6.81 (m, 2H), 4.88 (p, <i>J</i> = 6.5 Hz, 1H), 4.12 (td, <i>J</i> = 5.2, 3.2 Hz, 1H), 4.08 (dd, <i>J</i> = 8.5, 6.6 Hz, 1H), 3.97 (s, 3H), 3.92 (dd, <i>J</i> = 9.9, 4.9 Hz, 1H), 3.84 (dd, <i>J</i> = 9.9, 3.3 Hz, 1H), 3.80 (s, 3H), 3.63 (dd, <i>J</i> = 8.5, 6.5 Hz, 1H), 3.29 (s, 3H), 1.81 (s, 3H).
81		6-(3-Methoxy-2-methylphenyl)- <i>N</i> -((1 <i>r</i> ,3 <i>r</i>)-3-methoxycyclobutyl)-5-(5-methoxypyridin-2-yl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-14 Method 4	17.2 mg 37% 100%	526.2	526.2	¹ H NMR (600 MHz DMSO- <i>d</i> ₆) δ (ppm) 11.42 (d, <i>J</i> = 5.9 Hz, 1H), 8.40 (d, <i>J</i> = 3.0 Hz, 1H), 7.72 (s, 1H), 7.28 (d, <i>J</i> = 1.1 Hz, 1H), 7.28 – 7.20 (m, 2H), 7.02 – 6.96 (m, 2H), 6.82 (dd, <i>J</i> = 11.6, 8.3 Hz, 2H), 4.60 (h, <i>J</i> = 6.5 Hz, 1H),

Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
82		6-(3-Methoxy-2-methylphenyl)-N-((1 <i>r</i> ,3 <i>r</i>)-3-methoxycyclobutyl)-5-(5-(2-methoxyethoxy)pyridin-2-yl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-15 Method 4	26.1 mg 57% 100%	570.3	570.2	4.12 – 4.05 (m, 1H), 4.00 – 3.95 (m, 3H), 3.83 – 3.78 (m, 6H), 3.17 (s, 3H), 2.41 (ddd, J = 12.8, 8.0, 4.4 Hz, 2H), 2.31 (dt, J = 12.2, 6.0 Hz, 2H), 1.81 (s, 3H).

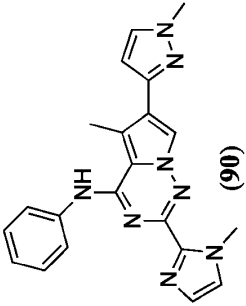
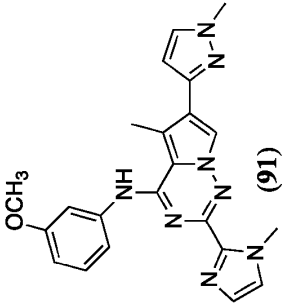
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
83		6-(3-Methoxy-2-methylphenyl)-N-((1 <i>r</i> ,3 <i>r</i>)-3-methoxycyclobutyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5-(5-propoxypyridin-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-16 Method 4	20.4 mg 41% 100%	554.3	554.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ (ppm) 11.45 (d, <i>J</i> = 6.0 Hz, 1H), 8.40 (d, <i>J</i> = 3.0 Hz, 1H), 7.72 (s, 1H), 7.29 (s, 1H), 7.27 – 7.20 (m, 2H), 7.00 (d, <i>J</i> = 8.6 Hz, 2H), 6.81 (dd, <i>J</i> = 17.9, 8.2 Hz, 2H), 4.59 (h, <i>J</i> = 5.9 Hz, 1H), 4.08 (ddd, <i>J</i> = 11.5, 6.8, 4.7 Hz, 1H), 3.99 (t, <i>J</i> = 6.5 Hz, 2H), 3.97 (s, 3H), 3.80 (s, 3H), 3.17 (s, 3H), 2.41 (ddd, <i>J</i> = 12.6, 7.9, 4.4 Hz, 2H), 2.30 (dd, <i>J</i> = 12.5, 6.1 Hz, 2H), 1.81 (s, 3H), 1.71 (h, <i>J</i> = 7.0 Hz, 2H), 0.95 (t, <i>J</i> = 7.4 Hz, 3H).
84		6-(3-Methoxy-2-methylphenyl)-N-((1 <i>s</i> ,3 <i>s</i>)-3-methoxycyclobutyl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-17 Method 4	30 mg 13% 100%	433.2	433.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 7.62 (s, 1H), 7.25 (d, <i>J</i> = 1.1 Hz, 1H), 7.20 (t, <i>J</i> = 7.9 Hz, 1H), 7.05 (d, <i>J</i> = 7.4 Hz, 1H), 6.99 – 6.94 (m, 2H), 6.77 (d, <i>J</i> = 7.5 Hz, 1H), 4.36 (h, <i>J</i> = 8.0 Hz, 1H), 3.93 (s, 3H), 3.81 (s, 3H), 3.67 (p, <i>J</i> =

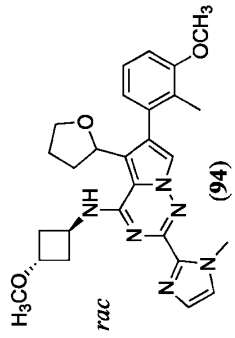
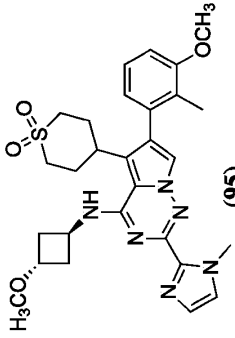
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
							7.2 Hz, 1H), 3.15 (s, 3H), 2.70 – 2.62 (m, 2H), 2.29 (s, 3H), 2.13 (dt, <i>J</i> = 11.7, 8.8 Hz, 2H), 1.98 (s, 3H).
85		6-(3-Methoxy-2-methylphenyl)- <i>N</i> -(((1 <i>r</i> ,3 <i>r</i>)-3-methoxycyclobutyl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-17 Method 4	4.9 mg 4.7% 99%	433.2	433.4	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 7.63 (s, 1H), 7.25 (s, 1H), 7.20 (t, <i>J</i> = 7.9 Hz, 1H), 7.04 (d, <i>J</i> = 6.5 Hz, 1H), 6.96 (d, <i>J</i> = 8.9 Hz, 2H), 6.78 (d, <i>J</i> = 7.6 Hz, 1H), 4.77 (q, <i>J</i> = 7.3 Hz, 1H), 4.03 (td, <i>J</i> = 6.8, 3.4 Hz, 1H), 3.94 (s, 3H), 3.82 (s, 3H), 3.16 (s, 3H), 2.45 – 2.42 (m, 2H), 2.35 – 2.32 (m, 2H), 2.31 (s, 3H), 1.99 (s, 3H).

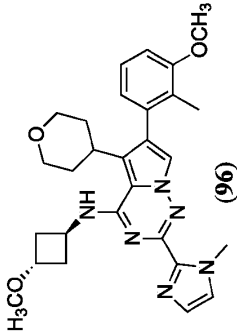
Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
86		<i>rac</i> 6-(3-Methoxy-2-methylphenyl)- <i>N</i> -((1 <i>R</i> ,3 <i>S</i>)-3-methoxycyclopentyl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-17 Method 4	34 mg 10.6% 100%	447.2	447.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 7.61 (s, 1H), 7.25 (d, <i>J</i> = 1.1 Hz, 1H), 7.20 (t, <i>J</i> = 7.9 Hz, 1H), 7.00 – 6.94 (m, 2H), 6.83 (d, <i>J</i> = 8.1 Hz, 1H), 6.77 (d, <i>J</i> = 7.6 Hz, 1H), 4.74 (d, <i>J</i> = 8.3 Hz, 1H), 3.94 (s, 3H), 3.92 (dt, <i>J</i> = 5.3, 2.6 Hz, 1H), 3.81 (s, 3H), 3.23 (s, 3H), 2.22 (s, 3H), 1.99 (s, 5H), 1.93 (d, <i>J</i> = 13.8 Hz, 1H), 1.83 (dt, <i>J</i> = 13.1, 7.4 Hz, 3H).
87		<i>rac</i> 6-(3-Methoxy-2-methylphenyl)- <i>N</i> -((1 <i>R</i> ,3 <i>R</i>)-3-methoxycyclopentyl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-17 Method 4	23.8 mg 8.9% 100%	447.2	447.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 7.61 (s, 1H), 7.25 (s, 1H), 7.20 (t, <i>J</i> = 7.9 Hz, 1H), 6.98 – 6.94 (m, 2H), 6.77 (d, <i>J</i> = 7.5 Hz, 1H), 6.68 (d, <i>J</i> = 7.6 Hz, 1H), 4.75 (h, <i>J</i> = 7.8 Hz, 1H), 3.95 (s, 3H), 3.89 (dq, <i>J</i> = 5.8, 3.0 Hz, 1H), 3.81 (s, 3H), 3.18 (s, 3H), 2.28 (s, 3H), 2.10 (dq, <i>J</i> = 14.1, 7.9 Hz, 2H), 2.05 – 1.99 (m, 1H), 1.99 (s, 3H), 1.86

Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
							(ddd, <i>J</i> = 14.0, 8.5, 5.9 Hz, 1H), 1.73 – 1.60 (m, 2H).
88		<i>N</i> -((1 <i>r</i> ,3 <i>r</i>)-3-Isopropoxycyclobutyl)-6-(3-methoxy-2-methylphenyl)-5-methyl-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-17 Method 4	29.2 mg 11.7% 97%	461.3	461.4	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 7.63 (s, 1H), 7.26 (s, 1H), 7.20 (t, <i>J</i> = 7.9 Hz, 1H), 7.01 – 6.94 (m, 3H), 6.78 (d, <i>J</i> = 7.6 Hz, 1H), 4.69 (d, <i>J</i> = 5.8 Hz, 1H), 4.28 (td, <i>J</i> = 6.9, 3.5 Hz, 1H), 3.94 (s, 3H), 3.82 (s, 3H), 3.54 (p, <i>J</i> = 6.1 Hz, 1H), 2.47 – 2.42 (m, 2H), 2.32 – 2.25 (m, 5H), 1.99 (s, 3H), 1.07 (d, <i>J</i> = 6.1 Hz, 6H).

Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
89		<i>rac</i> <i>N</i> -((1 <i>R</i> ,3 <i>R</i>)-3-isopropoxycyclopentyl)-6-(3-methoxy-2-methylphenyl)-5-methyl-1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-17 Method 4	50 mg 12.5% 100%	475.3	475.4	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 7.61 (s, 1H), 7.26 (d, <i>J</i> = 1.0 Hz, 1H), 7.20 (t, <i>J</i> = 7.9 Hz, 1H), 6.98 – 6.94 (m, 2H), 6.77 (d, <i>J</i> = 7.6 Hz, 1H), 6.67 (d, <i>J</i> = 7.7 Hz, 1H), 4.77 (h, <i>J</i> = 7.9 Hz, 1H), 4.12 (tt, <i>J</i> = 6.2, 3.4 Hz, 1H), 3.95 (s, 3H), 3.81 (s, 3H), 3.58 (hept, <i>J</i> = 5.7 Hz, 1H), 2.28 (s, 3H), 2.11 (dq, <i>J</i> = 13.2, 7.4 Hz, 1H), 2.04 – 1.96 (m, 2H), 1.99 (s, 3H), 1.86 (ddd, <i>J</i> = 13.7, 8.3, 6.2 Hz, 1H), 1.66 (dq, <i>J</i> = 12.5, 7.9 Hz, 1H), 1.56 (ddd, <i>J</i> = 12.7, 8.0, 4.2 Hz, 1H), 1.06 (dd, <i>J</i> = 6.1, 1.1 Hz, 6H).

Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
90		5-Methyl-2-(1-methyl-1H-imidazol-2-yl)-6-(1-methyl-1H-pyrazol-3-yl)-N-phenylpyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-17 Method 4	29 mg 23.3% 100%	385.2	385.2	¹ H NMR (500 MHz, DMSO- <i>d</i> ₆) δ (ppm) 8.71 (s, 1H), 8.05 (s, 1H), 7.75 – 7.70 (m, 3H), 7.38 (t, <i>J</i> = 7.9 Hz, 2H), 7.23 – 7.20 (m, 1H), 7.19 – 7.13 (m, 1H), 6.96 (d, <i>J</i> = 1.1 Hz, 1H), 6.57 (d, <i>J</i> = 2.2 Hz, 1H), 3.89 (s, 3H), 3.76 (s, 3H), 2.85 (s, 3H).
91		<i>N</i> -(3-Methoxyphenyl)-5-methyl-2-(1-methyl-1H-imidazol-2-yl)-6-(1-methyl-1H-pyrazol-3-yl)pyrrolo[2,1-f][1,2,4]triazin-4-amine	Int-17 Method 4	33.0 mg 24.7% 100%	415.2	415.2	¹ H NMR (600 MHz, DMSO- <i>d</i> ₆) δ (ppm) 8.64 (s, 1H), 8.06 (s, 1H), 7.73 (d, <i>J</i> = 2.2 Hz, 1H), 7.55 (t, <i>J</i> = 2.2 Hz, 1H), 7.32 – 7.22 (m, 3H), 6.97 (d, <i>J</i> = 1.1 Hz, 1H), 6.72 (ddd, <i>J</i> = 7.8, 2.6, 1.3 Hz, 1H), 6.57 (d, <i>J</i> = 2.2 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.78 (s, 3H), 2.84 (s, 3H).

Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
92		<i>rac</i> 6-(3-Methoxy-2-methylphenyl)- <i>N</i> -(((1 <i>r</i> ,3 <i>r</i>)-3-methoxycyclobutyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5-(tetrahydrofuran-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-26 Method 4	2.7 mg 3% 99%	489.2	489.2	
93		4-(6-(3-Methoxy-2-methylphenyl)-4-(((1 <i>r</i> ,3 <i>r</i>)-3-methoxycyclobutyl)amino)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-5-yl)tetrahydro-2 <i>H</i> -thiopyran 1,1-dioxide	Int-27 Method 4	2.3 mg 43% 96%	551.2	551.2	

Ex	Structure	Name	Final Step	Amount Yield Purity	Calc'd [M+1]	Found [M+1]	¹ H NMR
94		6-(3-Methoxy-2-methylphenyl)-N-((1 <i>r</i> ,3 <i>r</i>)-3-methoxycyclobutyl)-2-(1-methyl-1 <i>H</i> -imidazol-2-yl)-5-(tetrahydro-2 <i>H</i> -pyran-4-yl)pyrrolo[2,1- <i>f</i>][1,2,4]triazin-4-amine	Int-28 Method 4	75.9 mg 41% 100%	503.3	503.2	¹ H NMR (500 MHz, dms ^o) δ 7.51 (d, <i>J</i> = 2.2 Hz, 1H), 7.26 (s, 1H), 7.18 (t, <i>J</i> = 7.9 Hz, 1H), 6.97 (d, <i>J</i> = 9.7 Hz, 2H), 6.82 (t, <i>J</i> = 7.8 Hz, 2H), 4.73 – 4.66 (m, 1H), 4.05 (d, <i>J</i> = 6.8 Hz, 1H), 3.94 (d, <i>J</i> = 2.2 Hz, 3H), 3.82 (d, <i>J</i> = 2.2 Hz, 3H), 3.74 (m, 1H), 3.38 (d, <i>J</i> = 11.0 Hz, 4H), 3.17 (d, <i>J</i> = 2.3 Hz, 3H), 2.38 (d, <i>J</i> = 8.2 Hz, 4H), 1.92 (d, <i>J</i> = 2.2 Hz, 3H), 1.64 (s, 2H), 1.53 (s, 1H), 1.45 (s, 1H).

4.2 Biological Examples

[00936] Biological Example 1: Protocols for cell-based assays

[00937] Protocol for Phospho-Smad2/3 Inhibition Assay

[00938] This assay is referred to as the “Phospho-Smad2/3 Inhibition Assay” throughout this application.

[00939] Cell lines: Human tumor-derived pancreatic cancer cell line Panc-1 (expressing KRas G12D mutant) and mouse muscle myoblast C2C12 were purchased from American Type Culture Collection and grown in complete DMEM-High Glucose, supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL), and 10% heat-inactivated FBS at 37°C in a humidified incubator with 5% CO₂.

[00940] Method: Cells were plated at 350000 cells/well density in a 12-well plate, allowed 3 hours to adhere to the plate, then starved in the appropriate medium in the presence of 0.5% FBS overnight. The small molecules to be tested were added to the cells in the final concentration of 10 µM in the presence of 0.3% DMSO for 3 hours incubation at 37°C. For IC₅₀ value determination, serial dilutions of compounds were added to cells under the same conditions. Next, Panc-1 cells were stimulated with 10 ng/ml TGF-β1 for 1 hour, and C2C12 cells were stimulated with 10 ng/ml TGF-β1 for 20 minutes (recombinant human TGF-β1, R&D Systems). After stimulation cells were lysed with lysis buffer containing 1% Triton X-100, EDTA, and Halt™ Protease & Phosphatase Inhibitor Cocktail (Thermo Scientific). Protein concentration was assessed by BCA protein assay (Thermo Scientific). Phosphorylation level of Smad2/Smad3 was determined by western blot.

[00941] Western blot protocol: Equal amounts of protein (15-50 µg) were separated by SDS-PAGE and transferred to nitrocellulose membranes (Invitrogen by Thermo Fisher Scientific). The membrane was stained with Ponceau S Stain (Boston BioProducts) to verify uniform protein loading. Membranes were blocked with 10% milk and phosphorylation levels of Smad2/Smad3 were assessed by incubating overnight at 4°C with the following antibodies: Phospho-Smad2 (Ser465/467) and Phospho-Smad3 (Ser423/425), both from Cell Signaling Technology. Then the membranes were incubated with HRP-conjugated secondary antibody (Jackson ImmunoResearch, West Grove, PA). Bands were incubated in Amersham ECL Prime Western Blotting Detection Reagent (GE Healthcare) and visualized using the ChemiDoc MP imaging system (Bio-Rad).

[00942] Protocol for JNK Activation Assay

[00943] This assay is referred to as the “JNK Activation Assay” throughout this application.

[00944] Cell lines: Human tumor-derived pancreatic cancer cell line Panc-1 (expressing KRas G12C mutant) was purchased from American Type Culture Collection and grown in complete DMEM-High Glucose medium, supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL), and 10% heat-inactivated FBS at 37°C in a humidified incubator with 5% CO₂.

[00945] Method 1: Cells were plated at 350000 cells/well density in a 12-well plate, allowed 3 hours to adhere to the plate, then starved in the appropriate medium in the presence of 0.5% FBS overnight. The small molecules to be tested were added to the cells in the final concentration of 10 µM in the presence of 0.3% DMSO for 6 hours incubation at 37°C. For IC₅₀ value determination, serial dilutions of compounds were added to cells under the same conditions. Next, cells were stimulated with 1.5 ng/ml EGF for 15 minutes then cells were lysed with lysis buffer containing 1% Triton X-100, EDTA, and Halt™ Protease & Phosphatase Inhibitor Cocktail (Thermo Scientific). Protein concentration was assessed by BCA protein assay (Thermo Scientific). Phosphorylation level of JNK was determined by western blot.

[00946] Method 2: Cells were plated at 350000 cells/well density in a 12-well plate in the presence of 10% FBS. The next day small molecules to be tested were added to the cells in the final concentration of 10 µM in the presence of 0.3% DMSO for 6 hours incubation at 37°C. For IC₅₀ value determination, serial dilutions of compounds were added to cells under the same conditions. Next, cells were lysed with lysis buffer containing 1% Triton X-100, EDTA, and Halt™ Protease & Phosphatase Inhibitor Cocktail (Thermo Scientific). Protein concentration was assessed by BCA protein assay (Thermo Scientific). Phosphorylation level of JNK was determined by western blot.

[00947] Western blot protocol: Equal amounts of protein (15-50 µg) were separated by SDS-PAGE and transferred to nitrocellulose membranes (Invitrogen by Thermo Fisher Scientific). The membrane was stained with Ponceau S Stain (Boston BioProducts) to verify uniform protein loading. Membranes were blocked with 10% milk and phosphorylation levels of JNK were assessed by incubating overnight at 4°C with the antibody Phospho-SAPK/JNK (Thr183/Tyr185), from Cell Signaling Technology. Then the membranes were incubated with HRP-conjugated secondary antibody (Jackson ImmunoResearch, West Grove, PA). Bands were incubated in Amersham ECL Prime Western Blotting Detection Reagent (GE Healthcare) and

visualized using the ChemiDoc MP imaging system (Bio-Rad).

[00948] Protocol for MAPK p38 Activation Assay

[00949] This assay is referred to as the “MAPK p38 Activation Assay” throughout this application.

[00950] Cell lines: Human tumor-derived pancreatic cancer cell line Panc-1 (expressing KRas G12D mutant) was purchased from American Type Culture Collection and grown in complete DMEM-High Glucose medium, supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL), and 10% heat-inactivated FBS at 37°C in a humidified incubator with 5% CO₂.

[00951] Method 1: Cells were plated at 350000 cells/well density in a 12-well plate, allowed 3 hours to adhere to the plate, then starved in the appropriate medium in the presence of 0.5% FBS overnight. The small molecules to be tested were added to the cells in the final concentration of 10 µM in the presence of 0.3% DMSO for 6 hours incubation at 37°C. For IC₅₀ value determination, serial dilutions of compounds were added to cells under the same conditions. Next, cells were stimulated with 1.5 ng/ml EGF for 15 minutes then cells were lysed with lysis buffer containing 1% Triton X-100, EDTA, and Halt™ Protease & Phosphatase Inhibitor Cocktail (Thermo Scientific). Protein concentration was assessed by BCA protein assay (Thermo Scientific). Phosphorylation level of MAPK p38 was determined by western blot.

[00952] Method 2: Cells were plated at 350000 cells/well density in a 12-well plate in 10% FBS. The next day small molecules to be tested were added to the cells in the final concentration of 10 µM in the presence of 0.3% DMSO for 6 hours incubation at 37°C. For IC₅₀ value determination, serial dilutions of compounds were added to cells under the same conditions. Next, cells were lysed with lysis buffer containing 1% Triton X-100, EDTA, and Halt™ Protease & Phosphatase Inhibitor Cocktail (Thermo Scientific). Protein concentration was assessed by BCA protein assay (Thermo Scientific). Phosphorylation level of MAPK p38 was determined by western blot.

[00953] Western blot protocol: Equal amounts of protein (15-50 µg) were separated by SDS-PAGE and transferred to nitrocellulose membranes (Invitrogen by Thermo Fisher Scientific). The membrane was stained with Ponceau S Stain (Boston BioProducts) to verify uniform protein loading. Membranes were blocked with 10% milk and phosphorylation levels of MAPK p38 were assessed by incubating overnight at 4°C with the following antibody: Phospho-p38 MAPK (Thr180/Tyr182), from Cell Signaling Technology. Then the membranes were incubated with

HRP-conjugated secondary antibody (Jackson ImmunoResearch, West Grove, PA). Bands were incubated in Amersham ECL Prime Western Blotting Detection Reagent (GE Healthcare) and visualized using the ChemiDoc MP imaging system (Bio-Rad).

[00954] Protocol for Western Erk1/2 cell-based phosphorylation assay

[00955] This assay is referred to as the “Erk1/2 Phosphorylation Assay” throughout this application.

[00956] Cell lines: Human tumor-derived pancreatic cancer cell line Panc-1 (expressing KRas G12D mutant) was purchased from American Type Culture Collection and grown in complete DMEM-High Glucose medium, supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL), and 10% heat-inactivated FBS at 37°C in a humidified incubator with 5% CO₂.

[00957] Method 1: Cells were plated at 350000 cells/well density in a 12-well plate, allowed 3 hours to adhere to the plate, then starved in the appropriate medium in the presence of 0.5% FBS overnight. The small molecules to be tested were added to the cells in the final concentration of 10 µM in the presence of 0.3% DMSO for 6 hours incubation at 37°C. For IC₅₀ value determination, serial dilutions of compounds were added to cells under the same conditions. Next, cells were stimulated with 1.5 ng/ml EGF for 15 minutes then cells were lysed with lysis buffer containing 1% Triton X-100, EDTA, and Halt™ Protease & Phosphatase Inhibitor Cocktail (Thermo Scientific). Protein concentration was assessed by BCA protein assay (Thermo Scientific). Phosphorylation level of Erk1/2 was determined by western blot.

[00958] Method 2: Cells were plated at 350000 cells/well density in a 12-well plate in 10% FBS. The next day small molecules to be tested were added to the cells in the final concentration of 10 µM in the presence of 0.3% DMSO for 6 hours incubation at 37°C. For IC₅₀ value determination, serial dilutions of compounds were added to cells under the same conditions. Next, cells were lysed with lysis buffer containing 1% Triton X-100, EDTA, and Halt™ Protease & Phosphatase Inhibitor Cocktail (Thermo Scientific). Protein concentration was assessed by BCA protein assay (Thermo Scientific). Phosphorylation level of Erk1/2 was determined by western blot.

[00959] Western blot protocol: Equal amounts of protein (15-50 µg) were separated by SDS-PAGE and transferred to nitrocellulose membranes (Invitrogen by Thermo Fisher Scientific). The membrane was stained with Ponceau S Stain (Boston BioProducts) to verify uniform protein loading. Membranes were blocked with 10% milk and phosphorylation levels of Erk1/2 were

assessed by incubating overnight at 4°C with anti-phospho-p44/42 (Thr202/Tyr204) antibody (Cell Signaling) followed by HRP-conjugated secondary antibody (Jackson ImmunoResearch, West Grove, PA). Bands were incubated in Amersham ECL Prime Western Blotting Detection Reagent (GE Healthcare) and visualized using the ChemiDoc MP imaging system (Bio-Rad).

[00960] Protocol for Western Akt cell-based phosphorylation assay

[00961] This assay is referred to as the “Akt Phosphorylation Assay” throughout this application.

[00962] Human tumor-derived pancreatic cancer cell line Panc-1 (expressing KRas G12D mutant) was purchased from American Type Culture Collection and grown in complete DMEM-High Glucose supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL), and 10% heat-inactivated FBS at 37°C in a humidified incubator with 5% CO₂.

[00963] Method 1: Cells were plated at 350000 cells/well density in a 12-well plate, allowed 3 hours to adhere to the plate, then starved in the appropriate medium in the presence of 0.5% FBS overnight. The small molecules to be tested were added to the cells in the final concentration of 10 µM in the presence of 0.3% DMSO for 6 hours incubation at 37°C. Next, cells were stimulated with 1.5 ng/ml EGF for 15 minutes then cells were lysed with lysis buffer containing 1% Triton X-100, EDTA, and Halt™ Protease & Phosphatase Inhibitor Cocktail (Thermo Scientific). Protein concentration was assessed by BCA protein assay (Thermo Scientific). Phosphorylation level of Akt was determined by western blot.

[00964] Method 2: Cells were plated at 350000 cells/well density in a 12-well plate in 10% FBS. The next day small molecules to be tested were added to the cells in the final concentration of 10 µM in the presence of 0.3% DMSO for 6 hours incubation at 37°C. For IC₅₀ value determination, serial dilutions of compounds were added to cells under the same conditions. Next, cells were lysed with lysis buffer containing 1% Triton X-100, EDTA, and Halt™ Protease & Phosphatase Inhibitor Cocktail (Thermo Scientific). Protein concentration was assessed by BCA protein assay (Thermo Scientific). Phosphorylation level of Akt was determined by western blot.

[00965] Western blot protocol: Equal amounts of protein (15-50 µg) were separated by SDS-PAGE and transferred to nitrocellulose membranes (Invitrogen by Thermo Fisher Scientific). The membrane was stained with Ponceau S Stain (Boston BioProducts) to verify uniform protein loading. Membranes were blocked with 10% milk and phosphorylation levels of Akt were

assessed by incubating overnight at 4°C with anti-phospho-Akt (Ser473) antibody (Cell Signaling) followed by HRP-conjugated secondary antibody (Jackson Immunoresearch, West Grove, PA). Bands were incubated in Amersham ECL Prime Western Blotting Detection Reagent (GE Healthcare) and visualized using the ChemiDoc MP imaging system (Bio-Rad).

[00966] **Tables 1 and 2** shows inhibition data for selected compounds tested in one or more of the cellular assays described above.

[00967] Protocol for mouse TNF-alpha and IL6 quantification assay

[00968] These assays are referred to as the “IL-6 Quantification Assay” and the “TNF-alpha Quantification Assay”, respectively, throughout this application.

[00969] Cell lines: Abelson murine leukemia virus transformed macrophage cell line RAW 264.7 was purchased from ATCC and grown in complete DMEM-High Glucose medium supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL), and 10% heat-inactivated FBS at 37°C in a humidified incubator with 5% CO₂.

[00970] Method: Cells were plated at 40000 cells/well density in a 96-wells plate. After a 3-hour incubation, macrophages were starved with DMEM plus 0.5% FBS o/n. The next day the small molecules to be tested were added to the cells in the final concentration of 30 µM (with 0.3% DMSO) 3 hours prior to LPS stimulation (100 ng/ml). After LPS stimulation cells were incubated at 37°C for 16h. At the end of the incubation period, culture media were collected and production of LPS-induced TNFα and IL6 cytokine was measured using ELISA detection kits.

[00971] Sandwich ELISA: The ELISA Immunoassays Quantikine Mouse TNF-alpha (catalog number MTA00B) and IL6 (catalog number M6000B) were purchased from R&D Systems Inc., Minneapolis, MN. These 4.5 hours solid phase ELISAs were used to measure mouse TNF-alpha or IL6 levels in macrophages culture supernatants. Assays were executed according to the manufacturer specifications.

[00972] Protocol for proliferation assay

[00973] This assay is referred to as the “Proliferation Assay” or “Cell Viability Assay” throughout this application.

[00974] Cell lines: Human tumor-derived cell lines were purchased from American Type Culture Collection. Human tumor-derived pancreatic cancer cell line MiaPaca-2 (expressing KRAS G12C mutant) and Panc-1 (expressing KRas G12D mutant), and Human non-small cell lung cancer (NSCLC) cell line A549 (expressing KRas G12S mutant) were grown in complete

DMEM-High Glucose medium. Human colon cancer cell line SW-620 (expressing KRas G12V mutant) was grown in RPMI 1640 medium. All cell lines were supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL), and 10% heat-inactivated FBS at 37°C in a humidified incubator with 5% CO₂.

[00975] Method: Cells were plated at 2000 to 5000 cells/well density in 96-wells plate and cultured overnight. Small molecules to be tested were added to the cells in the final concentration of 10 µM in the presence of 0.3% DMSO and 10% FBS and incubated for 2-4 days at 37°C in a humidified incubator with 5% CO₂. For IC₅₀ value determination, serial dilutions of compounds were added to cells under the same conditions.

[00976] Assay: At the end of the incubation period, cell viability was determined using the CellTiter 96® Aqueous One Solution Cell Proliferation Assay according to manufacturer specifications (Promega, Madison, WI). The percentage of small molecules inhibition of cellular proliferation was calculated from raw data.

[00977] **Tables 1 and 2** show the data for these selected compounds tested in one or more of the cellular assays described above, such as in Human tumor-derived pancreatic cancer cell line Panc-1.

Table 1: Inhibition of Smad2/3, JNK, and MAPK p38 (at 10 µM), each in Panc-1 pancreatic cancer cell line

Compound	% inh of Smad2/3 phosphorylation in Panc-1	%inh of JNK in Panc-1	%inh of MAPK p38 in Panc-1
1	A*	H*	F*
2	B*	H*	H*
3	0	H*	H*
4	B*	H*	H*
5	A*	H*	F*
6	A	H*	F*
7	B*	H*	H*
8	A	F	E
9	0	ND	ND
10	A*	ND	ND

Compound	% inh of Smad2/3 phosphorylation in Panc-1	%inh of JNK in Panc-1	%inh of MAPK p38 in Panc-1
11	0	ND	ND
12	D*	ND	ND
13	0	ND	ND
14	C*	ND	ND
15	0	ND	ND
16	A*	ND	ND
17	A*	ND	ND
18	A*	ND	ND
19	D	ND	ND
20	D	ND	ND
21	D	ND	ND
22	A*	ND	ND
23	A	ND	ND
24	A	ND	ND
25	D*	ND	ND
26	D*	ND	ND
27	B	ND	ND
28	A*	ND	ND
29	D	ND	ND
31	D*	ND	ND
32	D*	ND	ND
33	D*	ND	ND
34	A	ND	ND
35	A*	ND	ND
36	A*	ND	ND
37	C*	ND	ND

Compound	% inh of Smad2/3 phosphorylation in Panc-1	%inh of JNK in Panc-1	%inh of MAPK p38 in Panc-1
38	A	ND	ND
39	A	ND	ND
40	A	ND	ND
47	B	ND	ND
48	A	ND	ND
49	D	ND	ND
51	D	ND	ND
52	C	ND	ND
53	C	ND	ND
54	A*	ND	ND
55	B*	ND	ND
56	C	ND	ND
57	A*	ND	ND
58	C	ND	ND
59	A*	ND	ND
60	A	ND	ND
61	C	ND	ND
62	B	ND	ND
63	D	ND	ND
64	D	ND	ND
65	D	ND	ND
66	A	ND	ND
67	A*	ND	ND
68	D	ND	ND
70	A	ND	ND
71	A*	ND	ND

Compound	% inh of Smad2/3 phosphorylation in Panc-1	%inh of JNK in Panc-1	%inh of MAPK p38 in Panc-1
72	A*	ND	ND
73	A*	ND	ND
74	A*	ND	ND
75	C*	ND	ND
76	B*	ND	ND
77	D	ND	ND
78	C*	ND	ND
79	D	ND	ND
80	D	ND	ND
81	D	ND	ND
82	A	ND	ND
83	A	ND	ND
84	A	ND	ND
85	A*	ND	ND
86	C	ND	ND
87	C	ND	ND
88	D	ND	ND
89	D	ND	ND
90	D*	ND	ND
91	0	ND	ND
92	A	ND	ND
93	A	ND	ND
94	D	ND	ND

0 = 0% inhibition, A = 1-25% inhibition, B = 26-45% inhibition, C = 46-75% inhibition, D = 76-100% inhibition, E = 1-30% inhibition, F = 31-74% inhibition, G = 75-99% inhibition, H = 100% inhibition, A* = 1-25% activation, B* = 26-45% activation, C* = 46-75% activation, D* = 76-100% activation, E* = 1-30% activation, F* = 31-74% activation, G* = 75-99% activation, H* $\geq$ 100% activation, ND = not determined.

Table 2: % Inhibition at 10 μ M of Erk1/2, Akt, IL-6, TNF-alpha and MiaPaca-2**proliferation**

Compound	% inh of Erk1/2 phosphorylation in Panc-1		% inh of Akt phosphorylation in Panc-1		Proliferation in MiaPaca-2: IC50 (μ M)	IL-6: % inh.	TNF α : % inh.
	+ EGF	+ serum	+ EGF	+ serum			
1	D*	ND	D*	ND	K	F	E
2	D*	ND	D*	ND	I	E	E
3	D*	ND	D*	ND	K	E	0
4	D*	ND	D*	ND	K	G	E
5	D*	ND	D*	ND	I	E	E
6	D*	ND	D*	ND	I	0	E
7	D*	ND	D*	ND	I	0	E
8	B	ND	D*	ND	I	0	E
9	ND	C*	ND	D*	L	G	0
10	ND	B*	ND	D*	L	G	0
11	ND	D*	ND	D*	L	H	E
12	ND	0	ND	D*	K	F	0
13	ND	C*	ND	C*	J	ND	ND
14	ND	A*	ND	A	I	ND	ND
15	ND	B*	ND	C*	I	ND	ND
16	ND	D*	ND	C*	L	H	E
17	ND	A	ND	B	I	G	E
18	ND	D*	ND	D*	L	F	E
19	ND	D	ND	D	K	H	E
20	ND	D	ND	D	I	H	H
21	ND	C	ND	B	I	E	E
22	ND	A*	ND	C*	K	ND	ND
23	ND	C*	ND	C*	J	ND	ND
24	ND	A*	ND	A*	I	ND	ND

Compound	% inh of Erk1/2 phosphorylation in Panc-1		% inh of Akt phosphorylation in Panc-1		Proliferation in MiaPaca-2: IC50 (uM)	IL-6: % inh.	TNF α : % inh.
	+ EGF	+ serum	+ EGF	+ serum			
25	ND	A*	ND	A	I	ND	ND
26	ND	A	ND	A*	I	ND	ND
27	ND	D*	ND	D*	L	ND	ND
28	ND	D*	ND	D*	K	ND	ND
29	ND	A	ND	B*	I	ND	ND
31	ND	0	ND	C*	K	ND	ND
32	ND	C*	ND	D*	J	ND	ND
33	ND	0	ND	A*	I	ND	ND
34	ND	A*	ND	B*	I	ND	ND
35	ND	A	ND	A*	I	ND	ND
36	ND	D*	ND	C*	L	ND	ND
37	ND	D*	ND	D*	L	ND	ND
38	ND	D*	ND	D*	L	ND	ND
39	ND	B*	ND	D*	L	ND	ND
40	ND	D*	ND	D*	L	ND	ND
47	ND	0	ND	D*	J	ND	ND
48	ND	A*	ND	A*	K	ND	ND
49	ND	C	ND	C	K	ND	ND
51	ND	D	ND	D	I	ND	ND
52	ND	A	ND	A*	J	ND	ND
53	ND	C	ND	C	I	ND	ND
54	ND	D*	ND	D*	I	ND	ND
55	ND	D*	ND	D*	I	ND	ND
56	ND	D	ND	C	I	ND	ND
57	ND	D*	ND	D*	L	ND	ND
58	ND	A*	ND	A*	I	ND	ND

Compound	% inh of Erk1/2 phosphorylation in Panc-1		% inh of Akt phosphorylation in Panc-1		Proliferation in MiaPaca-2: IC50 (uM)	IL-6: % inh.	TNF α : % inh.
	+ EGF	+ serum	+ EGF	+ serum			
59	ND	B*	ND	C*	I	ND	ND
60	ND	C*	ND	C*	I	ND	ND
61	ND	D*	ND	D*	I	ND	ND
62	ND	D*	ND	D*	L	ND	ND
63	ND	B	ND	A	I	ND	ND
64	ND	B	ND	A	I	ND	ND
65	ND	B*	ND	A*	I	ND	ND
66	ND	B	ND	D*	I	ND	ND
67	ND	C	ND	C*	I	ND	ND
68	ND	C	ND	A*	J	ND	ND
70	ND	A*	ND	B*	I	ND	ND
71	ND	0	ND	0	I	ND	ND
72	ND	A*	ND	B*	I	ND	ND
73	ND	0	ND	0	I	ND	ND
74	ND	A*	ND	C*	I	ND	ND
75	ND	D*	ND	D*	K	ND	ND
76	ND	B*	ND	D*	I	ND	ND
77	ND	A*	ND	C*	I	ND	ND
78	ND	A*	ND	A*	I	ND	ND
79	ND	D	ND	C	I	ND	ND
80	ND	C	ND	C	J	ND	ND
81	ND	C	ND	C	J	ND	ND
82	ND	C	ND	A	K	ND	ND
83	ND	D*	ND	D*	K	ND	ND
84	ND	A*	ND	D*	I	ND	ND
85	ND	B*	ND	A*	K	ND	ND

Compound	% inh of Erk1/2 phosphorylation in Panc-1		% inh of Akt phosphorylation in Panc-1		Proliferation in MiaPaca-2: IC50 (uM)	IL-6: % inh.	TNF α : % inh.
	+ EGF	+ serum	+ EGF	+ serum			
86	ND	A	ND	D*	I	ND	ND
87	ND	A	ND	D*	J	ND	ND
88	ND	B*	ND	D*	I	ND	ND
89	ND	C	ND	B*	I	ND	ND
90	ND	0	ND	0	I	ND	ND
91	ND	0	ND	D*	I	ND	ND
92	ND	A	ND	B*	I	ND	ND
93	ND	B	ND	A	I	ND	ND
94	ND	D	ND	D	J	ND	ND

0 = 0% inhibition, A = 1-25% inhibition, B = 26-49% inhibition, C = 50-84% inhibition, D = 85-100% inhibition,

A* = 1-25% activation, B* = 26-49% activation, C* = 46-84% activation, D* = 85-100% activation;

E = 1-24% inhibition, F = 25-49% inhibition, G = 50-74% inhibition, H = 75-100% inhibition, E* = 1-24%

activation, F* = 25-49% activation, G* = 50-74% activation, H* = 75-100% activation;

I = > 1 uM IC₅₀, J = 0.51-1 uM IC₅₀, K = 0.15-0.5 uM IC₅₀, L = < 0.15 uM IC₅₀, ND = not determined.

[00978] **Biological Example 2: Cell-Based Proliferation Following Incubation with Compound**

[00979] Protocol for proliferation assay

[00980] This assay is referred to as the “Proliferation Assay” or “Cell Viability Assay” throughout this application.

[00981] Cell lines: these Human tumor-derived cell lines were purchased from American Type Culture Collection. Human tumor-derived pancreatic cancer cell line MiaPaca-2 (expressing KRAS G12C mutant) and Panc-1 (expressing KRas G12D mutant), and Human melanoma cell line A375 (wild type Kras) were grown in complete DMEM-High Glucose medium. Human non-small cell lung cancer (NSCLC) cell lines NCI-H727 (expressing KRas G12V mutant), NCI-H358 (expressing KRas G12C mutant), and Human tumor-derived multiple myeloma cell line MM.1R (expressing wild type KRAS), and Human derived myeloma RPMI8226 (expressing wild type KRas), and Human derived Acute Myeloid Leukemia (AML)

Kasumi-1 (expressing wild type KRas), were grown in RPMI 1640 medium. Human tumor-derived breast cancer cell line BT-549 (expressing wild type KRAS) was grown in RPMI 1640 medium in the presence of 11.8U insulin. The colon cancer cell line GP2d (expressing KRas G12D mutant) was purchased from MilliporeSigma and grown in DMEM-High Glucose medium. All cell lines were supplemented with penicillin (100 U/mL), streptomycin (100 µg/mL), and 10% heat-inactivated FBS at 37°C in a humidified incubator with 5% CO₂.

[00982] Method: Cells were plated at 2000 to 5000 cells/well density in 96-wells plate and cultured overnight. Small molecules that were tested were added to the cells in the final concentration of 10 µM in the presence of 0.3% DMSO and 10% FBS, and incubated for 2-4 days at 37°C in a humidified incubator with 5% CO₂. For IC₅₀ value determination, serial dilutions of compounds were added to cells under the same conditions.

[00983] Assay: At the end of the incubation period, cell viability was determined using the CellTiter 96® Aqueous One Solution Cell Proliferation Assay according to manufacturer specifications (Promega, Madison, WI). The percentage of small molecules inhibition of cellular proliferation was calculated from raw data.

[00984] **Table 3** shows data for these selected compounds tested in one or more of the cellular assays described above, such as in Human tumor-derived pancreatic cancer cell line Panc-1.

Table 3: Proliferation assay IC₅₀ data

Cell Line	Tumor Type	KRas mutation	Compound 9 IC ₅₀ (uM)	Compound 11 IC ₅₀ (uM)
Kasumi-1	Acute Myloid Leukemia (AML)	WT	P	P
BT-549	Breast (TNBC)	WT	ND	M
GP2d	colorectal	G12D	ND	M
A375	melanoma	WT	N	N
MM.1R	Multiple Myeloma	WT	P	P
IM.9	Multiple Myeloma	WT	O	N
RPMI8226	myeloma	WT	P	P
NCI-H358	NSCLC	G12C	ND	N
NCI-H727	NSCLC	G12V	P	P
MiaPaca-2	pancreatic	G12C	N	N

Cell Line	Tumor Type	KRas mutation	Compound 9 IC ₅₀ (uM)	Compound 11 IC ₅₀ (uM)
Panc1	pancreatic	G12D	ND	M

I = > 1 uM IC₅₀, J = 1-0.51 uM IC₅₀, K = 0.5-0.15 uM IC₅₀, L = < 0.15 uM – 50 nM IC₅₀,

M = 50-10 nM IC₅₀, N = <10-1 nM IC₅₀, O = < 1-0.1 nM IC₅₀, P = < 0.1 nM IC₅₀, ND = not determined

[00985] Biological Example 3: Ras GTP binding domain inhibition assay

[00986] The assays described in Example 3 are collectively referred to as the “Ras Superfamily Assay” throughout this application.

[00987] A Ras Superfamily Activity Assay (as disclosed in International Application No. PCT/US2018/038613, filed June 20, 2018, which is incorporated by reference in its entirety) was used as a specific assay to evaluate compounds against the following for the following Ras Superfamily proteins: KRas wild type, KRas G12D mutant, and Rac-1.

[00988] Buffer-I:

[00989] 25 mM Tris-HCl, pH 7.4

[00990] 27 mM KCl

[00991] 137 mM NaCl

[00992] 1 mM MgCl₂

[00993] 1 mM DTT

[00994] Buffer-II:

[00995] 50 mM Tris-HCl, pH 7.0

[00996] 1 mM MgCl₂

[00997] 1 mM DTT

[00998] The small GTPases proteins: KRas wild type, KRas G12D mutants, and Rac-1, were expressed as His-tagged proteins. In addition, the Guanosine nucleotide Exchange Factor (GEF) Sos protein (residues 556-1049) was expressed as a His-tagged protein. In cells, the guanine nucleotide exchange factor Sos protein promotes activation of Ras proteins by stimulating an exchange of GDP for GTP. The inclusion of Sos to the Ras GTP binding domain inhibition assay may be considered as an alternative representation of physiological cellular conditions for evaluating the inhibitory activity of some of the tested small molecules.

[00999] For the assay, all purified small GTPases proteins were diluted in Buffer-I or Buffer-II to a final concentration of 10-30 µg/mL. 200 µL of each diluted protein was added to a nickel-

coated 96-well plate and incubated overnight at 4⁰ C. Then the protein solution was discarded and 200 μ L of Buffer-I or Buffer-II was added to each well in the presence of 1% DMSO. Compounds to be tested were added to the protein-coated wells at final concentration of 20 μ M, and incubated for 3 hours at room temperature with and without 10-30 μ g/mL of Sos added to the final hour of the incubation. When performing IC₅₀ measurements a serial dilution of all tested concentrations was added. Then Cy3-GTP or Cy5-GTP was added to each well to a final concentration of 100 nM. The labeled GTP was incubated for 45 minutes at room temperature. Following GTP incubation, wells were washed 3X in Buffer-I or Buffer-II and 200 μ L of Buffer-I or Buffer-II was added to each well. Following washes, the amount of bound labeled-GTP was measured using a SpectraMax M3 (Molecular Devices).

[001000] **Table 4** shows % inhibition data for selected compounds tested in the screening assays described above.

Table 4: % Inhibition at 20 μ M of K-Ras mutant and wild-type protein, and Rac-1 protein

Compound	KRas wild type: % inh.	KRas wild type + SOS: % inh.	KRas G12D mutant: % inh.	KRas G12D mutant + SOS: % inh.	Rac-1: % inh.
1	D	D	D	D	D
2	D	D	D	D	D
3	D	D	C	C	C
4	C	C	D	D	D
5	0	B	B	B	A
6	0	0	A	A	A
7	A	A	A	A	A
8	0	A	A	A	A
9	C	C	C	A	C
10	D	D	D	D	C
11	D	D	D	D	D
12	C	D	D	D	D
13	D	D	D	D	D
14	A	0	B	A	A

Compound	KRas wild type: % inh.	KRas wild type + SOS: % inh.	KRas G12D mutant: % inh.	KRas G12D mutant + SOS: % inh.	Rac-1: % inh.
15	A	A	B	B	B
16	D	D	D	D	D
17	A	A	A	A	A
18	D	D	D	D	D
19	B	A	B	A	A
20	B	A	B	A	B
21	0	0	A	A	0
22	C	C	D	D	D
23	D	D	D	C	D
24	D	D	D	D	D
25	0	A	A	0	0
26	A	0	A	A	B
29	A	A	A	A	A
31	0	0	B	B	C
32	D	D	C	C	D
33	0	A	B	A	C
34	A	0	0	0	0
35	A	0	0	0	0
36	D	C	D	D	D
37	D	D	D	D	D
38	D	D	D	D	D
39	D	D	D	D	D
40	C	B	C	D	C
47	A	A	B	B	B
48	B	A	A	A	A
49	A	A	A	A	A
51	A	A	B	A	A

Compound	KRas wild type: % inh.	KRas wild type + SOS: % inh.	KRas G12D mutant: % inh.	KRas G12D mutant + SOS: % inh.	Rac-1: % inh.
52	A	0	B	A	D
53	A	0	A	0	A
54	0	A	B	A	B
55	0	A	B	A	A
56	0	A	B	A	B
57	D	D	D	D	D
58	A	A	B	A	B
59	A	0	0	0	A
60	0	0	0	0	A
61	0	0	0	0	A
62	D	D	D	D	D
63	0	0	A	0	A
64	0	0	A	0	0
65	0	0	A	0	A
66	A	A	A	0	0
67	A	A	0	A	0
68	0	A	0	0	A
70	0	0	0	0	0
71	0	A	A	A	A
72	A	A	0	A	A
73	0	0	0	0	A
74	A	B	A	A	A
75	B	B	D	C	D
76	0	A	A	0	0
77	0	0	0	0	0
78	A	A	0	0	0
79	A	A	B	B	A

Compound	KRas wild type: % inh.	KRas wild type + SOS: % inh.	KRas G12D mutant: % inh.	KRas G12D mutant + SOS: % inh.	Rac-1: % inh.
80	A	A	A	B	A
81	A	A	A	A	B
82	0	0	0	0	0
83	A	0	B	A	0
84	B	B	0	C	B
85	B	A	B	B	B
86	C	B	B	C	C
87	B	B	0	C	B
88	B	A	A	A	B
89	A	0	0	A	A
90	0	0	A	A	A
91	0	0	A	A	B
92	D	D	D	D	D
93	0	A	A	0	0
94	A	A	A	A	0

0 = 0% inhibition, A = 1-25% inhibition, B = 26-49% inhibition, C = 50-75% inhibition, D = 76-100% inhibition,

ND = not determined

[001001] Biological Example 4: Kinetic Solubility

[001002] Kinetic solubility assay in pH 7.4 Buffer + 2% DMSO ("Kinetic Solubility Assay") was performed according to the following protocol: Briefly, using a 20 mM stock solution of the tested compounds in 100% DMSO, dilutions were prepared to a theoretical concentration of 400 μ M in duplicates in phosphate-buffered saline pH 7.4 (138 mM NaCl, 2.7 mM KCl, 10 mM K-phosphate) with 2% final DMSO. The tested compounds dilutions in PBS were further allowed to equilibrate at 25°C on a thermostatic shaker for two hours and then filtered through HTS filter plates using a vacuum manifold. The filtrates of the test compounds were diluted 2-fold with acetonitrile with 2% DMSO before measuring.

[001003] In parallel, using a 20 mM stock solution of the tested compounds in 100% DMSO,

dilutions were prepared to theoretical concentrations of 0 μM (blank), 10 μM , 25 μM , 50 μM , 100 μM , and 200 μM in 50% acetonitrile/PBS with 2% final DMSO to generate calibration curves. Ondansetron was used as a reference compound to control proper assay performance. 200 μL of each sample was transferred to a 96-well plate and measured in the 230-550 nm range with a 5 nm step.

[001004] The concentrations of compounds in PBS filtrate are calculated using a dedicated Microsoft Excel calculation script. Proper absorbance wavelengths for calculations are selected for each compound manually based on absorbance maximums (absolute absorbance unit values for the minimum and maximum concentration points within the 0 – 3 OD range). Each final dataset is visually evaluated by the operator, and goodness of fit (R^2) is calculated for each calibration curve. The effective range of this assay is approximately 2-400 μM and the compounds returning values close to the upper limit of the range may have higher actual solubility (e.g., 5'-deoxy-5-fluorouridine).

[001005] **Table 5** shows kinetic solubility data for selected compounds tested in the Kinetic Solubility assay described above.

Table 5: Kinetic Solubility in pH 7.4 Buffer + 2% DMSO

Compound	Solubility (μM)
9	C
11	D
27	A
38	B
40	B

A denotes < 10 μM , B denotes 10 – 30 μM , C denotes > 30 μM , D denotes > 100 μM .

[001006] Biological Example 5: Assessment of Metabolic Stability in Mouse Liver Microsomes

[001007] Metabolic Stability Assay: Microsomal incubations were carried out in 96-well plates in 5 aliquots of 30 μL each (one for each time point). Liver microsomal incubation medium comprised of phosphate buffer (100 mM, pH 7.4), MgCl_2 (3.3 mM), NADPH (3 mM), glucose-6-phosphate (5.3 mM), glucose-6-phosphate dehydrogenase (0.67 units/ml) with 0.42 mg of liver microsomal protein per mL. In the control reactions the NADPH-cofactor system was substituted with phosphate buffer. Test compounds (2 μM , final solvent concentration 1.6

(%) were incubated with microsomes at 37 °C, shaking at 100 rpm. Each reaction was performed in duplicates. Five time points over 40 minutes were analyzed. The reactions were stopped by adding 5 volumes of methanol containing internal standard to incubation aliquots, followed by protein sedimentation by centrifuging at 5500 rpm for 4 minutes. Supernatants were analyzed using the HPLC system coupled with tandem mass spectrometer.

[001008] The elimination constant (k_{el}), half-life ($t_{1/2}$) and intrinsic clearance (Cl_{int}) were determined in plot of $\ln(AUC)$ versus time, using linear regression analysis:

$$k_{el} = -slope \qquad t_{1/2} = \frac{0.693}{k} \qquad Cl_{int} = \frac{0.693}{t_{1/2}} \times \frac{\mu l_{incubation}}{mg_{microsomes}}$$

In order to indicate the quality of the linear regression analysis, the R (correlation coefficient) values are provided. In some cases, the last time point is excluded from the calculations to ensure acceptable logarithmic linearity of decay.

[001009] **Table 6** shows metabolic stability data for selected compounds tested in the Mouse Liver Microsome Metabolic Stability assay described above.

Table 6: Mouse Liver Microsome Metabolic Stability Assay

Compound	t _{1/2} (min)
9	A
11	B

A denotes < 10 min, B denotes > 10 min.

[001010] Biological Example 6: Assessment of Pharmacokinetics in Mouse (Balb C)

[001011] In Vivo PK/PD Procedures:

[001012] Animals (mouse) are fed a standard laboratory rodent diet and housed in individual cages on a 12-hour light and 12-hour dark cycle with room temperature maintained at $22 \pm 30^{\circ}\text{C}$ and relative humidity at $50 \pm 20\%$. Animals are typically fasted overnight before dosing, with food returned after the 6-hour blood samples are obtained. Water is provided *ad libitum* throughout the study.

[001013] The dosing of each test compound was in a solution formulation. Three animals are dosed *via* gavage needle for oral administration. All blood samples (30-50 μL per sample) are taken *via* saphenous vein at 15 and 30 min and 1, 2, 4, 6, 8, 10, and 24 h after dosing. Blood samples are collected in Greiner MiniCollect K2EDTA tubes, placed on ice, and within 30

minutes, centrifuged at 15,000g for 5 min to obtain plasma samples. All plasma samples are stored at -70°C until analysis.

[001014] Bioanalysis of PK/PD Samples:

[001015] Plasma samples are prepared as follows. Three volumes of acetonitrile containing internal standard is added to one volume of plasma to precipitate proteins. Samples are centrifuged (3000 g for 10 min) and supernatant removed for analysis by LC-MS/MS.

Calibration standards and quality controls are made by preparation of a 1 mg/mL stock solution in methanol and subsequently a series of working solutions in methanol : water (1:1, v/v) which are spiked into blank plasma to yield a series of calibration standard samples in the range of 1.0 ng/mL to 10 $\mu\text{g/mL}$ and quality control samples at three concentration levels (low, middle and high). All incurred PK/PD plasma samples are treated identically to the calibration standards and quality control samples. LC-MS/MS analysis is performed utilizing multiple reaction monitoring for detection of characteristic ions for each drug candidate, additional related analytes and internal standard.

[001016] Pharmacokinetic Data Analysis:

[001017] The bioanalytical assay used a Shimadzu HPLC with mobile phases **A**: 0.1% formic acid in water and **B**: 0.1% formic acid in acetonitrile. Quantification of dosed compound was by an AB/MDS Sciex MS/MS System using Multiple Reaction Monitoring (MRM) positive ions. Plasma concentrations are measured as described above to determine a concentration vs. time profile. The area under the plasma concentration vs time curve (AUC) is calculated using the linear trapezoidal method. Fitting of the data to obtain pharmacokinetic parameters is generally carried out using non-compartmental analysis.

[001018] **Table 7** shows pharmacokinetic data for selected compounds tested in the Mouse Balb C assay described above.

Table 7: Mouse (Balb C) Pharmacokinetic Assay

Compound	PK Dose (mg/kg)	PK Tmax (h)	PK Cmax (μM)	PK AUClast ($\mu\text{M}\cdot\text{h}$)	PK AUCinf obs ($\mu\text{M}\cdot\text{h}$)	PK t1/2 (h)
11	50	0.25	8.94	16.9	17.3	6.73

[001019] **Biological Example 7: ATPase Activity Inhibition Assay**

[001020] The capacity of the compounds disclosed herein to inhibit ATPase activity of commercially available 19S Regulatory Particle of the Proteasome (P19S-RP, Bovine 19S -

PA700, UBPBio, Dallas, TX) was assayed using the ADPGlo™ Kinase assay (Promega) following the manufacturer guidelines. This assay allows detection of ADP generated in a kinase/ATPase reaction.

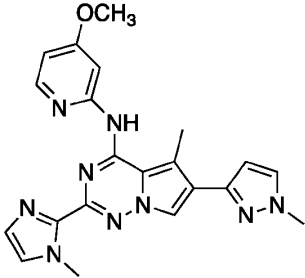
[001021] Method

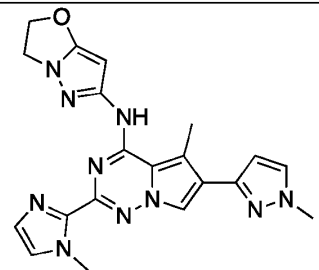
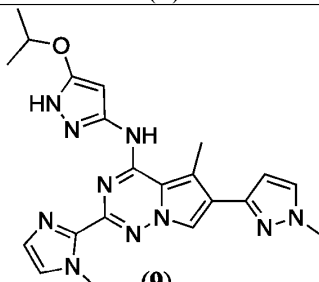
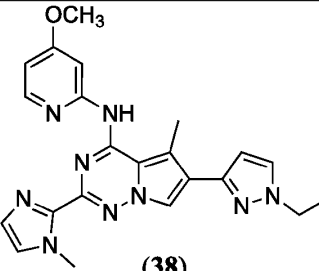
[001022] ATPase reaction: Reactions were set up in nuclease-free PCR tubes combining 10-60nM of P19S-RP and 30-300uM range of testing compound in 1x kinase buffer (40mM Tris-Cl pH7.5; 20mM MgCl₂; 0.1mg/mL BSA) to allow small molecule binding to the P19S-PR enzymes complex. Reactions were kept at room temperature for 30 minutes to 1h. After this pre-incubation step, 30uM of ultrapure ATP was added to each reaction in order to initiate ATPase reactions. ATPase reactions were incubated on a thermocycler set to 37°C for 30 minutes to 3h.

[001023] ADPGlo assay: after completing the ATPase reaction, reactions were equilibrated at room temperature and ADPGlo reagent was added (1:1 ratio) to stop reactions and to deplete left over ATP in the reactions (40 minutes, RT). Next, reactions were transferred to 96 well white opaque plates, and the kinase detection reagent was added to the reactions to convert ADP generated in the reaction back to ATP, which will be used as a substrate to generate light on a luciferase/luciferin reaction.

[001024] Detection and analysis: Luminescent signals were detected on a SpectraMax M2 (Molecular Devices) plate reader using the luminescence feature. The luminescent signal is proportional to the amount of ADP generated in the ATPase reaction.

[001025] Table 8: ATPase Assay Results

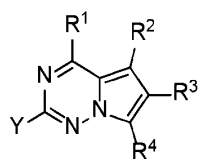
Compound	Concentration (uM)	% inhibition
 (A)	100	B

Compound	Concentration (uM)	% inhibition
 (B)	300	B
 (9)	100	B
 (38)	100	A

A denotes % inh < 33%, B denotes 33% < % inh < 66%, C denotes % inh > 66%.

Exemplary Embodiments

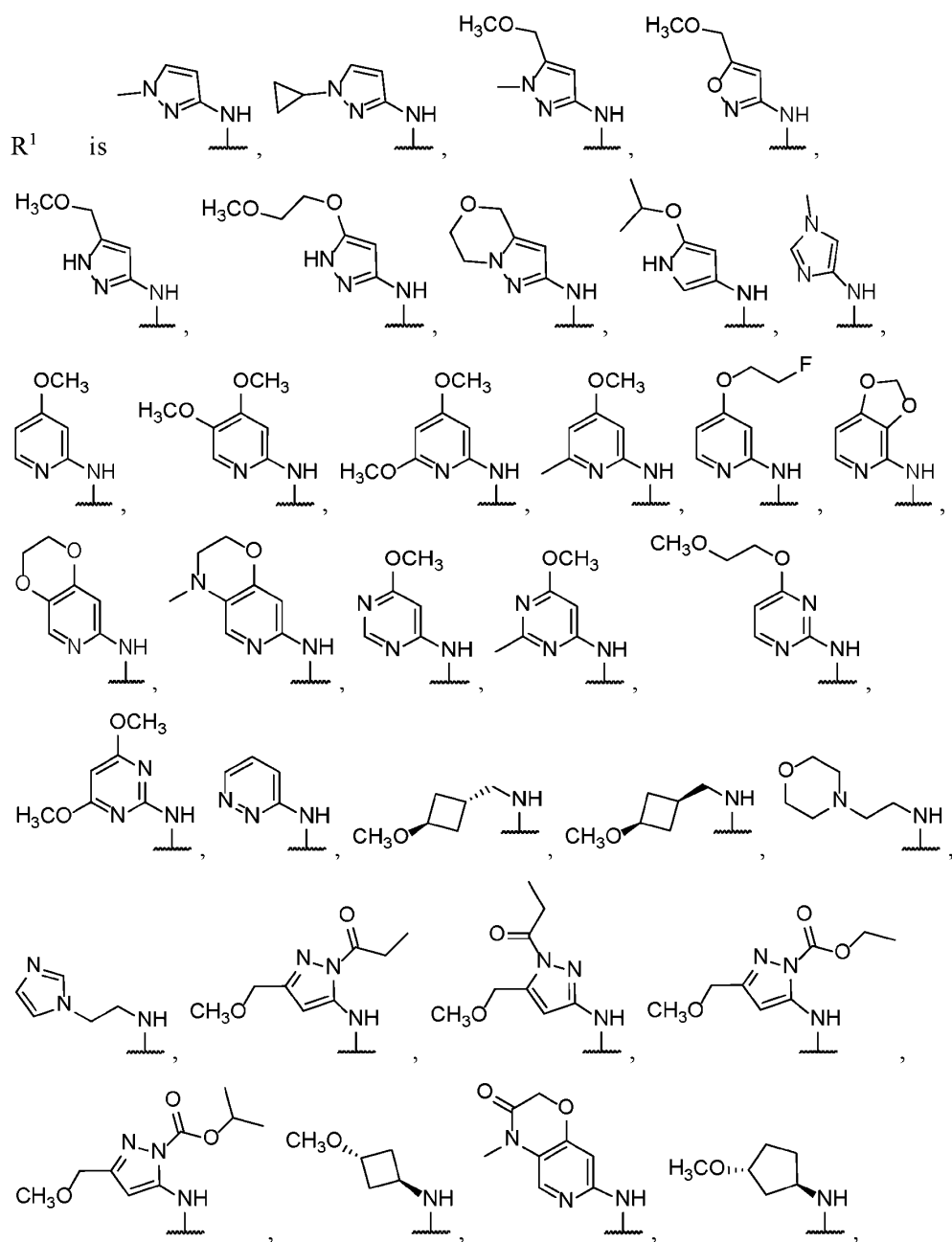
[001026] A1. A compound of Formula I:

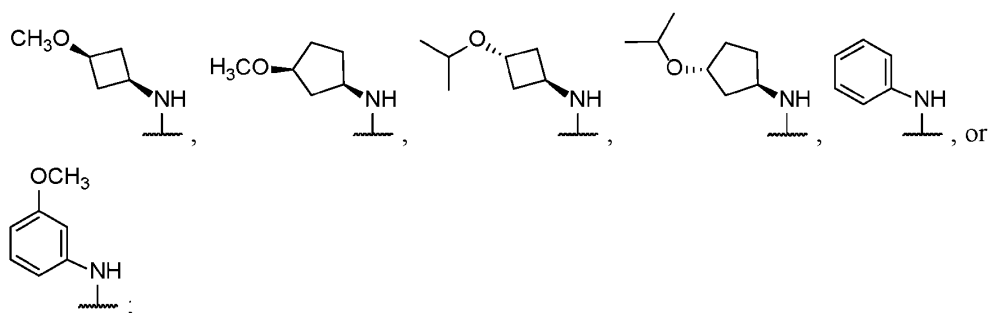


Formula I

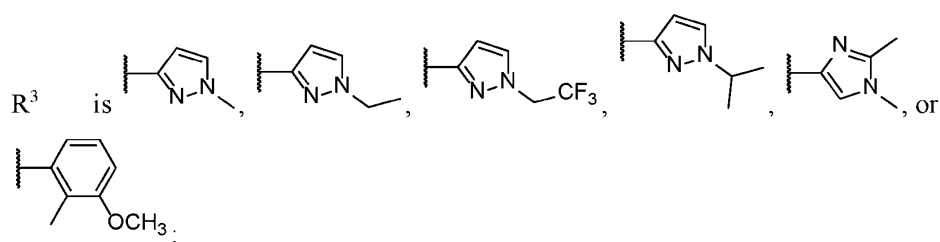
or a pharmaceutically acceptable form thereof, wherein:

Y is an imidazolyl; wherein the imidazolyl is optionally substituted with 1 R⁵ substituent and optionally substituted with 1-2 R⁶ substituents;





R^2 is C_{1-2} alkyl or C_{1-2} haloalkyl;



R^4 is hydrogen or C_{1-6} alkyl;

R^5 and R^6 are each independently C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, C_{1-6} heteroalkyl, halo, $-NR^9R^{10}$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-C(O)NR^9R^{10}$, $-(CO)R^8$, $-(CO)OH$, $-(CO)OR^8$, or CN, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, and C_{1-6} heteroalkyl are each independently optionally substituted with 1-3 R^7 substituents;

R^7 is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, $-NR^9R^{10}$, $-(CO)R^8$, $-(CO)OH$, $-(CO)OR^8$, $-C(O)NR^9R^{10}$, oxo, $-OH$, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, C_{1-6} haloalkoxy, or 5-6 membered heteroaryl;

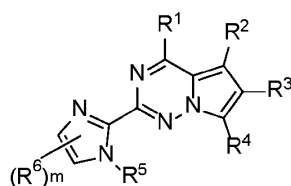
R^8 is C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^7 substituents; and

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, $-OH$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-7} heterocycloalkyl, aryl, or 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, C_{1-6} alkoxy, C_{1-6}

haloalkoxy, C₃₋₇ heterocycloalkyl, aryl, and 5-10 membered heteroaryl are optionally substituted with 1-3 R⁷ substituents, or R⁹ and R¹⁰ are combined to form a 3-7 membered heterocycloalkyl including the nitrogen atom to which they are both attached.

[001027] A2. The compound of embodiment A1, wherein Y is a C-linked imidazolyl that is substituted with 1 R⁵ substituent at a nitrogen of the imidazolyl ring and optionally substituted with 1-2 R⁶ substituents at carbons of the imidazolyl ring.

[001028] A3. The compound of embodiment A1 or embodiment A2, wherein the compound is a compound of Formula IA:

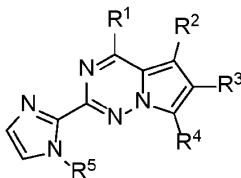


Formula IA

wherein m is 0, 1 or 2;

or a pharmaceutically acceptable form thereof.

[001029] A4. The compound of any one of embodiments A1-A3, wherein m is 0 and the compound is a compound of Formula IA(1):



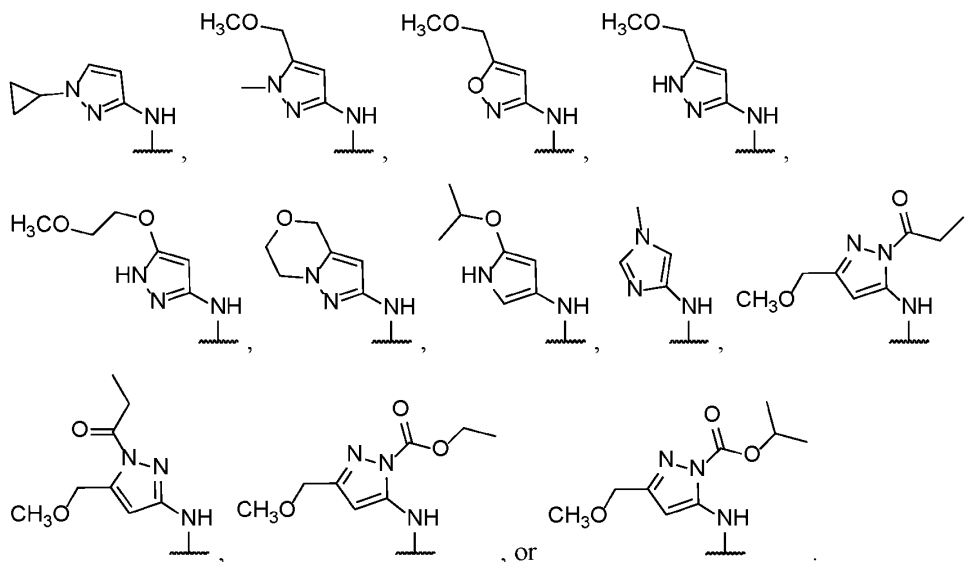
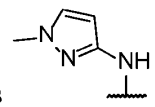
Formula IA(1)

or a pharmaceutically acceptable form thereof.

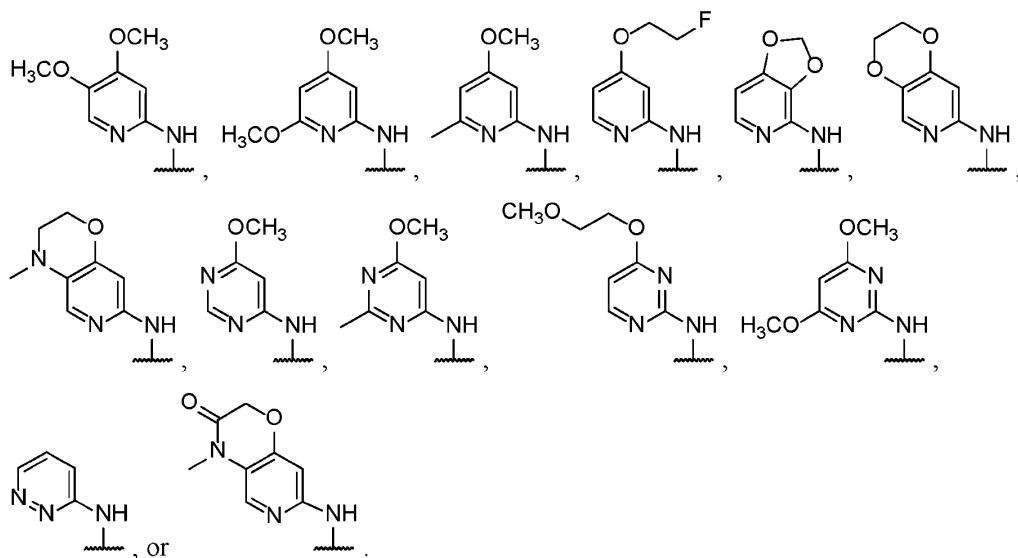
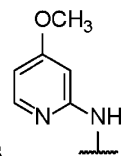
[001030] A5. The compound of embodiment A3, wherein m is 1.

[001031] A6. The compound of embodiment A3, wherein m is 2.

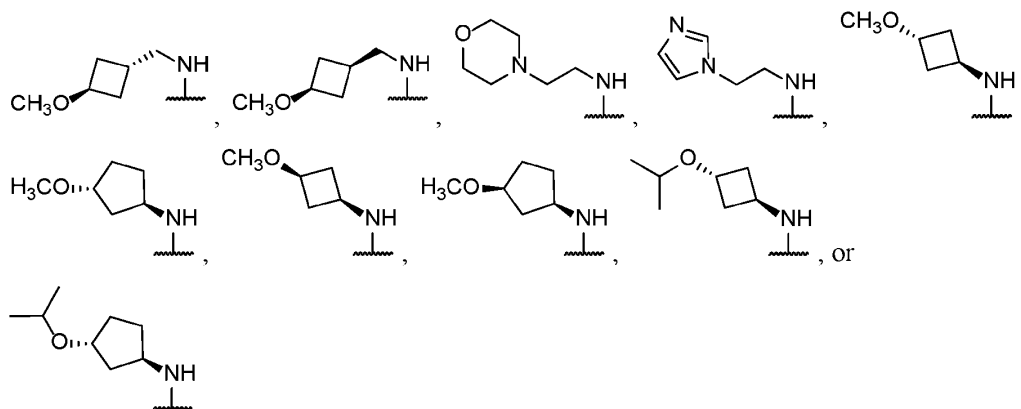
[001032] A7. The compound of any one of embodiments A1-A6, wherein R¹ is



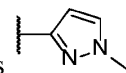
[001033] A8. The compound of any one of embodiments A1-A6, wherein R¹ is



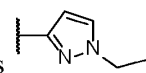
[001034] A9. The compound of any one of embodiments A1-A6, wherein R^1 is



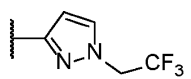
[001035] A10. The compound of any one of embodiments A1-A9, wherein R^3 is



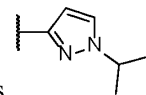
[001036] A11. The compound of any one of embodiments A1-A9, wherein R^3 is



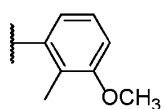
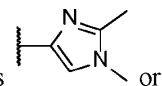
[001037] A12. The compound of any one of embodiments A1-A9, wherein R^3 is



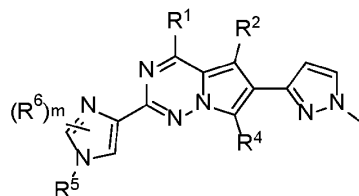
[001038] A13. The compound of any one of embodiments A1-A9, wherein R^3 is



[001039] A14. The compound of any one of embodiments A1-A9, wherein R^3 is

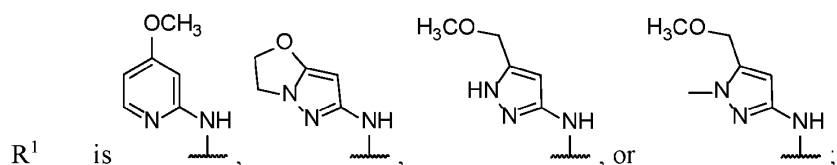


[001040] A15. A compound of Formula IB:



Formula IB

or a pharmaceutically acceptable form thereof, wherein:



R^2 is C_{1-2} alkyl or C_{1-2} haloalkyl;

R^4 is hydrogen or C_{1-6} alkyl;

R^5 and R^6 are each independently C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, C_{1-6} heteroalkyl, halo, $-NR^9R^{10}$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-C(O)NR^9R^{10}$, $-(CO)R^8$, $-(CO)OH$, $-(CO)OR^8$, or CN, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, and C_{1-6} heteroalkyl are each independently optionally substituted with 1-3 R^7 substituents;

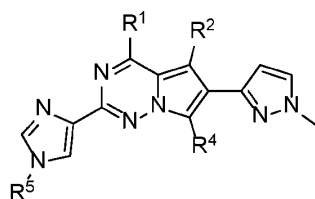
R^7 is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, $-NR^9R^{10}$, $-(CO)R^8$, $-(CO)OH$, $-(CO)OR^8$, $-C(O)NR^9R^{10}$, oxo, $-OH$, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, C_{1-6} haloalkoxy, or 5-6 membered heteroaryl;

R^8 is C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^7 substituents;

R^9 and R^{10} are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, $-OH$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-7} heterocycloalkyl, aryl, or 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-7} heterocycloalkyl, aryl, and 5-10 membered heteroaryl are optionally substituted with 1-3 R^7 substituents, or R^9 and R^{10} are combined to form a 3-7 membered heterocycloalkyl including the nitrogen atom to which they are both attached; and

m is 0, 1 or 2.

[001041] A16. The compound of embodiment A15, wherein m is 0 and the compound is a compound of Formula IB(1):

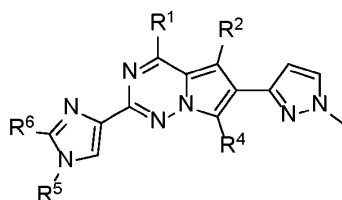


Formula IB(1)

or a pharmaceutically acceptable form thereof.

[001042] A17. The compound of embodiment A15, wherein m is 1.

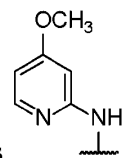
[001043] A18. The compound of embodiment A17, wherein the compound is a compound of Formula IB(2):



Formula IB(2)

or a pharmaceutically acceptable form thereof.

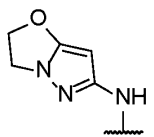
[001044] A19. The compound of embodiment A15, wherein m is 2.



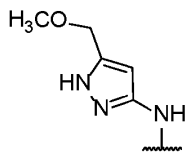
[001045] A20. The compound of any one of embodiments A15-A19, wherein R¹ is

[001046]

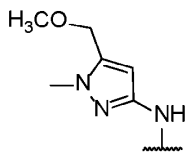
[001047] A21. The compound of any one of embodiments A15-A19, wherein R¹ is



[001048] A22. The compound of any one of embodiments A15-A19, wherein R¹ is



[001049] A23. The compound of any one of embodiments A15-A19, wherein R^1 is



[001050] A24. The compound of any one of embodiments A1-A23, wherein R^2 is methyl, ethyl, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CF}_2\text{CH}_3$, or $-\text{CF}_2\text{CF}_3$.

[001051] A25. The compound of any one of embodiments A1-A24, wherein R^2 is methyl.

[001052] A26. The compound of any one of embodiments A1-A25, wherein R^4 is hydrogen or C_{1-6} alkyl.

[001053] A27. The compound of any one of embodiments A1-A26, wherein R^4 is hydrogen, methyl, ethyl, or isopropyl.

[001054] A28. The compound of any one of embodiments A1-A27, wherein R^4 is hydrogen.

[001055] A29. The compound of any one of embodiments A1-A28, wherein R^5 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, C_{1-6} heteroalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-\text{C}(\text{O})\text{NR}^9\text{R}^{10}$, $-(\text{CO})\text{R}^8$, or $-\text{C}(\text{O})\text{OR}^8$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, and C_{1-6} heteroalkyl are each independently optionally substituted with 1-3 R^7 substituents.

[001056] A30. The compound of any one of embodiments A1-A29, wherein R^5 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^7 substituents.

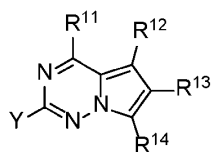
[001057] A31. The compound of any one of embodiments A1-A30, wherein R^5 is methyl, ethyl, or isopropyl, wherein the methyl, ethyl, and isopropyl are each independently optionally substituted with 1-3 R^7 , wherein R^7 is $-\text{OH}$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

[001058] A32. The compound of any one of embodiments A1-A31, wherein R^5 is methyl, ethyl, or isopropyl.

[001059] A33. The compound of any one of embodiments A1-A32, wherein R^5 is methyl.

[001060] A34. The compound of any one of embodiments A1-A33, wherein R^6 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^7 substituents.

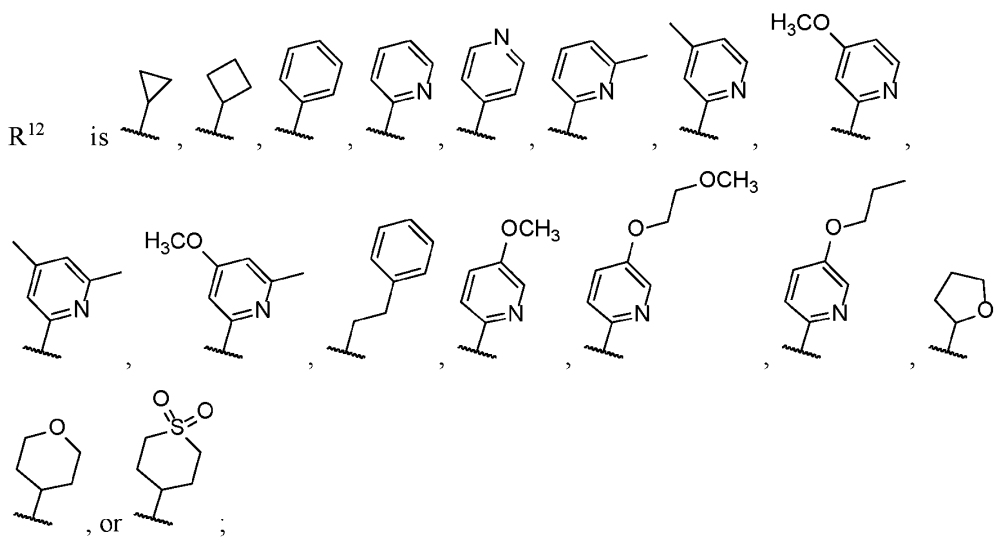
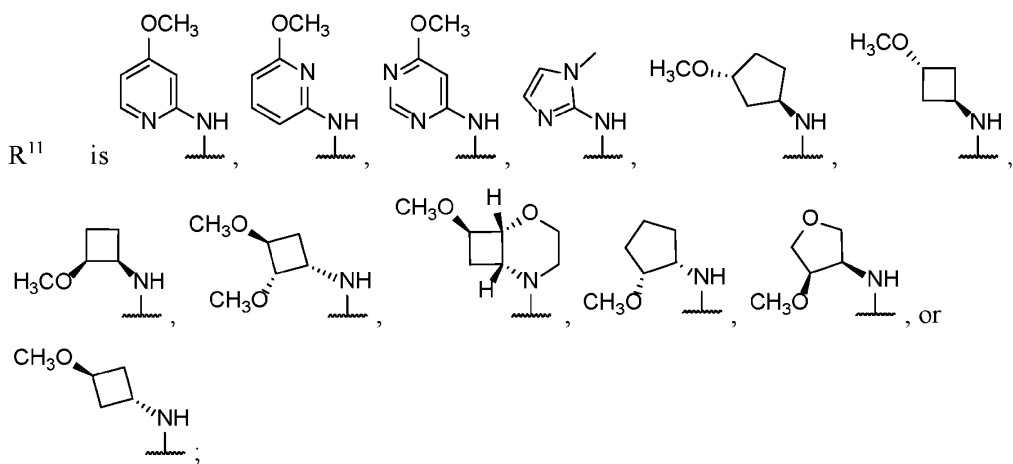
- [001061] A35. The compound of any one of embodiments A1-A34, wherein R^6 is methyl, ethyl, or isopropyl, wherein the methyl, ethyl, and isopropyl are each independently optionally substituted with 1-3 R^7 , wherein R^7 is -OH, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.
- [001062] A36. The compound of any one of embodiments A1-A35, wherein R^6 is methyl, ethyl, or isopropyl.
- [001063] A37. The compound of any one of embodiments A1-A36, wherein R^6 is methyl.
- [001064] A38. The compound of any one of embodiments A1-A37, wherein R^7 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, $-NR^9R^{10}$, $-(CO)R^8$, oxo, C_{1-6} alkoxy, or C_{3-6} cycloalkoxy.
- [001065] A39. The compound of any one of embodiments A1-A38, wherein R^7 is independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-5} cycloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} heteroalkyl, 3-5 membered heterocycloalkyl, $-NR^9R^{10}$, $-(CO)R^8$, oxo, C_{1-4} alkoxy, or C_{3-5} cycloalkoxy.
- [001066] A40. The compound of any one of embodiments A1-A39, wherein R^7 is independently selected from the group consisting of methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, C_{2-3} hydroxyalkyl, C_{2-4} heteroalkyl, $-NR^9R^{10}$, $-(CO)R^8$, oxo, methoxy, ethoxy, isopropoxy, cyclopropoxy, or cyclobutoxy.
- [001067] A41. The compound of any one of embodiments A1-A40, wherein R^8 is methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or C_{2-4} heteroalkyl.
- [001068] A42. The compound of any one of embodiments A1-A41, wherein R^9 and R^{10} are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} heteroalkyl, -OH, or C_{1-4} alkoxy.
- [001069] A43. The compound of any one of embodiments A1-A42, wherein R^9 and R^{10} are each independently selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, methoxy, or ethoxy.
- [001070] A44. The compound of any one of embodiments A1-A43, wherein R^9 and R^{10} are each independently selected from the group consisting of hydrogen or methyl.
- [001071] A45. The compound of any one of embodiments A1-A44, wherein R^9 and R^{10} are each hydrogen.
- [001072] A46. A compound of Formula II:

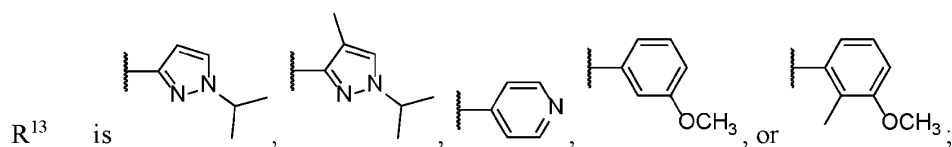


Formula II

or a pharmaceutically acceptable form thereof, wherein:

Y is an imidazolyl; wherein the imidazolyl is optionally substituted with 1 R¹⁵ substituent and optionally substituted with 1-2 R¹⁶ substituents;





R^{14} is hydrogen or C_{1-6} alkyl;

R^{15} and R^{16} are each independently C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, C_{1-6} heteroalkyl, halo, $-NR^{19}R^{20}$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-C(O)NR^{19}R^{20}$, $-(CO)R^{18}$, $-(CO)OH$, $-(CO)OR^{18}$, or CN, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, and C_{1-6} heteroalkyl are each independently optionally substituted with 1-3 R^{17} substituents;

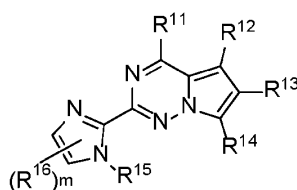
R^{17} is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, $-NR^{19}R^{20}$, $-(CO)R^{18}$, $-(CO)OH$, $-(CO)OR^{18}$, $-C(O)NR^{19}R^{20}$, oxo, $-OH$, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, C_{1-6} haloalkoxy, or 5-6 membered heteroaryl;

R^{18} is C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^{17} substituents; and

R^{19} and R^{20} are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, $-OH$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-7} heterocycloalkyl, aryl, or 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-7} heterocycloalkyl, aryl, and 5-10 membered heteroaryl are optionally substituted with 1-3 R^{17} substituents, or R^{19} and R^{20} are combined to form a 3-7 membered heterocycloalkyl including the nitrogen atom to which they are both attached.

[001073] A47. The compound of embodiment A46, wherein Y is a C-linked imidazolyl that is substituted with 1 R^{15} substituent at a nitrogen of the imidazolyl ring and optionally substituted with 1-2 R^{16} substituents at carbons of the imidazolyl ring.

[001074] A48. The compound of embodiment A46 or embodiment A47, wherein the compound is a compound of Formula IIA:

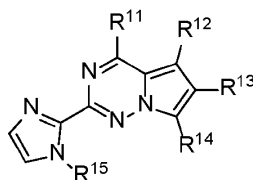


Formula IIA

wherein m is 0, 1 or 2;

or a pharmaceutically acceptable form thereof.

[001075] A49. The compound of any one of embodiments A46-A48, wherein m is 0 and the compound is a compound of Formula IIA(1):



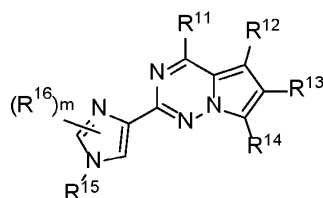
Formula IIA(1)

or a pharmaceutically acceptable form thereof.

[001076] A50. The compound of any one of embodiments A46-A48, wherein m is 1.

[001077] A51. The compound of any one of embodiments A46-A48, wherein m is 2.

[001078] A52. The compound of embodiment A46 or embodiment A47, wherein the compound is a compound of Formula IIB:

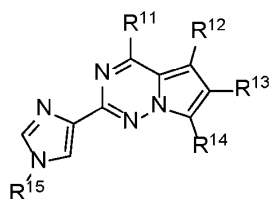


Formula IIB

wherein m is 0, 1 or 2;

or a pharmaceutically acceptable form thereof.

[001079] A53. The compound of any one of embodiments A46, A47, or A52, wherein m is 0 and the compound is a compound of Formula IIB(1):

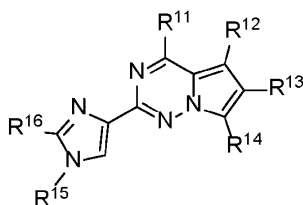


Formula IIB(1)

or a pharmaceutically acceptable form thereof.

[001080] A54. The compound of any one of embodiments A46, A47, or A52, wherein m is 1.

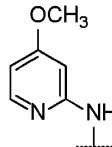
[001081] A55. The compound of embodiment A54, wherein the compound is a compound of Formula IIB(2):

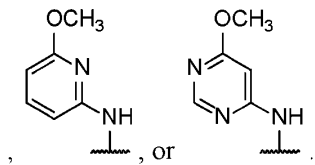


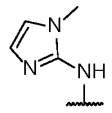
Formula IIB(2)

or a pharmaceutically acceptable form thereof.

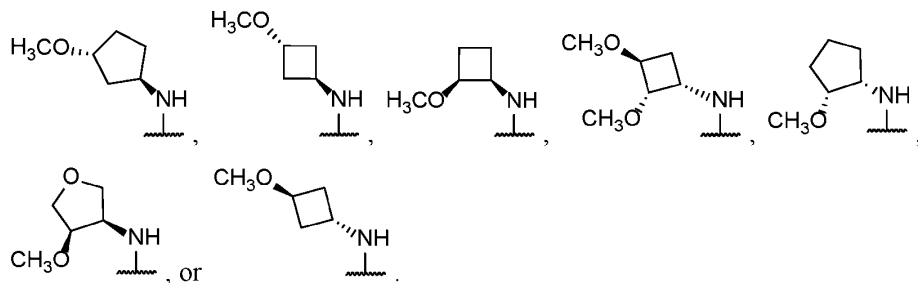
[001082] A56. The compound of any one of embodiments A46, A47, or A52, wherein m is 2.

[001083] A57. The compound of any one of embodiments A46-A56, wherein R¹¹ is .



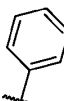
[001084] A58. The compound of any one of embodiments A46-A56, wherein R¹¹ is .

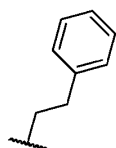
[001085] A59. The compound of any one of embodiments A46-A56, wherein R^{11} is

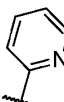


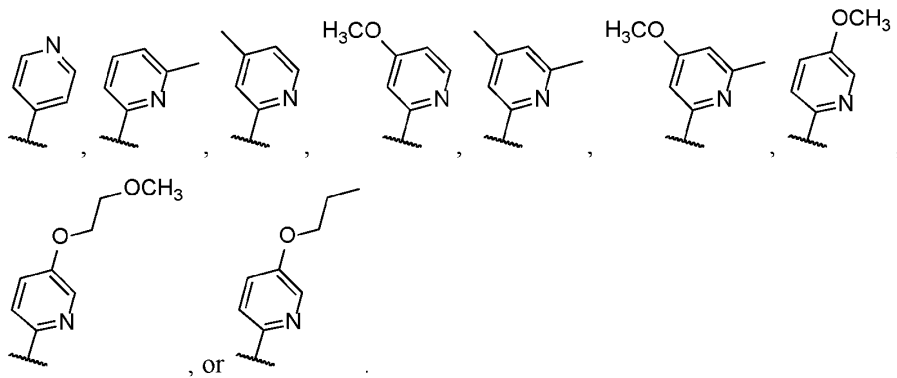
[001086] A60. The compound of any one of embodiments A46-A59, wherein R^{12} is  or



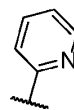
[001087] A61. The compound of any one of embodiments A46-A59, wherein R^{12} is  or



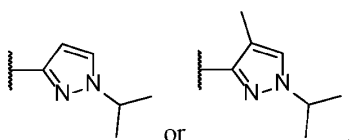
[001088] A62. The compound of any one of embodiments A46-A59, wherein R^{12} is , ,



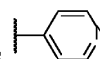
[001089] A63. The compound of any one of embodiments A46-A59, wherein R¹² is



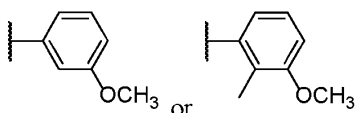
[001090] A64. The compound of any one of embodiments A46-A63, wherein R¹³ is



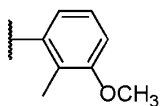
[001091] A65. The compound of any one of embodiments A46-A63, wherein R¹³ is



[001092] A66. The compound of any one of embodiments A46-A63, wherein R¹³ is



[001093] A67. The compound of any one of embodiments A46-A63, wherein R¹³ is



[001094] A68. The compound of any one of embodiments A46-A67, wherein R¹⁴ is hydrogen or C₁₋₆ alkyl.

[001095] A69. The compound of any one of embodiments A46-A68, wherein R¹⁴ is hydrogen, methyl, ethyl, or isopropyl.

[001096] A70. The compound of any one of embodiments A46-A69, wherein R¹⁴ is hydrogen.

[001097]

[001098] A71. The compound of any one of embodiments A46-A70, wherein R¹⁵ is C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, aryl, C₅₋₁₀ heteroaryl, C₃₋₇ heterocycloalkyl, C₁₋₆ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -C(O)NR¹⁹R²⁰, -(CO)R¹⁸, or -C(O)OR¹⁸, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, aryl, C₅₋₁₀ heteroaryl, C₃₋₇ heterocycloalkyl, and C₁₋₆ heteroalkyl are each independently optionally substituted with 1-3 R¹⁷ substituents.

[001099] A72. The compound of any one of embodiments A46-A71, wherein R¹⁵ is C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, or C₁₋₆ heteroalkyl, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl, are each independently optionally substituted with 1-3 R¹⁷ substituents.

- [001100] A73. The compound of any one of embodiments A46-A72, wherein R^{15} is methyl, ethyl, or isopropyl, wherein the methyl, ethyl, and isopropyl are each independently optionally substituted with 1-3 R^{17} , wherein R^{17} is -OH, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.
- [001101] A74. The compound of any one of embodiments A46-A73, wherein R^{15} is methyl, ethyl, or isopropyl.
- [001102] A75. The compound of any one of embodiments A46-A74, wherein R^{15} is methyl.
- [001103] A76. The compound of any one of embodiments A46-A75, wherein R^{16} is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^{17} substituents.
- [001104] A77. The compound of any one of embodiments A46-A76, wherein R^{16} is methyl, ethyl, or isopropyl, wherein the methyl, ethyl, and isopropyl are each independently optionally substituted with 1-3 R^{17} , wherein R^{17} is -OH, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.
- [001105] A78. The compound of any one of embodiments A46-A77, wherein R^{16} is methyl, ethyl, or isopropyl.
- [001106] A79. The compound of any one of embodiments A46-A78, wherein R^{16} is methyl.
- [001107] A80. The compound of any one of embodiments A46-A79, wherein R^{17} is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, $-NR^{19}R^{20}$, $-(CO)R^{18}$, oxo, C_{1-6} alkoxy, or C_{3-6} cycloalkoxy.
- [001108] A81. The compound of any one of embodiments A46-A80, wherein R^{17} is independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-5} cycloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} heteroalkyl, 3-5 membered heterocycloalkyl, $-NR^{19}R^{20}$, $-(CO)R^{18}$, oxo, C_{1-4} alkoxy, or C_{3-5} cycloalkoxy.
- [001109] A82. The compound of any one of embodiments A46-A81, wherein R^{17} is independently selected from the group consisting of methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, C_{2-3} hydroxyalkyl, C_{2-4} heteroalkyl, $-NR^{19}R^{20}$, $-(CO)R^{18}$, oxo, methoxy, ethoxy, isopropoxy, cyclopropoxy, or cyclobutoxy.
- [001110] A83. The compound of any one of embodiments A46-A82, wherein R^{18} is methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or C_{2-4} heteroalkyl.

- [001111] A84. The compound of any one of embodiments A46-A83, wherein R^{19} and R^{20} are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} heteroalkyl, $-OH$, or C_{1-4} alkoxy.
- [001112] A85. The compound of any one of embodiments A46-A84, wherein R^{19} and R^{20} are each independently selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, methoxy, or ethoxy.
- [001113] A86. The compound of any one of embodiments A46-A85, wherein R^{19} and R^{20} are each independently selected from the group consisting of hydrogen or methyl.
- [001114] A87. The compound of any one of embodiments A46-A86, wherein R^{19} and R^{20} are each hydrogen.
- [001115] A88. The compound of any one of embodiments A1-A87, wherein the compound has a MW of no more than 1,000 g/mol.
- [001116] A89. The compound of any one of embodiments A1-A88, wherein the compound has a MW of no more than 900 g/mol, no more than 800 g/mol, no more than 700 g/mol, no more than 600 g/mol, or no more than 500 g/mol.
- [001117] A90. The compound of any one of embodiments A1-A89, wherein the compound has a MW of no more than 600 g/mol.
- [001118] A91. The compound of any one of embodiments A1-A90, wherein the compound has a MW of no more than 500 g/mol.
- [001119] A92. The compound of any one of embodiments A1-A91, wherein the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof, optionally wherein the compound is selected from the group consisting of 9, 10, 11, 16, 18, 19, 36, 37, 38, 39, 40, and 62, or a pharmaceutically acceptable form thereof, or optionally wherein the compound is selected from the group consisting of 36, 37, 38, 39, 40, and 62, or a pharmaceutically acceptable form thereof.
- [001120] A93. The compound of any one of embodiments A1-A92, wherein the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14,

15, 22, 23, 24, 25, 26, 27, 28, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, and 69, or a pharmaceutically acceptable form thereof.

[001121] A94. The compound of any one of embodiments A1-A92, wherein the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 25, 26, 27, 28, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, and 45, or a pharmaceutically acceptable form thereof.

[001122] A95. The compound of any one of embodiments A1-A92, wherein the compound is selected from the group consisting of Compounds 22, 23, 24, and 30, or a pharmaceutically acceptable form thereof.

[001123] A96. The compound of any one of embodiments A1-A92, wherein the compound is selected from the group consisting of Compounds 31, 32, 33, and 69, or a pharmaceutically acceptable form thereof.

[001124] A97. The compound of any one of embodiments A1-A92, wherein the compound is selected from the group consisting of Compounds 16, 17, 18, 19, 20, 21, 29, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, and 68, or a pharmaceutically acceptable form thereof.

[001125] A98. The compound of any one of embodiments A1-A92, wherein the compound is selected from the group consisting of Compounds 16, 17, 18, 19, 20, 21, 29, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, and 62, or a pharmaceutically acceptable form thereof.

[001126] A99. The compound of any one of embodiments A1-A92, wherein the compound is selected from the group consisting of Compounds 63, 64, and 65, or a pharmaceutically acceptable form thereof.

[001127] A100. The compound of any one of embodiments A1-A92, wherein the compound is selected from the group consisting of Compounds 66, 67, and 68, or a pharmaceutically acceptable form thereof.

[001128] A101. The compound of any one of embodiments A1-A100, wherein the pharmaceutically acceptable form of the compound is an isomer, isotopic variant, pharmaceutically acceptable salt, polymorph, or solvate of said compound.

[001129] A102. The compound of any one of embodiments A1-A101, wherein the pharmaceutically acceptable form of the compound is exclusive of a salt form.

- [001130] A103. The compound of any one of embodiments A1-A102, wherein the isomer of the compound is a diastereomer or enantiomer of the compound.
- [001131] A104. The compound of any one of embodiments A1-A103, wherein the compound is a tautomer of the compound.
- [001132] A105. The compound of any one of embodiments A1-A104, wherein the compound is a racemate or a mixture of diastereomers.
- [001133] A106. The compound of any one of embodiments A1-A104, wherein the compound is a single enantiomer or a single diastereomer.
- [001134] A107. The compound of embodiment A106, wherein the compound is a single enantiomer.
- [001135] A108. The compound of embodiment A107, wherein the compound is an (R)-enantiomer; optionally wherein the compound has an enantiomeric excess of greater than 10% of the (R)-enantiomer; optionally wherein the compound has an enantiomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (R)-enantiomer; optionally wherein the compound has an enantiomeric excess of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (R)-enantiomer.
- [001136] A109. The compound of embodiment A107, wherein the compound is an (S)-enantiomer; optionally wherein the compound has an enantiomeric excess of greater than 10% of the (S)-enantiomer; optionally wherein the compound has an enantiomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (S)-enantiomer; optionally wherein the compound has an enantiomeric excess of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (S)-enantiomer.
- [001137] A110. The compound of embodiment A106, wherein the compound is a single diastereomer; optionally wherein the compound is a (R)/(R)-, (R)/(S)-, (S)/(R)-, or (S)/(S)-single diastereomer.

- [001138] A111. The compound of embodiment A110, wherein the compound is an (R)/(R)-diastereomer; optionally wherein the compound has a diastereomeric excess of greater than 10% of the (R)/(R)-diastereomer; optionally wherein the compound has a diastereomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (R)/(R)-diastereomer; optionally wherein the compound has a diastereomeric of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (R)/(R)-diastereomer.
- [001139] A112. The compound of embodiment A110, wherein the compound is an (R)/(S)-diastereomer; optionally wherein the compound has a diastereomeric excess of greater than 10% of the (R)/(S)-diastereomer; optionally wherein the compound has a diastereomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (R)/(S)-diastereomer; optionally wherein the compound has a diastereomeric of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (R)/(S)-diastereomer.
- [001140] A113. The compound of embodiment A110, wherein the compound is an (S)/(R)-diastereomer; optionally wherein the compound has a diastereomeric excess of greater than 10% of the (S)/(R)-diastereomer; optionally wherein the compound has a diastereomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (S)/(R)-diastereomer; optionally wherein the compound has a diastereomeric of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (S)/(R)-diastereomer.
- [001141] A114. The compound of embodiment A110, wherein the compound is an (S)/(S)-diastereomer; optionally wherein the compound has a diastereomeric excess of greater than 10% of the (S)/(S)-diastereomer; optionally wherein the compound has a diastereomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or

more, 40% or more, 45% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (S)/(S)-diastereomer; optionally wherein the compound has a diastereomeric of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (S)/(S)-diastereomer.

[001142] A115. The compound of any one of embodiments A1-A114, wherein the compound or pharmaceutically acceptable form thereof is a modulator of Ras superfamily activity according to a Ras Superfamily Activity Assay.

[001143] A116. The compound of embodiment A115, wherein the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 20 μ M according to a Ras Superfamily Activity Assay.

[001144] A117. The compound of embodiment A116, wherein the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 9, 10, 11, 12, 13, 16, 18, 22, 23, 24, 27, 28, 32, 33, 36, 37, 38, 39, 40, 57, 62, 75, 84, 86, and 92, or a pharmaceutically acceptable form thereof.

[001145] A118. The compound of any one of embodiments A1-A117, wherein the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 according to Erk1/2 Phosphorylation Assay.

[001146] A119. The compound of embodiment A118, wherein the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Erk1/2 Phosphorylation Assay.

[001147] A120. The compound of embodiment A119, wherein the compound is selected from the group consisting of Compounds 19, 20, 21, 49, 51, 53, 56, 67, 68, 79, 80, 81, 82, 89, and 94, or a pharmaceutically acceptable form thereof.

[001148] A121. The compound of any one of embodiments A1-A117, wherein the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 according to Erk1/2 Phosphorylation Assay.

- [001149] A122. The compound of embodiment A121, wherein the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Erk1/2 Phosphorylation Assay.
- [001150] A123. The compound of embodiment A122, wherein the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 16, 18, 23, 27, 28, 36, 37, 38, 40, 54, 55, 57, 60, 61, 62, 75, and 83, or a pharmaceutically acceptable form thereof.
- [001151] A124. The compound of any one of embodiments A1-A123, wherein the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt according to Akt Phosphorylation Assay.
- [001152] A125. The compound of embodiment A124, wherein the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Akt Phosphorylation Assay.
- [001153] A126. The compound of embodiment A125, wherein the compound is selected from the group consisting of Compounds 19, 20, 49, 51, 53, 56, 79, 80, 81, and 94, or a pharmaceutically acceptable form thereof.
- [001154] A127. The compound of any one of embodiments A1-A123, wherein the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt according to Akt Phosphorylation Assay.
- [001155] A128. The compound of embodiment A127, wherein the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Akt Phosphorylation Assay.
- [001156] A129. The compound of embodiment A128, wherein the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 18, 22, 27, 28, 32, 36, 37, 38, 39, 40, 47, 54, 55, 57, 59, 60, 61, 62, 66, 67, 74, 75, 76, 83, 84, 86, 87, 88, and 91, or a pharmaceutically acceptable form thereof.

- [001157] A130. The compound of any one of embodiments A1-A129, wherein the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 according to Phospho-Smad2/3 Inhibition Assay.
- [001158] A131. The compound of embodiment A130, wherein the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay.
- [001159] A132. The compound of embodiment A131, wherein the compound is selected from the group consisting of Compounds 19, 20, 21, 29, 49, 51, 56, 58, 61, 63, 64, 65, 68, 77, 79, 80, 81, 87, 88, 89, and 94, or a pharmaceutically acceptable form thereof.
- [001160] A133. The compound of any one of embodiments A1-A129, wherein the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 according to Phospho-Smad2/3 Inhibition Assay.
- [001161] A134. The compound of embodiment A133, wherein the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay.
- [001162] A135. The compound of embodiment A134, wherein the compound is Compound 12, 14, 25, 26, 31, 32, 33, 37, 78, and 90, or a pharmaceutically acceptable form thereof.
- [001163] A136. The compound of any one of embodiments A1-A135, wherein the compound or pharmaceutically acceptable form thereof inhibits JNK according to JNK Activation Assay.
- [001164] A137. The compound of embodiment A136, wherein the compound or pharmaceutically acceptable form thereof inhibits JNK by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to JNK Activation Assay.
- [001165] A138. The compound of embodiment A137, wherein the compound is Compound 8, or a pharmaceutically acceptable form thereof.

- [001166] A139. The compound of any one of embodiments A1-A135, wherein the compound or pharmaceutically acceptable form thereof activates JNK according to JNK Activation Assay.
- [001167] A140. The compound of embodiment A139, wherein the compound or pharmaceutically acceptable form thereof activates JNK by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to JNK Activation Assay.
- [001168] A141. The compound of embodiment A140, wherein the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, and 7, or a pharmaceutically acceptable form thereof.
- [001169] A142. The compound of any one of embodiments A1-A141, wherein the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 according to MAPK p38 Activation Assay.
- [001170] A143. The compound of embodiment A142, wherein the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to MAPK p38 Activation Assay.
- [001171] A144. The compound of embodiment 143, wherein the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by 90% or more, or 95% or more at 10 μ M according to MAPK p38 Activation Assay.
- [001172] A145. The compound of any one of embodiments A1-A141, wherein the compound or pharmaceutically acceptable form thereof activates MAPK p38 according to MAPK p38 Activation Assay.
- [001173] A146. The compound of embodiment A145, wherein the compound or pharmaceutically acceptable form thereof activates MAPK p38 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to MAPK p38 Activation Assay.

- [001174] A147. The compound of embodiment A146, wherein the compound is selected from the group consisting of Compounds 2, 3, 4, 5, 6, and 7, or a pharmaceutically acceptable form thereof.
- [001175] A148. The compound of any one of embodiments A1-A147, wherein the compound or pharmaceutically acceptable form thereof inhibits IL-6 according to IL-6 Quantification Assay.
- [001176] A149. The compound of embodiment A148, wherein the compound or pharmaceutically acceptable form thereof inhibits IL-6 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to IL-6 Quantification Assay.
- [001177] A150. The compound of embodiment A149, wherein the compound is selected from the group consisting of Compounds 4, 9, 10, 11, 16, 17, 19, 20, 92, and 94 or a pharmaceutically acceptable form thereof.
- [001178] A151. The compound of any one of embodiments A1-A150, wherein the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha according to TNF-alpha Quantification Assay.
- [001179] A152. The compound of embodiment A151, wherein the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to TNF-alpha Quantification Assay.
- [001180] A153. The compound of embodiment A152, wherein the compound is Compound 20 and 94, or a pharmaceutically acceptable form thereof.
- [001181] A154. The compound of any one of embodiments A1-A153, wherein the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 according to Proliferation Assay.
- [001182] A155. The compound of embodiment A154, wherein the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC₅₀ value of 1 μ M or less, 0.9 μ M or less, 0.8 μ M or less, 0.75 μ M or less, 0.7 μ M or less, 0.6 μ M or less, 0.5 μ M or less, 0.4 μ M or less, 0.3 μ M or less, 0.25 μ M or less, 0.2 μ M or less, 0.15 μ M or less, 0.1 μ M or less, 0.09 μ M or less, 0.05 μ M or less, or 0.03 μ M or less, according to Proliferation Assay.

- [001183] A156. The compound of embodiment A155, wherein the compound is selected from the group consisting of Compounds 1, 3, 4, 9, 10, 11, 12, 13, 16, 18, 19, 22, 23, 28, 31, 32, 36, 37, 38, 39, 40, 47, 48, 49, 52, 57, 62, 65, 68, 75, 80, 81, 82, 83, 85, 87, and 94, or a pharmaceutically acceptable form thereof.
- [001184] A157. The compound of embodiment A155 or embodiment A156, wherein the compound is selected from the group consisting of Compounds 9, 10, 11, 16, 18, 19, 28, 36, 37, 38, 39, 40, 48, 57, 62, and 65, or a pharmaceutically acceptable form thereof.
- [001185] A158. The compound of any one of embodiments A155-A157, wherein the compound is selected from the group consisting of Compounds 9, 10, 11, 36, 37, 38, 39, 40, 62, and 65, or a pharmaceutically acceptable form thereof.
- [001186] A159. The compound of any one of embodiments A1-A158, wherein the compound or pharmaceutically acceptable form thereof has a kinetic solubility of 10 μM or more, 20 μM or more, 30 μM or more, 40 μM or more, 50 μM or more, 60 μM or more, 70 μM or more, 80 μM or more, 90 μM or more, 100 μM or more, 150 μM or more, or 200 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay.
- [001187] A160. The compound of embodiment A159, wherein the compound is selected from the group consisting of Compounds 9 and 11, or a pharmaceutically acceptable form thereof.
- [001188] A161. The compound of embodiment A159 or embodiment A160, wherein the compound is Compound 9, or a pharmaceutically acceptable form thereof.
- [001189] A162. The compound of any one of embodiments A1-A161, wherein the compound or pharmaceutically acceptable form thereof has a half-life of 10 minutes or more, 20 minutes or more, 30 minutes or more, 40 minutes or more, or 50 minutes or more in mouse liver microsomes according to Mouse Liver Microsome Metabolic Stability Assay.
- [001190] A163. The compound of embodiment A162, wherein the compound is Compound 11, or a pharmaceutically acceptable form thereof.
- [001191] A164. The compound of any one of embodiments A1-A163, wherein the compound or pharmaceutically acceptable form thereof inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, according to Proliferation Assay.
- [001192] A165. The compound of embodiment A164, wherein the compound or pharmaceutically acceptable form thereof inhibits proliferation in Kasumi-1, BT-549, GP2d,

A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, with an IC₅₀ value of 50 nM or less, 40 nM or less, 30 nM or less, 20 nM or less, 10 nM or less, 1 nM or less, 0.1 nM or less, or 0.01 nM or less according to Proliferation Assay.

[001193] A166. The compound of embodiment A164 or embodiment A165, wherein the compound or pharmaceutically acceptable form thereof inhibits proliferation in MM.R1 with an IC₅₀ value of 1 nM or less, 0.1 nM or less, or 0.01 nM or less according to Proliferation Assay.

[001194] A167. The compound of any one of claims A164-A166, wherein the compound is selected from the group consisting of Compounds 9 and 11, or a pharmaceutically acceptable form thereof.

[001195] A168. A pharmaceutical composition comprising the compound or pharmaceutically acceptable form thereof, of any one of embodiments A1-A167, and a pharmaceutically acceptable carrier, excipient or diluent.

[001196] A169. A method of modulating a Ras superfamily protein, comprising contacting the Ras superfamily protein with an effective amount of the compound of any one of embodiments A1-A167, or pharmaceutically acceptable form thereof.

[001197] A170. A method of modulating a Ras superfamily protein, comprising contacting the Ras superfamily protein with an effective amount of the pharmaceutical composition of embodiment A168.

[001198] A171. The method of embodiment A169 or embodiment A170, wherein the Ras superfamily protein is present in a cell.

[001199] A172. The method of any one of claims 169-171, wherein the method inhibits the Ras superfamily protein.

[001200] A173. The method of any one of embodiments A169-A172, wherein the Ras superfamily protein is a Ras protein, or a mutant thereof.

[001201] A174. The method of embodiment A173, wherein the Ras protein is DIRAS1; DIRAS2; DIRAS3; ERAS; GEM; HRAS; KRAS; MRAS; NKIRAS1; NKIRAS2; NRAS; RALA; RALB; RAPIA; RAPIB; RAP2A; RAP2B; RAP2C; RASDI; RASD2; RASL1OA; RASL1OB; RASL1IA; RASL1IB; RASL12; REM1; REM2; RERG; RERGL; RRAD; RRAS; or RRAS2.

- [001202] A175. The method of embodiment A173 or embodiment A174, wherein the Ras protein is HRAS; KRAS; or NRAS, or a mutant thereof.
- [001203] A176. The method of any one of embodiments A173-A175, wherein the Ras protein is a KRAS mutant.
- [001204] A177. The method of embodiment A176, wherein the KRAS mutant is a KRas G12D mutant, KRas G12C mutant, or KRas Q61H mutant.
- [001205] A178. The method of any one of embodiments A173-A175, wherein the Ras protein is HRAS or a mutant thereof.
- [001206] A179. The method of any one of embodiments A173-A175, wherein the Ras protein is NRAS or a mutant thereof.
- [001207] A180. The method of any one of embodiments A169-A173, wherein the Ras superfamily protein is a Rac protein, or a mutant thereof.
- [001208] A181. The method of embodiment A180, wherein the Rac protein is RAC1; RAC2; RAC3; RHOG, or a mutant thereof.
- [001209] A182. The method of embodiment A180 or embodiment A181, wherein the Rac protein is wild-type RAC1.
- [001210] A183. The method of any one of embodiments A169-A173, wherein the Ras superfamily protein is a Rho protein, or a mutant thereof.
- [001211] A184. The method of embodiment A183, wherein the Rho protein is RHOA; RHOB; RHOBTB1; RHOBTB2; RHOBTB3; RHOC; RHOD; RHOF; RHOH; RHOJ; RHOQ; RHOU; RHOV; RND1; RND2; RND3; CDC42, or a mutant thereof.
- [001212] A185. The method of embodiment A183 or embodiment A184, wherein the Rho protein is wild-type RHOA.
- [001213] A186. The method of any one of embodiments A169-A173, wherein the Ras superfamily protein is a Cdc42 protein, or a mutant thereof.
- [001214] A187. The method of any one of embodiments A169-A173, wherein the Ras superfamily protein is a Rheb protein, or a mutant thereof.
- [001215] A188. The method of any one of embodiments A169-A187, wherein the contacting of the Ras superfamily protein takes place in a cell.
- [001216] A189. The method of embodiment A188, wherein the cell is in a subject.

- [001217] A190. The method of embodiment A188 or embodiment A189, wherein the cell is a mammalian cell.
- [001218] A191. The method of any one of embodiments A188-A190, wherein the cell is a human cell.
- [001219] A192. The method of any one of embodiments A188-A191, wherein the subject suffers from a cancer.
- [001220] A193. The method of any one of embodiments A169-A192, wherein the modulation takes place in a subject suffering from a cancer.
- [001221] A194. The method of embodiment A192 or embodiment A193, wherein the cancer is a solid tumor or is a blood borne tumor (or a hematological cancer).
- [001222] A195. The method of any one of embodiments A192-A194, wherein the cancer is hepatocellular carcinoma, prostate cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, colon cancer, small intestine cancer, biliary tract cancer, endometrium cancer, skin cancer (melanoma), cervix cancer, urinary tract cancer, glioblastoma, esophageal carcinoma, mesothelioma, or multiple myeloma; optionally wherein the cancer is hepatocellular carcinoma, pancreatic cancer, glioblastoma, esophageal carcinoma, mesothelioma, or small cell lung cancer (SCLC).
- [001223] A196. The method of embodiment A195, wherein the cancer is pancreatic cancer.
- [001224] A197. The method of embodiment A195, wherein the cancer is colon cancer.
- [001225] A198. The method of embodiment A195, wherein the cancer is triple negative breast cancer.
- [001226] A199. The method of embodiment A195, wherein the cancer is multiple myeloma.
- [001227] A200. The method of any one of embodiments A192-A199, wherein the cancer is a cancer dependent on a Ras superfamily protein.
- [001228] A201. The method of any one of embodiments A189-A200, wherein the subject is a human.
- [001229] A202. A method of modulating caspase activity, comprising contacting the caspase with an effective amount of the compound of any one of embodiments A1-A167, or pharmaceutically acceptable form thereof.
- [001230] A203. A method of modulating caspase activity, comprising contacting the caspase with an effective amount of the pharmaceutical composition of embodiment A168.

- [001231] A204. The method of embodiment A202 or embodiment A203, wherein the method activates the caspase.
- [001232] A205. The method of any one of embodiments A202-A204, wherein the caspase is caspase 3, caspase 6, or caspase 9.
- [001233] A206. The method of any one of embodiments A202-A205, wherein the contacting of the caspase takes place in a cell.
- [001234] A207. The method of embodiment A206, wherein the modulation caspase activity induces apoptosis of the cell.
- [001235] A208. The method of embodiment A206 or A207, wherein the cell is in a subject.
- [001236] A209. The method of any one of embodiments A206-A208, wherein the cell is a mammalian cell.
- [001237] A210. The method of any one of embodiments A206-A209, wherein the cell is a human cell.
- [001238] A211. The method of any one of embodiments A206-A210, wherein the subject suffers from a cancer.
- [001239] A212. The method of any one of embodiments A202-A211, wherein the modulation takes place in a subject suffering from a cancer.
- [001240] A213. The method of embodiment A211 or embodiment A212, wherein the cancer is a solid tumor or is a blood borne tumor (or a hematological cancer).
- [001241] A214. The method of any one of embodiments A211-A213, wherein the cancer is hepatocellular carcinoma, prostate cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, colon cancer, small intestine cancer, biliary tract cancer, endometrium cancer, skin cancer (melanoma), cervix cancer, urinary tract cancer, glioblastoma, esophageal carcinoma, mesothelioma, or multiple myeloma; optionally wherein the cancer is hepatocellular carcinoma, pancreatic cancer, glioblastoma, esophageal carcinoma, mesothelioma, or small cell lung cancer (SCLC).
- [001242] A215. The method of embodiment A214, wherein the cancer is pancreatic cancer.
- [001243] A216. The method of embodiment A214, wherein the cancer is colon cancer.
- [001244] A217. The method of embodiment A214, wherein the cancer is triple negative breast cancer.
- [001245] A218. The method of embodiment A214, wherein the cancer is multiple myeloma.

- [001246] A219. The method of any one of embodiments A208-A218, wherein the subject is a human.
- [001247] A220. A method of inhibiting one or more proteasome ATPase, comprising contacting a proteasome ATPase with an effective amount of the compound of any one of embodiments A1-A167, or pharmaceutically acceptable form thereof.
- [001248] A221. A method of inhibiting one or more AAA-ATPase of a 19S regulatory particle, comprising contacting an AAA-ATPase with an effective amount of the compound of any one of embodiments A1-A167, or pharmaceutically acceptable form thereof.
- [001249] A222. The method of embodiment A220 or A221, wherein the contacting takes place in a cell.
- [001250] A223. The method of embodiment A222, wherein the cell is in a subject.
- [001251]
- [001252] A224. The method of embodiment A222 or A223, wherein the cell is a mammalian cell.
- [001253] A225. The method of embodiment A222 or A223, wherein the cell is a human cell.
- [001254] A226. The method of any one of embodiments A223-A225, wherein the subject is suffering from cancer.
- [001255] A227. The method of any one of embodiments A220-A226, wherein the inhibition takes place in a subject suffering from a cancer.
- [001256] A228. The method of embodiment A226 or A227, wherein the cancer is a solid tumor or is a blood borne tumor (or a hematological cancer).
- [001257] A229. The method of any one of embodiments A226-A228, wherein the cancer is hepatocellular carcinoma, prostate cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, colon cancer, small intestine cancer, biliary tract cancer, endometrium cancer, skin cancer (melanoma), cervix cancer, urinary tract cancer, glioblastoma, esophageal carcinoma, mesothelioma, or multiple myeloma; optionally wherein the cancer is hepatocellular carcinoma, pancreatic cancer, glioblastoma, esophageal carcinoma, mesothelioma, or small cell lung cancer (SCLC).
- [001258] A230. A method of treating cancer in a subject, comprising administering a therapeutically effective amount of the compound of any one of embodiments A1-A167, or pharmaceutically acceptable form thereof, to the subject having cancer.

- [001259] A231. A method of treating cancer in a subject, comprising administering a therapeutically effective amount of the pharmaceutical composition of embodiment A168 to the subject having cancer.
- [001260] A232. The method of embodiment A230 or embodiment A231, wherein the cancer is a solid tumor or is a blood borne tumor (or a hematological cancer).
- [001261] A233. The method of any one of embodiments A230-A232, wherein the cancer is hepatocellular carcinoma, prostate cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, colon cancer, small intestine cancer, biliary tract cancer, endometrium cancer, skin cancer (melanoma), cervix cancer, urinary tract cancer, glioblastoma, esophageal carcinoma, mesothelioma, or multiple myeloma; optionally wherein the cancer is hepatocellular carcinoma, pancreatic cancer, glioblastoma, esophageal carcinoma, mesothelioma, or small cell lung cancer (SCLC).
- [001262] A234. The method of embodiment A233, wherein the cancer is pancreatic cancer.
- [001263] A235. The method of embodiment A233, wherein the cancer is colon cancer.
- [001264] A236. The method of embodiment A233, wherein the cancer is triple negative breast cancer.
- [001265] A237. The method of embodiment A233, wherein the cancer is multiple myeloma.
- [001266] A238. The method of any one of embodiments A230-A237, wherein the cancer is a cancer dependent on a Ras superfamily protein.
- [001267] A239. The method of embodiment A238, wherein the Ras superfamily protein is a Ras protein, or a mutant thereof.
- [001268] A240. The method of embodiment A249, wherein the Ras protein is DIRAS I; DIRAS2; DIRAS3; ERAS; GEM; HRAS; KRAS; MRAS; NKIRASI; NKIRAS2; NRAS; RALA; RALB; RAPIA; RAPIB; RAP2A; RAP2B; RAP2C; RASDI; RASD2; RASLIOA; RASLIOB; RASLI IA; RASLIIB; RASLI2; REMI; REM2; RERG; RERGL; RRAD; RRAS; or RRAS2.
- [001269] A241. The method of embodiment A240, wherein the Ras protein is HRAS; KRAS; or NRAS, or a mutant thereof.
- [001270] A242. The method of embodiment A241, wherein the Ras protein is a KRAS mutant.
- [001271] A243. The method of embodiment A242, wherein the KRAS mutant is a KRas G12D mutant, KRas G12C mutant, or KRas Q61H mutant.

- [001272] A244. The method of embodiment A241, wherein the Ras protein is HRAS or a mutant thereof.
- [001273] A245. The method of embodiment A241, wherein the Ras protein is NRAS or a mutant thereof.
- [001274] A246. The method of embodiment A238, wherein the Ras superfamily protein is a Rac protein, or a mutant thereof.
- [001275] A247. The method of embodiment A246, wherein the Rac protein is RAC1; RAC2; RAC3; RHOG, or a mutant thereof.
- [001276] A248. The method of embodiment A247, wherein the Rac protein is wild-type RAC1.
- [001277] A249. The method of embodiment A238, wherein the Ras superfamily protein is a Rho protein, or a mutant thereof.
- [001278] A250. The method of embodiment A249, wherein the Rho protein is RHOA; RHOB; RHOBTB1; RHOBTB2; RHOBTB3; RHOC; RHOD; RHOF; RHOH; RHOJ; RHOQ; RHOU; RHOV; RND1; RND2; RND3; CDC42, or a mutant thereof.
- [001279] A251. The method of embodiment A250, wherein the Rho protein is wild-type RHOA.
- [001280] A252. The method of embodiment A238, wherein the Ras superfamily protein is a Cdc42 protein, or a mutant thereof.
- [001281] A253. The method of embodiment A238, wherein the Ras superfamily protein is a Rheb protein, or a mutant thereof.
- [001282] A254. The method of any one of embodiments A230-A253, wherein the administration activates caspase activity in a cancerous cell of the subject.
- [001283] A255. The method of embodiment A254, wherein the activation induces apoptosis of the cancerous cell.
- [001284] A256. The method of any one of embodiments A230-A255, wherein the subject is a human.
- [001285] A257. A method of modulating Erk1/2 activity, comprising contacting an Erk1/2 protein with an effective amount of the compound of any one of embodiments A1-A167, or pharmaceutically acceptable form thereof.

- [001286] A258. A method of modulating Erk1/2 activity, comprising contacting an Erk1/2 protein with an effective amount of the pharmaceutical composition of embodiment A168.
- [001287] A259. The method of embodiment A257 or embodiment A258, wherein the method inhibits phosphorylation of the Erk1/2 protein.
- [001288] A260. The method of embodiment A257 or embodiment A258, wherein the method activates phosphorylation of the Erk1/2 protein.
- [001289] A261. A method of modulating Akt activity, comprising contacting an Akt protein with an effective amount of the compound of any one of embodiments A1-A167, or pharmaceutically acceptable form thereof.
- [001290] A262. A method of modulating Akt activity, comprising contacting an AKT protein with an effective amount of the pharmaceutical composition of embodiment A168.
- [001291] A263. The method of embodiment A261 or embodiment A262, wherein the method inhibits phosphorylation of the Akt protein.
- [001292] A264. The method of embodiment A261 or embodiment A262, wherein the method activates phosphorylation of the Akt protein.
- [001293] A265. A method of modulating Smad2/3 activity, comprising contacting a Smad2/3 protein with an effective amount of the compound of any one of embodiments A1-A167, or pharmaceutically acceptable form thereof.
- [001294] A266. A method of modulating Smad2/3 activity, comprising contacting a Smad2/3 protein with an effective amount of the pharmaceutical composition of embodiment A168.
- [001295] A267. The method of embodiment A265 or embodiment A266, wherein the method inhibits phosphorylation of the Smad2/3 protein.
- [001296] A268. The method of embodiment A265 or embodiment A266, wherein the method activates phosphorylation of the Smad2/3 protein.
- [001297] A269. A method of modulating JNK activity, comprising contacting a JNK protein with an effective amount of the compound of any one of embodiments A1-A167, or pharmaceutically acceptable form thereof.
- [001298] A270. A method of modulating JNK activity, comprising contacting a JNK protein with an effective amount of the pharmaceutical composition of embodiment A168.
- [001299] A271. The method of embodiment A269 or embodiment A270, wherein the method inhibits phosphorylation of the JNK protein.

- [001300] A272. The method of embodiment A269 or embodiment A270, wherein the method activates phosphorylation of the JNK protein.
- [001301] A273. A method of modulating MAPK p38 activity, comprising contacting a MAPK p38 protein with an effective amount of the compound of any one of embodiments A1-A167, or pharmaceutically acceptable form thereof.
- [001302] A274. A method of modulating MAPK p38 activity, comprising contacting a MAPK p38 protein with an effective amount of the pharmaceutical composition of embodiment A168.
- [001303] A275. The method of embodiment A273 or embodiment A274, wherein the method inhibits phosphorylation of the MAPK p38 protein.
- [001304] A276. The method of embodiment A273 or embodiment A274, wherein the method activates phosphorylation of the MAPK p38 protein.
- [001305] A277. A method of modulating IL-6 activity, comprising contacting a IL-6 protein with an effective amount of the compound of any one of embodiments A1-A167, or pharmaceutically acceptable form thereof.
- [001306] A278. A method of modulating IL-6 activity, comprising contacting a IL-6 protein with an effective amount of the pharmaceutical composition of embodiment A168.
- [001307] A279. The method of embodiment A277 or embodiment A278, wherein the method inhibits IL-6 activity.
- [001308] A280. A method of modulating TNF-alpha activity, comprising contacting a TNF-alpha protein with an effective amount of the compound of any one of embodiments A1-A167, or pharmaceutically acceptable form thereof.
- [001309] A281. A method of modulating TNF-alpha activity, comprising contacting a TNF-alpha protein with an effective amount of the pharmaceutical composition of embodiment A168.
- [001310] A282. The method of embodiment A280 or embodiment A281, wherein the method inhibits TNF-alpha activity.
- [001311] A283. A method of treating a fibrotic disease in a subject, comprising administering a therapeutically effective amount of the compound of any one of embodiments A1-A167, or pharmaceutically acceptable form thereof, to the subject.

[001312] A284. A method of treating a fibrotic disease in a subject, comprising administering a therapeutically effective amount of the pharmaceutical composition of embodiment A168 to the subject.

[001313] A285. A method of treating an inflammatory disease in a subject, comprising administering a therapeutically effective amount of the compound of any one of embodiments A1-A167, or pharmaceutically acceptable form thereof, to the subject.

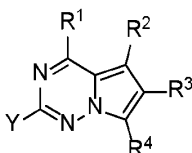
[001314] A286. A method of treating an inflammatory disease in a subject, comprising administering a therapeutically effective amount of the pharmaceutical composition of embodiment A168 to the subject.

[001315] This disclosure is not to be limited in scope by the embodiments disclosed in the examples which are intended as single illustrations of individual aspects, and any methods which are functionally equivalent are within the scope of this disclosure. Indeed, various modifications in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims. This disclosure is not to be limited in scope, or cabined in any way, by the use of any subheadings, which are provided only for the convenience of the reader.

[001316] All references, such as publications, patents, and patent applications, mentioned in this specification are herein incorporated by reference in their entirety to the same extent as if each individual publication, patent, and patent application, was specifically and individually indicated to be incorporated by reference in its entirety.

What is claimed is:

1. A compound of Formula I:



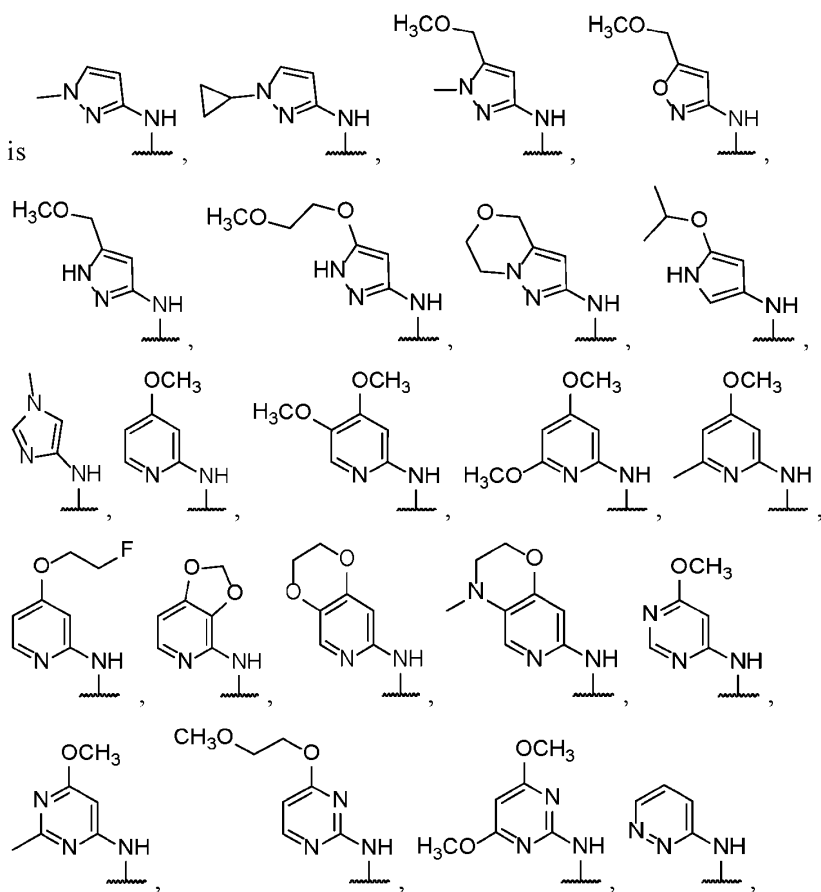
Formula I

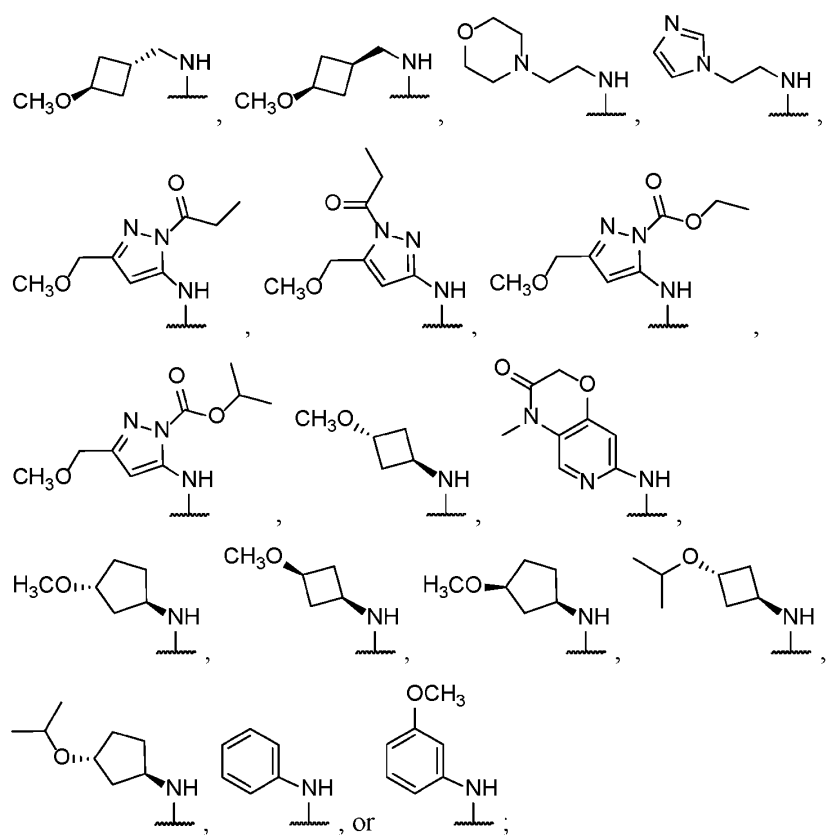
or a pharmaceutically acceptable form thereof, wherein:

- Y is an imidazolyl; wherein the imidazolyl is optionally substituted with 1 R⁵ substituent and optionally substituted with 1-2 R⁶ substituents;

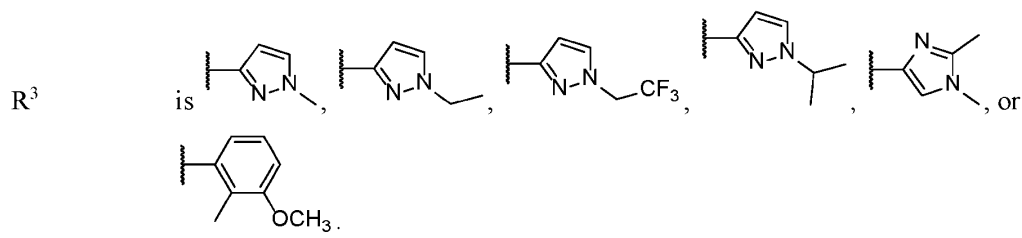
R¹

is





R² is C₁₋₂ alkyl or C₁₋₂ haloalkyl;



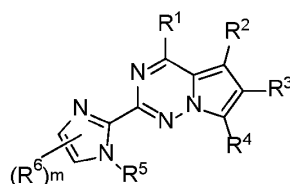
R^4 is hydrogen or C₁₋₆ alkyl;

R⁵ and R⁶ are each independently C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, aryl, C₅₋₁₀ heteroaryl, C₃₋₇ heterocycloalkyl, C₁₋₆ heteroalkyl, halo, -NR⁹R¹⁰, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -C(O)NR⁹R¹⁰, -(CO)R⁸, -(CO)OH, -(CO)OR⁸, or CN, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, aryl, C₅₋₁₀ heteroaryl, C₃₋₇ heterocycloalkyl, and C₁₋₆ heteroalkyl are each independently optionally substituted with 1-3 R⁷ substituents;

- R^7 is independently selected from the group consisting of halo, CN, C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, $-NR^9R^{10}$, $-(CO)R^8$, $-(CO)OH$, $-(CO)OR^8$, $-C(O)NR^9R^{10}$, oxo, $-OH$, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, C_{1-6} haloalkoxy, or 5-6 membered heteroaryl;
- R^8 is C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^7 substituents; and
- R^9 and R^{10} are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, $-OH$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-7} heterocycloalkyl, aryl, or 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-7} heterocycloalkyl, aryl, and 5-10 membered heteroaryl are optionally substituted with 1-3 R^7 substituents, or R^9 and R^{10} are combined to form a 3-7 membered heterocycloalkyl including the nitrogen atom to which they are both attached.

2. The compound of claim 1, wherein Y is a C-linked imidazolyl that is substituted with 1 R^5 substituent at a nitrogen of the imidazolyl ring and optionally substituted with 1-2 R^6 substituents at carbons of the imidazolyl ring.

3. The compound of claim 1 or claim 2, wherein the compound is a compound of Formula IA:

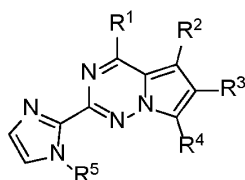


Formula IA

wherein m is 0, 1 or 2;

or a pharmaceutically acceptable form thereof.

4. The compound of any one of claims 1-3, wherein m is 0 and the compound is a compound of Formula IA(1):



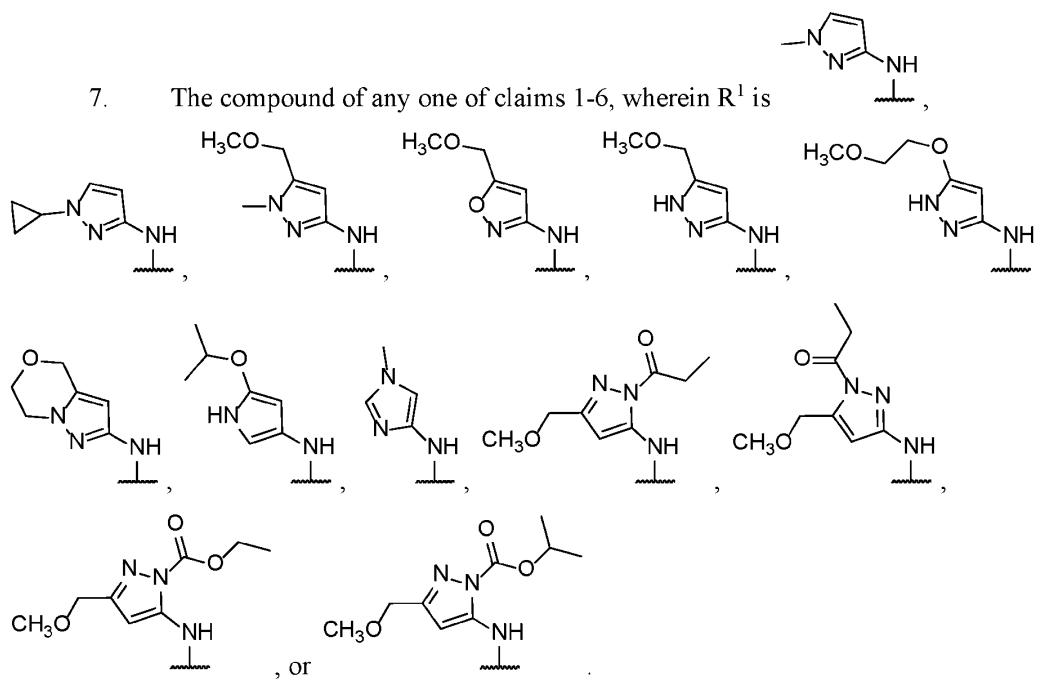
Formula IA(1)

or a pharmaceutically acceptable form thereof.

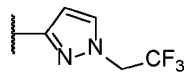
5. The compound of claim 3, wherein m is 1.

6. The compound of claim 3, wherein m is 2.

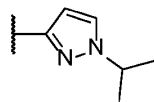
7. The compound of any one of claims 1-6, wherein R¹ is



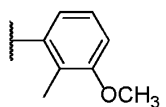
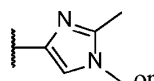
12. The compound of any one of claims 1-9, wherein R^3 is



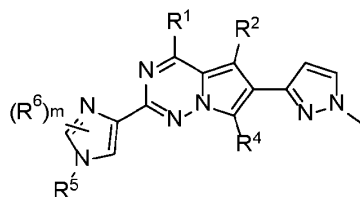
13. The compound of any one of claims 1-9, wherein R^3 is



14. The compound of any one of claims 1-9, wherein R^3 is

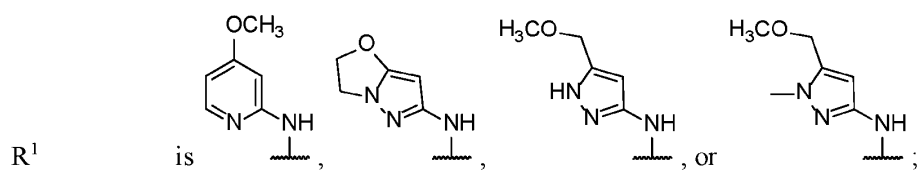


15. A compound of Formula IB:



Formula IB

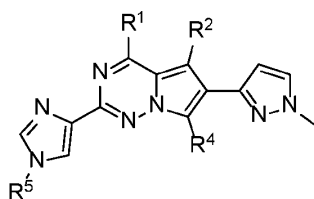
or a pharmaceutically acceptable form thereof, wherein:



- R^1 is , , , or ;
- R^2 is C_{1-2} alkyl or C_{1-2} haloalkyl;
- R^4 is hydrogen or C_{1-6} alkyl;
- R^5 and R^6 are each independently C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, C_{1-6} heteroalkyl, halo, $-NR^9R^{10}$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-C(O)NR^9R^{10}$, $-(CO)R^8$, $-(CO)OH$, $-(CO)OR^8$, or CN,

- wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, aryl, C₅₋₁₀ heteroaryl, C₃₋₇ heterocycloalkyl, and C₁₋₆ heteroalkyl are each independently optionally substituted with 1-3 R⁷ substituents;
- R⁷ is independently selected from the group consisting of halo, CN, C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, 3-6 membered heterocycloalkyl, -NR⁹R¹⁰, -(CO)R⁸, -(CO)OH, -(CO)OR⁸, -C(O)NR⁹R¹⁰, oxo, -OH, C₁₋₆ alkoxy, C₃₋₆ cycloalkoxy, C₁₋₆ haloalkoxy, or 5-6 membered heteroaryl;
- R⁸ is C₁₋₆ alkyl, C₃₋₆ cycloalkyl, or C₁₋₆ heteroalkyl, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, and C₁₋₆ heteroalkyl, are each independently optionally substituted with 1-3 R⁷ substituents;
- R⁹ and R¹⁰ are each independently selected from the group consisting of hydrogen, C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, -OH, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ heterocycloalkyl, aryl, or 5-10 membered heteroaryl, wherein the C₁₋₆ alkyl, C₃₋₇ cycloalkyl, C₁₋₆ haloalkyl, C₁₋₆ hydroxyalkyl, C₁₋₆ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, C₃₋₇ heterocycloalkyl, aryl, and 5-10 membered heteroaryl are optionally substituted with 1-3 R⁷ substituents, or R⁹ and R¹⁰ are combined to form a 3-7 membered heterocycloalkyl including the nitrogen atom to which they are both attached; and
- m is 0, 1 or 2.

16. The compound of claim 15, wherein m is 0 and the compound is a compound of Formula IB(1):

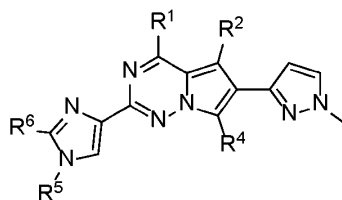


Formula IB(1)

or a pharmaceutically acceptable form thereof.

17. The compound of claim 15, wherein m is 1.

18. The compound of claim 17, wherein the compound is a compound of Formula IB(2):

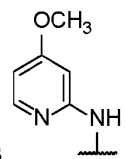


Formula IB(2)

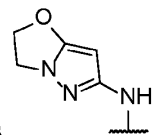
or a pharmaceutically acceptable form thereof.

19. The compound of claim 15, wherein m is 2.

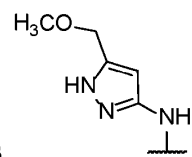
20. The compound of any one of claims 15-19, wherein R¹ is

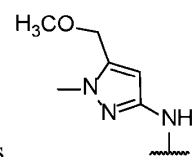


21. The compound of any one of claims 15-19, wherein R¹ is



22. The compound of any one of claims 15-19, wherein R¹ is





23. The compound of any one of claims 15-19, wherein R^1 is
24. The compound of any one of claims 1-23, wherein R^2 is methyl, ethyl, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, $-\text{CF}_3$, $-\text{CH}_2\text{CF}_3$, $-\text{CF}_2\text{CH}_3$, or $-\text{CF}_2\text{CF}_3$.
25. The compound of any one of claims 1-24, wherein R^2 is methyl.
26. The compound of any one of claims 1-25, wherein R^4 is hydrogen or C_{1-6} alkyl.
27. The compound of any one of claims 1-26, wherein R^4 is hydrogen, methyl, ethyl, or isopropyl.
28. The compound of any one of claims 1-27, wherein R^4 is hydrogen.
29. The compound of any one of claims 1-28, wherein R^5 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, C_{1-6} heteroalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, $-\text{C}(\text{O})\text{NR}^9\text{R}^{10}$, $-(\text{CO})\text{R}^8$, or $-\text{C}(\text{O})\text{OR}^8$, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, aryl, C_{5-10} heteroaryl, C_{3-7} heterocycloalkyl, and C_{1-6} heteroalkyl are each independently optionally substituted with 1-3 R^7 substituents.
30. The compound of any one of claims 1-29, wherein R^5 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^7 substituents.
31. The compound of any one of claims 1-30, wherein R^5 is methyl, ethyl, or isopropyl, wherein the methyl, ethyl, and isopropyl are each independently optionally substituted with 1-3 R^7 , wherein R^7 is $-\text{OH}$, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.

32. The compound of any one of claims 1-31, wherein R^5 is methyl, ethyl, or isopropyl.
33. The compound of any one of claims 1-32, wherein R^5 is methyl.
34. The compound of any one of claims 1-33, wherein R^6 is C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, C_{1-6} haloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^7 substituents.
35. The compound of any one of claims 1-34, wherein R^6 is methyl, ethyl, or isopropyl, wherein the methyl, ethyl, and isopropyl are each independently optionally substituted with 1-3 R^7 , wherein R^7 is -OH, C_{1-3} alkoxy, or C_{1-3} haloalkoxy.
36. The compound of any one of claims 1-35, wherein R^6 is methyl, ethyl, or isopropyl.
37. The compound of any one of claims 1-36, wherein R^6 is methyl.
38. The compound of any one of claims 1-37, wherein R^7 is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, $-NR^9R^{10}$, $-(CO)R^8$, oxo, C_{1-6} alkoxy, or C_{3-6} cycloalkoxy.
39. The compound of any one of claims 1-38, wherein R^7 is independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-5} cycloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} heteroalkyl, 3-5 membered heterocycloalkyl, $-NR^9R^{10}$, $-(CO)R^8$, oxo, C_{1-4} alkoxy, or C_{3-5} cycloalkoxy.
40. The compound of any one of claims 1-39, wherein R^7 is independently selected from the group consisting of methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, C_{2-3}

hydroxyalkyl, C₂₋₄ heteroalkyl, -NR⁹R¹⁰, -(CO)R⁸, oxo, methoxy, ethoxy, isopropoxy, cyclopropoxy, or cyclobutoxy.

41. The compound of any one of claims 1-40, wherein R⁸ is methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or C₂₋₄ heteroalkyl.

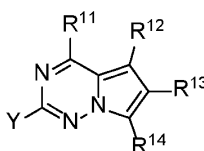
42. The compound of any one of claims 1-41, wherein R⁹ and R¹⁰ are each independently selected from the group consisting of hydrogen, C₁₋₄ alkyl, C₃₋₅ cycloalkyl, C₁₋₄ hydroxyalkyl, C₁₋₄ heteroalkyl, -OH, or C₁₋₄ alkoxy.

43. The compound of any one of claims 1-42, wherein R⁹ and R¹⁰ are each independently selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, methoxy, or ethoxy.

44. The compound of any one of claims 1-43, wherein R⁹ and R¹⁰ are each independently selected from the group consisting of hydrogen or methyl.

45. The compound of any one of claims 1-44, wherein R⁹ and R¹⁰ are each hydrogen.

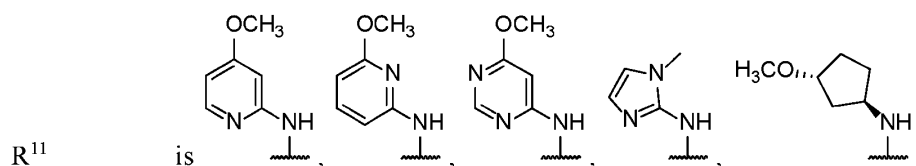
46. A compound of Formula II:

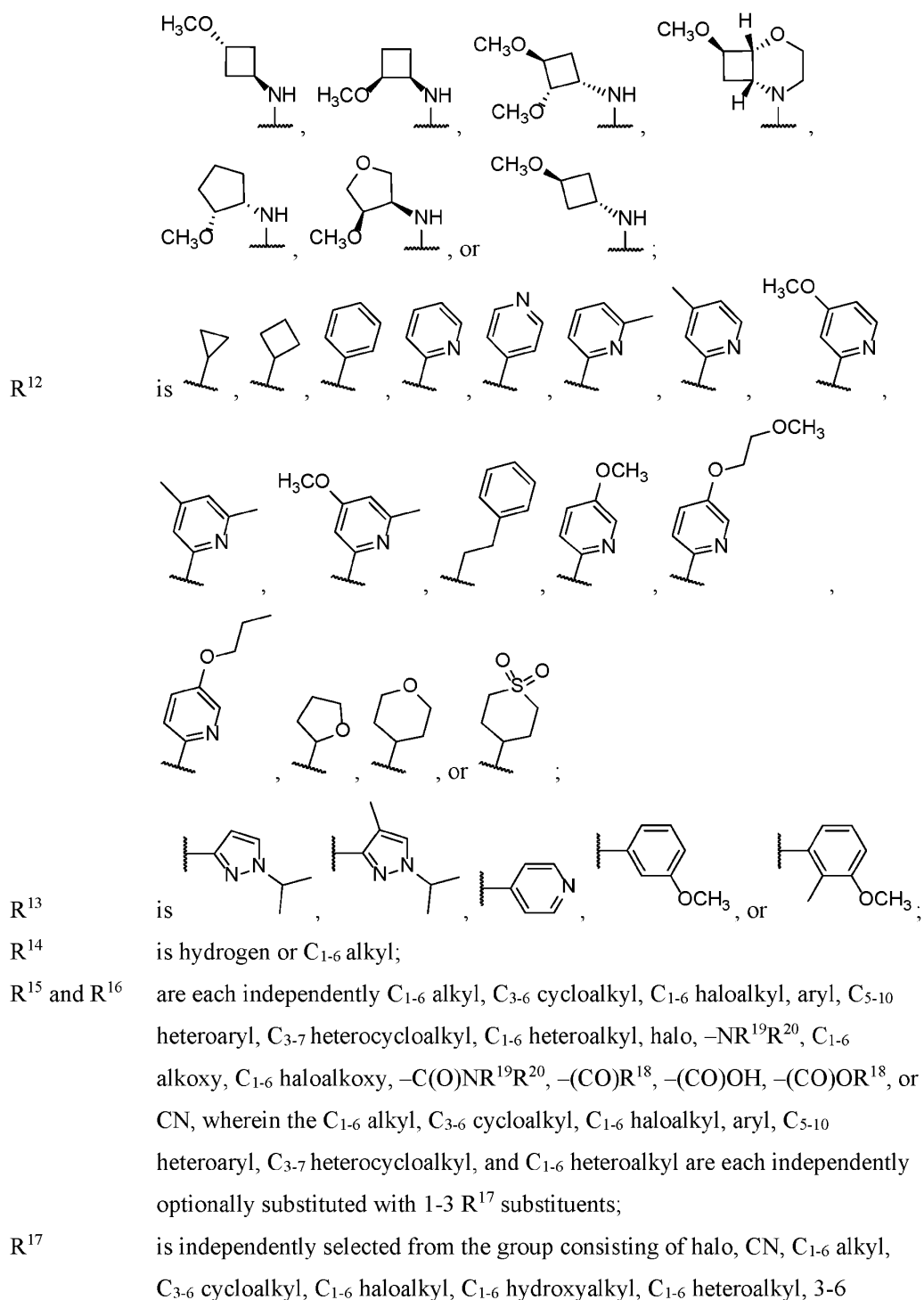


Formula II

or a pharmaceutically acceptable form thereof, wherein:

Y is an imidazolyl; wherein the imidazolyl is optionally substituted with 1 R¹⁵ substituent and optionally substituted with 1-2 R¹⁶ substituents;

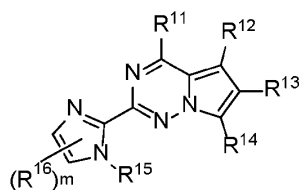




- membered heterocycloalkyl, $-\text{NR}^{19}\text{R}^{20}$, $-(\text{CO})\text{R}^{18}$, $-(\text{CO})\text{OH}$, $-(\text{CO})\text{OR}^{18}$, $-\text{C}(\text{O})\text{NR}^{19}\text{R}^{20}$, oxo, $-\text{OH}$, C_{1-6} alkoxy, C_{3-6} cycloalkoxy, C_{1-6} haloalkoxy, or 5-6 membered heteroaryl;
- R^{18} is C_{1-6} alkyl, C_{3-6} cycloalkyl, or C_{1-6} heteroalkyl, wherein the C_{1-6} alkyl, C_{3-6} cycloalkyl, and C_{1-6} heteroalkyl, are each independently optionally substituted with 1-3 R^{17} substituents; and
- R^{19} and R^{20} are each independently selected from the group consisting of hydrogen, C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, $-\text{OH}$, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-7} heterocycloalkyl, aryl, or 5-10 membered heteroaryl, wherein the C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{1-6} haloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, C_{1-6} alkoxy, C_{1-6} haloalkoxy, C_{3-7} heterocycloalkyl, aryl, and 5-10 membered heteroaryl are optionally substituted with 1-3 R^{17} substituents, or R^{19} and R^{20} are combined to form a 3-7 membered heterocycloalkyl including the nitrogen atom to which they are both attached.

47. The compound of claim 46, wherein Y is a C-linked imidazolyl that is substituted with 1 R^{15} substituent at a nitrogen of the imidazolyl ring and optionally substituted with 1-2 R^{16} substituents at carbons of the imidazolyl ring.

48. The compound of claim 46 or claim 47, wherein the compound is a compound of Formula IIA:



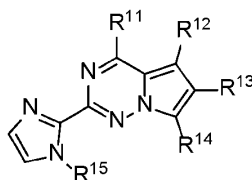
Formula IIA

wherein m is 0, 1 or 2;

or a pharmaceutically acceptable form thereof.

49. The compound of any one of claims 46-48, wherein m is 0 and the compound is a

compound of Formula IIA(1):



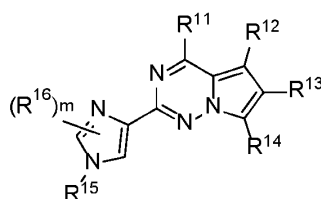
Formula IIA(1)

or a pharmaceutically acceptable form thereof.

50. The compound of any one of claims 46-48, wherein m is 1.

51. The compound of any one of claims 46-48, wherein m is 2.

52. The compound of claim 46 or claim 47, wherein the compound is a compound of Formula IIB:

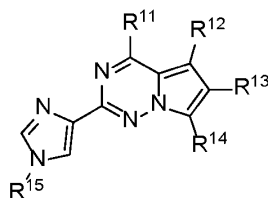


Formula IIB

wherein m is 0, 1 or 2;

or a pharmaceutically acceptable form thereof.

53. The compound of any one of claims 46, 47, or 52, wherein m is 0 and the compound is a compound of Formula IIB(1):

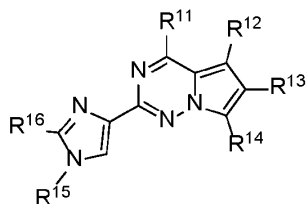


Formula IIB(1)

or a pharmaceutically acceptable form thereof.

54. The compound of any one of claims 46, 47, or 52, wherein m is 1.

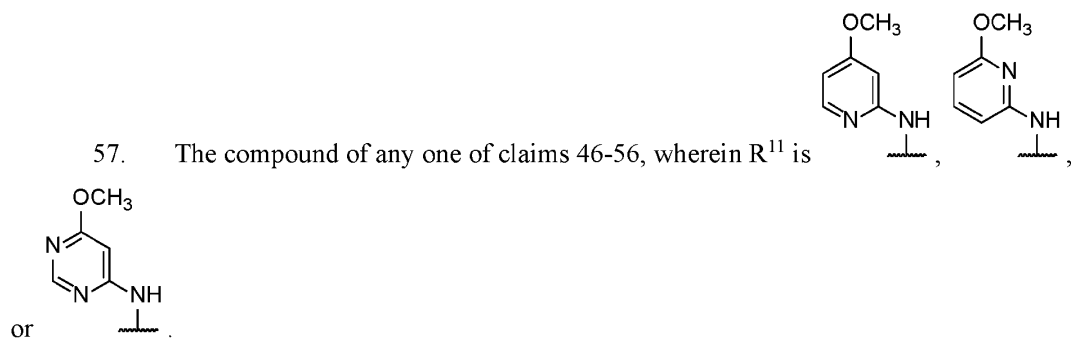
55. The compound of claim 54, wherein the compound is a compound of Formula IIB(2):



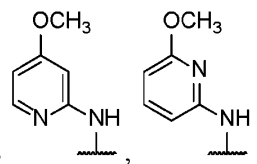
Formula IIB(2)

or a pharmaceutically acceptable form thereof.

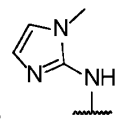
56. The compound of any one of claims 46, 47, or 52, wherein m is 2.



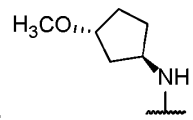
57. The compound of any one of claims 46-56, wherein R¹¹ is

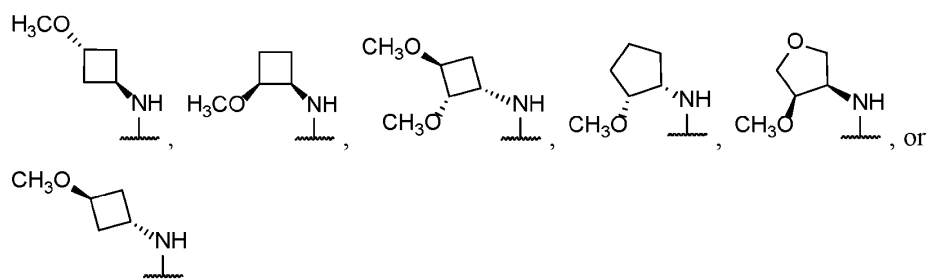


58. The compound of any one of claims 46-56, wherein R¹¹ is

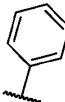
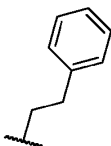


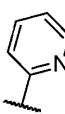
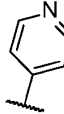
59. The compound of any one of claims 46-56, wherein R¹¹ is

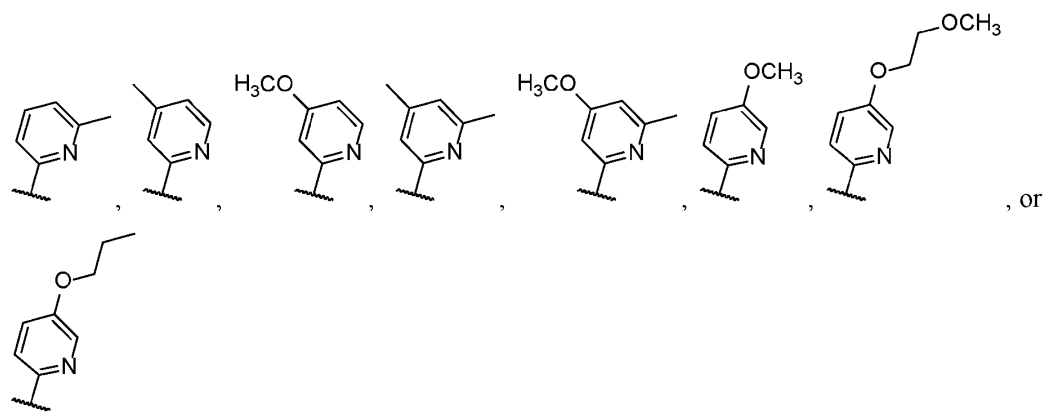


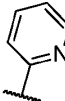


60. The compound of any one of claims 46-59, wherein R^{12} is  or .

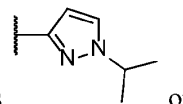
61. The compound of any one of claims 46-59, wherein R^{12} is  or .

62. The compound of any one of claims 46-59, wherein R^{12} is , ,

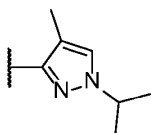


63. The compound of any one of claims 46-59, wherein R^{12} is .

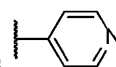
64. The compound of any one of claims 46-63, wherein R¹³ is



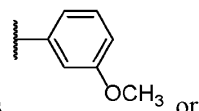
or



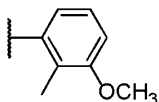
65. The compound of any one of claims 46-63, wherein R¹³ is



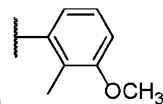
66. The compound of any one of claims 46-63, wherein R¹³ is



or



67. The compound of any one of claims 46-63, wherein R¹³ is



68. The compound of any one of claims 46-67, wherein R¹⁴ is hydrogen or C₁₋₆ alkyl.

69. The compound of any one of claims 46-68, wherein R¹⁴ is hydrogen, methyl, ethyl, or isopropyl.

70. The compound of any one of claims 46-69, wherein R¹⁴ is hydrogen.

71. The compound of any one of claims 46-70, wherein R¹⁵ is C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, aryl, C₅₋₁₀ heteroaryl, C₃₋₇ heterocycloalkyl, C₁₋₆ heteroalkyl, C₁₋₆ alkoxy, C₁₋₆ haloalkoxy, -C(O)NR¹⁹R²⁰, -(CO)R¹⁸, or -C(O)OR¹⁸, wherein the C₁₋₆ alkyl, C₃₋₆

cycloalkyl, C₁₋₆ haloalkyl, aryl, C₅₋₁₀ heteroaryl, C₃₋₇ heterocycloalkyl, and C₁₋₆ heteroalkyl are each independently optionally substituted with 1-3 R¹⁷ substituents.

72. The compound of any one of claims 46-71, wherein R¹⁵ is C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, or C₁₋₆ heteroalkyl, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl, are each independently optionally substituted with 1-3 R¹⁷ substituents.

73. The compound of any one of claims 46-72, wherein R¹⁵ is methyl, ethyl, or isopropyl, wherein the methyl, ethyl, and isopropyl are each independently optionally substituted with 1-3 R¹⁷, wherein R¹⁷ is -OH, C₁₋₃ alkoxy, or C₁₋₃ haloalkoxy.

74. The compound of any one of claims 46-73, wherein R¹⁵ is methyl, ethyl, or isopropyl.

75. The compound of any one of claims 46-74, wherein R¹⁵ is methyl.

76. The compound of any one of claims 46-75, wherein R¹⁶ is C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, or C₁₋₆ heteroalkyl, wherein the C₁₋₆ alkyl, C₃₋₆ cycloalkyl, C₁₋₆ haloalkyl, and C₁₋₆ heteroalkyl, are each independently optionally substituted with 1-3 R¹⁷ substituents.

77. The compound of any one of claims 46-76, wherein R¹⁶ is methyl, ethyl, or isopropyl, wherein the methyl, ethyl, and isopropyl are each independently optionally substituted with 1-3 R¹⁷, wherein R¹⁷ is -OH, C₁₋₃ alkoxy, or C₁₋₃ haloalkoxy.

78. The compound of any one of claims 46-77, wherein R¹⁶ is methyl, ethyl, or isopropyl.

79. The compound of any one of claims 46-78, wherein R¹⁶ is methyl.

80. The compound of any one of claims 46-79, wherein R^{17} is independently selected from the group consisting of C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{1-6} hydroxyalkyl, C_{1-6} heteroalkyl, 3-6 membered heterocycloalkyl, $-NR^{19}R^{20}$, $-(CO)R^{18}$, oxo, C_{1-6} alkoxy, or C_{3-6} cycloalkoxy.

81. The compound of any one of claims 46-80, wherein R^{17} is independently selected from the group consisting of C_{1-4} alkyl, C_{1-4} haloalkyl, C_{3-5} cycloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} heteroalkyl, 3-5 membered heterocycloalkyl, $-NR^{19}R^{20}$, $-(CO)R^{18}$, oxo, C_{1-4} alkoxy, or C_{3-5} cycloalkoxy.

82. The compound of any one of claims 46-81, wherein R^{17} is independently selected from the group consisting of methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, C_{2-3} hydroxyalkyl, C_{2-4} heteroalkyl, $-NR^{19}R^{20}$, $-(CO)R^{18}$, oxo, methoxy, ethoxy, isopropoxy, cyclopropoxy, or cyclobutoxy.

83. The compound of any one of claims 46-82, wherein R^{18} is methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, or C_{2-4} heteroalkyl.

84. The compound of any one of claims 46-83, wherein R^{19} and R^{20} are each independently selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{3-5} cycloalkyl, C_{1-4} hydroxyalkyl, C_{1-4} heteroalkyl, $-OH$, or C_{1-4} alkoxy.

85. The compound of any one of claims 46-84, wherein R^{19} and R^{20} are each independently selected from the group consisting of hydrogen, methyl, ethyl, isopropyl, cyclopropyl, cyclobutyl, methoxy, or ethoxy.

86. The compound of any one of claims 46-85, wherein R^{19} and R^{20} are each independently selected from the group consisting of hydrogen or methyl.

87. The compound of any one of claims 46-86, wherein R^{19} and R^{20} are each hydrogen.

88. The compound of any one of claims 1-87, wherein the compound has a MW of no more than 1,000 g/mol.

89. The compound of any one of claims 1-88, wherein the compound has a MW of no more than 900 g/mol, no more than 800 g/mol, no more than 700 g/mol, no more than 600 g/mol, or no more than 500 g/mol.

90. The compound of any one of claims 1-89, wherein the compound has a MW of no more than 600 g/mol.

91. The compound of any one of claims 1-90, wherein the compound has a MW of no more than 500 g/mol.

92. The compound of any one of claims 1-91, wherein the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, and 94, or a pharmaceutically acceptable form thereof, optionally wherein the compound is selected from the group consisting of 9, 10, 11, 16, 18, 19, 36, 37, 38, 39, 40, and 62, or a pharmaceutically acceptable form thereof, or optionally wherein the compound is selected from the group consisting of 36, 37, 38, 39, 40, and 62, or a pharmaceutically acceptable form thereof.

93. The compound of any one of claims 1-92, wherein the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 22, 23, 24, 25, 26, 27, 28, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, and 69, or a pharmaceutically acceptable form thereof.

94. The compound of any one of claims 1-92, wherein the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 25, 26, 27, 28,

34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, and 45, or a pharmaceutically acceptable form thereof.

95. The compound of any one of claims 1-92, wherein the compound is selected from the group consisting of Compounds 22, 23, 24, and 30, or a pharmaceutically acceptable form thereof.

96. The compound of any one of claims 1-92, wherein the compound is selected from the group consisting of Compounds 31, 32, 33, and 69, or a pharmaceutically acceptable form thereof.

97. The compound of any one of claims 1-92, wherein the compound is selected from the group consisting of Compounds 16, 17, 18, 19, 20, 21, 29, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, and 68, or a pharmaceutically acceptable form thereof.

98. The compound of any one of claims 1-92, wherein the compound is selected from the group consisting of Compounds 16, 17, 18, 19, 20, 21, 29, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, and 62, or a pharmaceutically acceptable form thereof.

99. The compound of any one of claims 1-92, wherein the compound is selected from the group consisting of Compounds 63, 64, and 65, or a pharmaceutically acceptable form thereof.

100. The compound of any one of claims 1-92, wherein the compound is selected from the group consisting of Compounds 66, 67, and 68, or a pharmaceutically acceptable form thereof.

101. The compound of any one of claims 1-100, wherein the pharmaceutically acceptable form of the compound is an isomer, isotopic variant, pharmaceutically acceptable salt, polymorph, or solvate of said compound.

102. The compound of any one of claims 1-101, wherein the pharmaceutically acceptable form of the compound is exclusive of a salt form.

103. The compound of any one of claims 1-102, wherein the isomer of the compound is a diastereomer or enantiomer of the compound.

104. The compound of any one of claims 1-103, wherein the compound is a tautomer of the compound.

105. The compound of any one of claims 1-104, wherein the compound is a racemate or a mixture of diastereomers.

106. The compound of any one of claims 1-104, wherein the compound is a single enantiomer or a single diastereomer.

107. The compound of claim 106, wherein the compound is a single enantiomer.

108. The compound of claim 107, wherein the compound is an (R)-enantiomer; optionally wherein the compound has an enantiomeric excess of greater than 10% of the (R)-enantiomer; optionally wherein the compound has an enantiomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (R)-enantiomer; optionally wherein the compound has an enantiomeric excess of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (R)-enantiomer.

109. The compound of claim 107, wherein the compound is an (S)-enantiomer; optionally wherein the compound has an enantiomeric excess of greater than 10% of the (S)-enantiomer; optionally wherein the compound has an enantiomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, 50% or

more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (S)-enantiomer; optionally wherein the compound has an enantiomeric excess of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (S)-enantiomer.

110. The compound of claim 106, wherein the compound is a single diastereomer; optionally wherein the compound is a (R)/(R)-, (R)/(S)-, (S)/(R)-, or (S)/(S)-single diastereomer.

111. The compound of claim 110, wherein the compound is an (R)/(R)-diastereomer; optionally wherein the compound has a diastereomeric excess of greater than 10% of the (R)/(R)-diastereomer; optionally wherein the compound has a diastereomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (R)/(R)-diastereomer; optionally wherein the compound has a diastereomeric of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (R)/(R)-diastereomer.

112. The compound of claim 110, wherein the compound is an (R)/(S)-diastereomer; optionally wherein the compound has a diastereomeric excess of greater than 10% of the (R)/(S)-diastereomer; optionally wherein the compound has a diastereomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (R)/(S)-diastereomer; optionally wherein the compound has a diastereomeric of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (R)/(S)-diastereomer.

113. The compound of claim 110, wherein the compound is an (S)/(R)-diastereomer; optionally wherein the compound has a diastereomeric excess of greater than 10% of the

(S)/(R)-diastereomer; optionally wherein the compound has a diastereomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (S)/(R)-diastereomer; optionally wherein the compound has a diastereomeric of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (S)/(R)-diastereomer.

114. The compound of claim 110, wherein the compound is an (S)/(S)-diastereomer; optionally wherein the compound has a diastereomeric excess of greater than 10% of the (S)/(S)-diastereomer; optionally wherein the compound has a diastereomeric excess of 15% or more, 20% or more, 25% or more, 30% or more, 35% or more, 40% or more, 45% or more, 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, 98% or more, or 99% or more of the (S)/(S)-diastereomer; optionally wherein the compound has a diastereomeric of about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99%, of the (S)/(S)-diastereomer.

115. The compound of any one of claims 1-114, wherein the compound or pharmaceutically acceptable form thereof is a modulator of Ras superfamily activity according to a Ras Superfamily Activity Assay.

116. The compound of claim 115, wherein the compound or pharmaceutically acceptable form thereof modulates Ras superfamily activity of one or more GTPase by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 20 μ M according to a Ras Superfamily Activity Assay.

117. The compound of claim 116, wherein the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 9, 10, 11, 12, 13, 16, 18, 22, 23, 24, 27, 28, 32, 33, 36, 37, 38, 39, 40, 57, 62, 75, 84, 86, and 92, or a pharmaceutically acceptable form thereof.

118. The compound of any one of claims 1-117, wherein the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 according to Erk1/2 Phosphorylation Assay.

119. The compound of claim 118, wherein the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Erk1/2 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Erk1/2 Phosphorylation Assay.

120. The compound of claim 119, wherein the compound is selected from the group consisting of Compounds 19, 20, 21, 49, 51, 53, 56, 67, 68, 79, 80, 81, 82, 89, and 94, or a pharmaceutically acceptable form thereof.

121. The compound of any one of claims 1-117, wherein the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 according to Erk1/2 Phosphorylation Assay.

122. The compound of claim 121, wherein the compound or pharmaceutically acceptable form thereof activates phosphorylation of Erk1/2 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Erk1/2 Phosphorylation Assay.

123. The compound of claim 122, wherein the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 9, 11, 13, 16, 18, 23, 27, 28, 36, 37, 38, 40, 54, 55, 57, 60, 61, 62, 75, and 83, or a pharmaceutically acceptable form thereof.

124. The compound of any one of claims 1-123, wherein the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt according to Akt Phosphorylation Assay.

125. The compound of claim 124, wherein the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Akt by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Akt Phosphorylation Assay.

126. The compound of claim 125, wherein the compound is selected from the group consisting of Compounds 19, 20, 49, 51, 53, 56, 79, 80, 81, and 94, or a pharmaceutically acceptable form thereof.

127. The compound of any one of claims 1-123, wherein the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt according to Akt Phosphorylation Assay.

128. The compound of claim 127, wherein the compound or pharmaceutically acceptable form thereof activates phosphorylation of Akt by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Akt Phosphorylation Assay.

129. The compound of claim 128, wherein the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 15, 16, 18, 22, 27, 28, 32, 36, 37, 38, 39, 40, 47, 54, 55, 57, 59, 60, 61, 62, 66, 67, 74, 75, 76, 83, 84, 86, 87, 88, and 91, or a pharmaceutically acceptable form thereof.

130. The compound of any one of claims 1-129, wherein the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 according to Phospho-Smad2/3 Inhibition Assay.

131. The compound of claim 130, wherein the compound or pharmaceutically acceptable form thereof inhibits phosphorylation of Smad2/3 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to Phospho-Smad2/3 Inhibition Assay.

132. The compound of claim 131, wherein the compound is selected from the group consisting of Compounds 19, 20, 21, 29, 49, 51, 56, 58, 61, 63, 64, 65, 68, 77, 79, 80, 81, 87, 88, 89, and 94, or a pharmaceutically acceptable form thereof.

133. The compound of any one of claims 1-129, wherein the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 according to Phospho-Smad2/3 Inhibition Assay.

134. The compound of claim 133, wherein the compound or pharmaceutically acceptable form thereof activates phosphorylation of Smad2/3 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to Phospho-Smad2/3 Inhibition Assay.

135. The compound of claim 134, wherein the compound is Compound 12, 14, 25, 26, 31, 32, 33, 37, 78, and 90, or a pharmaceutically acceptable form thereof.

136. The compound of any one of claims 1-135, wherein the compound or pharmaceutically acceptable form thereof inhibits JNK according to JNK Activation Assay.

137. The compound of claim 136, wherein the compound or pharmaceutically acceptable form thereof inhibits JNK by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to JNK Activation Assay.

138. The compound of claim 137, wherein the compound is Compound 8, or a pharmaceutically acceptable form thereof.

139. The compound of any one of claims 1-135, wherein the compound or pharmaceutically acceptable form thereof activates JNK according to JNK Activation Assay.

140. The compound of claim 139, wherein the compound or pharmaceutically acceptable form thereof activates JNK by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to JNK Activation Assay.

141. The compound of claim 140, wherein the compound is selected from the group consisting of Compounds 1, 2, 3, 4, 5, 6, and 7, or a pharmaceutically acceptable form thereof.

142. The compound of any one of claims 1-141, wherein the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 according to MAPK p38 Activation Assay.

143. The compound of claim 142, wherein the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to MAPK p38 Activation Assay.

144. The compound of claim 143, wherein the compound or pharmaceutically acceptable form thereof inhibits MAPK p38 by 90% or more, or 95% or more at 10 μ M according to MAPK p38 Activation Assay.

145. The compound of any one of claims 1-141, wherein the compound or pharmaceutically acceptable form thereof activates MAPK p38 according to MAPK p38 Activation Assay.

146. The compound of claim 145, wherein the compound or pharmaceutically acceptable form thereof activates MAPK p38 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, 95% or more, or equal or greater than 100% at 10 μ M according to MAPK p38 Activation Assay.

147. The compound of claim 146, wherein the compound is selected from the group consisting of Compounds 2, 3, 4, 5, 6, and 7, or a pharmaceutically acceptable form thereof.

148. The compound of any one of claims 1-147, wherein the compound or pharmaceutically acceptable form thereof inhibits IL-6 according to IL-6 Quantification Assay.

149. The compound of claim 148, wherein the compound or pharmaceutically acceptable form thereof inhibits IL-6 by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to IL-6 Quantification Assay.

150. The compound of claim 149, wherein the compound is selected from the group consisting of Compounds 4, 9, 10, 11, 16, 17, 19, 20, 92, and 94 or a pharmaceutically acceptable form thereof.

151. The compound of any one of claims 1-150, wherein the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha according to TNF-alpha Quantification Assay.

152. The compound of claim 151, wherein the compound or pharmaceutically acceptable form thereof inhibits TNF-alpha by 50% or more, 55% or more, 60% or more, 65% or more, 70% or more, 75% or more, 80% or more, 85% or more, 90% or more, or 95% or more at 10 μ M according to TNF-alpha Quantification Assay.

153. The compound of claim 152, wherein the compound is Compound 20 and 94, or a pharmaceutically acceptable form thereof.

154. The compound of any one of claims 1-153, wherein the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 according to Proliferation Assay.

155. The compound of claim 154, wherein the compound or pharmaceutically acceptable form thereof inhibits proliferation in MiaPaca2 with an IC_{50} value of 1 μM or less, 0.9 μM or less, 0.8 μM or less, 0.75 μM or less, 0.7 μM or less, 0.6 μM or less, 0.5 μM or less, 0.4 μM or less, 0.3 μM or less, 0.25 μM or less, 0.2 μM or less, 0.15 μM or less, 0.1 μM or less, 0.09 μM or less, 0.05 μM or less, or 0.03 μM or less, according to Proliferation Assay.

156. The compound of claim 155, wherein the compound is selected from the group consisting of Compounds 1, 3, 4, 9, 10, 11, 12, 13, 16, 18, 19, 22, 23, 28, 31, 32, 36, 37, 38, 39, 40, 47, 48, 49, 52, 57, 62, 65, 68, 75, 80, 81, 82, 83, 85, 87, and 94, or a pharmaceutically acceptable form thereof.

157. The compound of claim 155 or claim 156, wherein the compound is selected from the group consisting of Compounds 9, 10, 11, 16, 18, 19, 28, 36, 37, 38, 39, 40, 48, 57, 62, and 65, or a pharmaceutically acceptable form thereof.

158. The compound of any one of claims 155-157, wherein the compound is selected from the group consisting of Compounds 9, 10, 11, 36, 37, 38, 39, 40, 62, and 65, or a pharmaceutically acceptable form thereof.

159. The compound of any one of claims 1-158, wherein the compound or pharmaceutically acceptable form thereof has a kinetic solubility of 10 μM or more, 20 μM or more, 30 μM or more, 40 μM or more, 50 μM or more, 60 μM or more, 70 μM or more, 80 μM or more, 90 μM or more, 100 μM or more, 150 μM or more, or 200 μM or more in pH 7.4 buffer comprising 2% DMSO according to Kinetic Solubility Assay.

160. The compound of claim 159, wherein the compound is selected from the group consisting of Compounds 9 and 11, or a pharmaceutically acceptable form thereof.

161. The compound of claim 159 or claim 160, wherein the compound is Compound 9, or a pharmaceutically acceptable form thereof.

162. The compound of any one of claims 1-161, wherein the compound or pharmaceutically acceptable form thereof has a half-life of 10 minutes or more, 20 minutes or more, 30 minutes or more, 40 minutes or more, or 50 minutes or more in mouse liver microsomes according to Mouse Liver Microsome Metabolic Stability Assay.

163. The compound of claim 162, wherein the compound is Compound 11, or a pharmaceutically acceptable form thereof.

164. The compound of any one of claims 1-163, wherein the compound or pharmaceutically acceptable form thereof inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, according to Proliferation Assay.

165. The compound of claim 164, wherein the compound or pharmaceutically acceptable form thereof inhibits proliferation in Kasumi-1, BT-549, GP2d, A375, MM.1R, IM.9, RPMI8226, NCI-H358, NCI-H727, MiaPaca-2, or Panc1, with an IC_{50} value of 50 nM or less, 40 nM or less, 30 nM or less, 20 nM or less, 10 nM or less, 1 nM or less, 0.1 nM or less, or 0.01 nM or less according to Proliferation Assay.

166. The compound of claim 164 or claim 165, wherein the compound or pharmaceutically acceptable form thereof inhibits proliferation in MM.R1 with an IC_{50} value of 1 nM or less, 0.1 nM or less, or 0.01 nM or less according to Proliferation Assay.

167. The compound of any one of claims 164-166, wherein the compound is selected from the group consisting of Compounds 9 and 11, or a pharmaceutically acceptable form thereof.

168. A pharmaceutical composition comprising the compound or pharmaceutically acceptable form thereof, of any one of claims 1-167, and a pharmaceutically acceptable carrier, excipient or diluent.

169. A method of modulating a Ras superfamily protein, comprising contacting the Ras superfamily protein with an effective amount of the compound of any one of claims 1-167, or pharmaceutically acceptable form thereof.

170. A method of modulating a Ras superfamily protein, comprising contacting the Ras superfamily protein with an effective amount of the pharmaceutical composition of claim 168.

171. The method of claim 169 or claim 170, wherein the Ras superfamily protein is present in a cell.

172. The method of any one of claims 169-171, wherein the method inhibits the Ras superfamily protein.

173. The method of any one of claims 169-172, wherein the Ras superfamily protein is a Ras protein, or a mutant thereof.

174. The method of claim 173, wherein the Ras protein is DIRAS I; DIRAS2; DIRAS3; ERAS; GEM; HRAS; KRAS; MRAS; NKIRASI; NKIRAS2; NRAS; RALA; RALB; RAPIA; RAPIB; RAP2A; RAP2B; RAP2C; RASDI; RASD2; RASLIOA; RASLIOB; RASLIA; RASLIIB; RASL12; REMI; REM2; RERG; RERGL; RRAD; RRAS; or RRAS2.

175. The method of claim 173 or claim 174, wherein the Ras protein is HRAS; KRAS; or NRAS, or a mutant thereof.

176. The method of any one of claims 173-175, wherein the Ras protein is a KRAS mutant.

177. The method of claim 176, wherein the KRAS mutant is a KRas G12D mutant, KRas G12C mutant, or KRas Q61H mutant.

178. The method of any one of claims 173-175, wherein the Ras protein is HRAS or a mutant thereof.

179. The method of any one of claims 173-175, wherein the Ras protein is NRAS or a mutant thereof.

180. The method of any one of claims 169-173, wherein the Ras superfamily protein is a Rac protein, or a mutant thereof.

181. The method of claim 180, wherein the Rac protein is RAC1; RAC2; RAC3; RHOG, or a mutant thereof.

182. The method of claim 180 or claim 181, wherein the Rac protein is wild-type RAC1.

183. The method of any one of claims 169-173, wherein the Ras superfamily protein is a Rho protein, or a mutant thereof.

184. The method of claim 183, wherein the Rho protein is RHOA; RHOB; RHOBTB1; RHOBTB2; RHOBTB3; RHOC; RHOD; RHOF; RHOH; RHOJ; RHOQ; RHOU; RHOV; RND1; RND2; RND3; CDC42, or a mutant thereof.

185. The method of claim 183 or claim 184, wherein the Rho protein is wild-type RHOA.

186. The method of any one of claims 169-173, wherein the Ras superfamily protein is a Cdc42 protein, or a mutant thereof.

187. The method of any one of claims 169-173, wherein the Ras superfamily protein is a Rheb protein, or a mutant thereof.

188. The method of any one of claims 169-187, wherein the contacting of the Ras superfamily protein takes place in a cell.
189. The method of claim 188, wherein the cell is in a subject.
190. The method of claim 188 or claim 189, wherein the cell is a mammalian cell.
191. The method of any one of claims 188-190, wherein the cell is a human cell.
192. The method of any one of claims 188-191, wherein the subject suffers from a cancer.
193. The method of any one of claim 169-192, wherein the modulation takes place in a subject suffering from a cancer.
194. The method of claim 192 or claim 193, wherein the cancer is a solid tumor or is a blood borne tumor (or a hematological cancer).
195. The method of any one of claims 192-194, wherein the cancer is hepatocellular carcinoma, prostate cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, colon cancer, small intestine cancer, biliary tract cancer, endometrium cancer, skin cancer (melanoma), cervix cancer, urinary tract cancer, glioblastoma, esophageal carcinoma, mesothelioma, or multiple myeloma; optionally wherein the cancer is hepatocellular carcinoma, pancreatic cancer, glioblastoma, esophageal carcinoma, mesothelioma, or small cell lung cancer (SCLC).
196. The method of claim 195, wherein the cancer is pancreatic cancer.
197. The method of claim 195, wherein the cancer is colon cancer.
198. The method of claim 195, wherein the cancer is triple negative breast cancer.

199. The method of claim 195, wherein the cancer is multiple myeloma.
200. The method of any one of claims 192-199, wherein the cancer is a cancer dependent on a Ras superfamily protein.
201. The method of any one of claims 189-200, wherein the subject is a human.
202. A method of modulating caspase activity, comprising contacting the caspase with an effective amount of the compound of any one of claims 1-167, or pharmaceutically acceptable form thereof.
203. A method of modulating caspase activity, comprising contacting the caspase with an effective amount of the pharmaceutical composition of claim 168.
204. The method of claim 202 or claim 203, wherein the method activates the caspase.
205. The method of any one of claims 202-204, wherein the caspase is caspase 3, caspase 6, or caspase 9.
206. The method of any one of claims 202-205, wherein the contacting of the caspase takes place in a cell.
207. The method of claim 206, wherein the modulation caspase activity induces apoptosis of the cell.
208. The method of claim 206 or 207, wherein the cell is in a subject.
209. The method of any one of claims 206-208, wherein the cell is a mammalian cell.
210. The method of any one of claims 206-209, wherein the cell is a human cell.

211. The method of any one of claims 206-210, wherein the subject suffers from a cancer.
212. The method of any one of claims 202-211, wherein the modulation takes place in a subject suffering from a cancer.
213. The method of claim 211 or claim 212, wherein the cancer is a solid tumor or is a blood borne tumor (or a hematological cancer).
214. The method of any one of claims 211-213, wherein the cancer is hepatocellular carcinoma, prostate cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, colon cancer, small intestine cancer, biliary tract cancer, endometrium cancer, skin cancer (melanoma), cervix cancer, urinary tract cancer, glioblastoma, esophageal carcinoma, mesothelioma, or multiple myeloma; optionally wherein the cancer is hepatocellular carcinoma, pancreatic cancer, glioblastoma, esophageal carcinoma, mesothelioma, or small cell lung cancer (SCLC).
215. The method of claim 214, wherein the cancer is pancreatic cancer.
216. The method of claim 214, wherein the cancer is colon cancer.
217. The method of claim 214, wherein the cancer is triple negative breast cancer.
218. The method of claim 214, wherein the cancer is multiple myeloma.
219. The method of any one of claims 208-218, wherein the subject is a human.
220. A method of inhibiting one or more proteasome ATPase, comprising contacting a proteasome ATPase with an effective amount of the compound of any one of claims 1-167, or pharmaceutically acceptable form thereof.
221. A method of inhibiting one or more AAA-ATPase of a 19S regulatory particle,

comprising contacting an AAA-ATPase with an effective amount of the compound of any one of claims 1-167, or pharmaceutically acceptable form thereof.

222. The method of claim 220 or 221, wherein the contacting takes place in a cell.

223. The method of claim 222, wherein the cell is in a subject.

224. The method of claim 222 or 223, wherein the cell is a mammalian cell.

225. The method of claim 222 or 223, wherein the cell is a human cell.

226. The method of any one of claims 223-225, wherein the subject is suffering from cancer.

227. The method of any one of claims 220-226, wherein the inhibition takes place in a subject suffering from a cancer.

228. The method of claim 226 or 227, wherein the cancer is a solid tumor or is a blood borne tumor (or a hematological cancer).

229. The method of any one of claims 226-228, wherein the cancer is hepatocellular carcinoma, prostate cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, colon cancer, small intestine cancer, biliary tract cancer, endometrium cancer, skin cancer (melanoma), cervix cancer, urinary tract cancer, glioblastoma, esophageal carcinoma, mesothelioma, or multiple myeloma; optionally wherein the cancer is hepatocellular carcinoma, pancreatic cancer, glioblastoma, esophageal carcinoma, mesothelioma, or small cell lung cancer (SCLC)..

230. A method of treating cancer in a subject, comprising administering a therapeutically effective amount of the compound of any one of claims 1-167, or pharmaceutically acceptable form thereof, to the subject having cancer.

231. A method of treating cancer in a subject, comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 168 to the subject having cancer.

232. The method of claim 230 or claim 231, wherein the cancer is a solid tumor or is a blood borne tumor (or a hematological cancer).

233. The method of any one of claims 230-232, wherein the cancer is hepatocellular carcinoma, prostate cancer, pancreatic cancer, lung cancer, breast cancer, ovarian cancer, colon cancer, small intestine cancer, biliary tract cancer, endometrium cancer, skin cancer (melanoma), cervix cancer, urinary tract cancer, glioblastoma, esophageal carcinoma, mesothelioma, or multiple myeloma; optionally wherein the cancer is hepatocellular carcinoma, pancreatic cancer, glioblastoma, esophageal carcinoma, mesothelioma, or small cell lung cancer (SCLC).

234. The method of claim 233, wherein the cancer is pancreatic cancer.

235. The method of claim 233, wherein the cancer is colon cancer.

236. The method of claim 233, wherein the cancer is triple negative breast cancer.

237. The method of claim 233, wherein the cancer is multiple myeloma.

238. The method of any one of claims 230-237, wherein the cancer is a cancer dependent on a Ras superfamily protein.

239. The method of claim 238, wherein the Ras superfamily protein is a Ras protein, or a mutant thereof.

240. The method of claim 249, wherein the Ras protein is DIRAS I; DIRAS2; DIRAS3; ERAS; GEM; HRAS; KRAS; MRAS; NKIRASI; NKIRAS2; NRAS; RALA; RALB; RAPIA; RAPIB; RAP2A; RAP2B; RAP2C; RASDI; RASD2; RASL1OA; RASL1OB; RASLI

IA; RASLIIB; RASL12; REMI; REM2; RERG; RERGL; RRAD; RRAS; or RRAS2.

241. The method of claim 240, wherein the Ras protein is HRAS; KRAS; or NRAS, or a mutant thereof.

242. The method of claim 241, wherein the Ras protein is a KRAS mutant.

243. The method of claim 242, wherein the KRAS mutant is a KRas G12D mutant, KRas G12C mutant, or KRas Q61H mutant.

244. The method of claim 241, wherein the Ras protein is HRAS or a mutant thereof.

245. The method of claim 241, wherein the Ras protein is NRAS or a mutant thereof.

246. The method of claim 238, wherein the Ras superfamily protein is a Rac protein, or a mutant thereof.

247. The method of claim 246, wherein the Rac protein is RAC1; RAC2; RAC3; RHOG, or a mutant thereof.

248. The method of claim 247, wherein the Rac protein is wild-type RAC1.

249. The method of claim 238, wherein the Ras superfamily protein is a Rho protein, or a mutant thereof.

250. The method of claim 249, wherein the Rho protein is RHOA; RHOB; RHOBTB1; RHOBTB2; RHOBTB3; RHOC; RHOD; RHOF; RHOH; RHOJ; RHOQ; RHOU; RHOV; RND1; RND2; RND3; CDC42, or a mutant thereof.

251. The method of claim 250, wherein the Rho protein is wild-type RHOA.

252. The method of claim 238, wherein the Ras superfamily protein is a Cdc42 protein, or a mutant thereof.

253. The method of claim 238, wherein the Ras superfamily protein is a Rheb protein, or a mutant thereof.

254. The method of any one of claims 230-253, wherein the administration activates caspase activity in a cancerous cell of the subject.

255. The method of claim 254, wherein the activation induces apoptosis of the cancerous cell.

256. The method of any one of claims 230-255, wherein the subject is a human.

257. A method of modulating Erk1/2 activity, comprising contacting an Erk1/2 protein with an effective amount of the compound of any one of claims 1-167, or pharmaceutically acceptable form thereof.

258. A method of modulating Erk1/2 activity, comprising contacting an Erk1/2 protein with an effective amount of the pharmaceutical composition of claim 168.

259. The method of claim 257 or claim 258, wherein the method inhibits phosphorylation of the Erk1/2 protein.

260. The method of claim 257 or claim 258, wherein the method activates phosphorylation of the Erk1/2 protein.

261. A method of modulating Akt activity, comprising contacting an Akt protein with an effective amount of the compound of any one of claims 1-167, or pharmaceutically acceptable form thereof.

262. A method of modulating Akt activity, comprising contacting an AKT protein with an effective amount of the pharmaceutical composition of claim 168.

263. The method of claim 261 or claim 262, wherein the method inhibits phosphorylation of the Akt protein.

264. The method of claim 261 or claim 262, wherein the method activates phosphorylation of the Akt protein.

265. A method of modulating Smad2/3 activity, comprising contacting a Smad2/3 protein with an effective amount of the compound of any one of claims 1-167, or pharmaceutically acceptable form thereof.

266. A method of modulating Smad2/3 activity, comprising contacting a Smad2/3 protein with an effective amount of the pharmaceutical composition of claim 168.

267. The method of claim 265 or claim 266, wherein the method inhibits phosphorylation of the Smad2/3 protein.

268. The method of claim 265 or claim 266, wherein the method activates phosphorylation of the Smad2/3 protein.

269. A method of modulating JNK activity, comprising contacting a JNK protein with an effective amount of the compound of any one of claims 1-167, or pharmaceutically acceptable form thereof.

270. A method of modulating JNK activity, comprising contacting a JNK protein with an effective amount of the pharmaceutical composition of claim 168.

271. The method of claim 269 or claim 270, wherein the method inhibits phosphorylation of the JNK protein.

272. The method of claim 269 or claim 270, wherein the method activates phosphorylation of the JNK protein.

273. A method of modulating MAPK p38 activity, comprising contacting a MAPK p38 protein with an effective amount of the compound of any one of claims 1-167, or pharmaceutically acceptable form thereof.

274. A method of modulating MAPK p38 activity, comprising contacting a MAPK p38 protein with an effective amount of the pharmaceutical composition of claim 168.

275. The method of claim 273 or claim 274, wherein the method inhibits phosphorylation of the MAPK p38 protein.

276. The method of claim 273 or claim 274, wherein the method activates phosphorylation of the MAPK p38 protein.

277. A method of modulating IL-6 activity, comprising contacting a IL-6 protein with an effective amount of the compound of any one of claims 1-167, or pharmaceutically acceptable form thereof.

278. A method of modulating IL-6 activity, comprising contacting a IL-6 protein with an effective amount of the pharmaceutical composition of claim 168.

279. The method of claim 277 or claim 278, wherein the method inhibits IL-6 activity.

280. A method of modulating TNF-alpha activity, comprising contacting a TNF-alpha protein with an effective amount of the compound of any one of claims 1-167, or pharmaceutically acceptable form thereof.

281. A method of modulating TNF-alpha activity, comprising contacting a TNF-alpha

protein with an effective amount of the pharmaceutical composition of claim 168.

282. The method of claim 280 or claim 281, wherein the method inhibits TNF-alpha activity.

283. A method of treating a fibrotic disease in a subject, comprising administering a therapeutically effective amount of the compound of any one of claims 1-167, or pharmaceutically acceptable form thereof, to the subject.

284. A method of treating a fibrotic disease in a subject, comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 168 to the subject.

285. A method of treating an inflammatory disease in a subject, comprising administering a therapeutically effective amount of the compound of any one of claims 1-167, or pharmaceutically acceptable form thereof, to the subject.

286. A method of treating an inflammatory disease in a subject, comprising administering a therapeutically effective amount of the pharmaceutical composition of claim 168 to the subject.