

TRPA1 MODULATORS

5 CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] The present application claims priority to United States Provisional Patent Application No. 61/924,119 filed on January 6, 2014, which application is incorporated herein by reference in its entirety.

10 REFERENCE TO A "SEQUENCE LISTING," A TABLE, OR A COMPUTER PROGRAM LISTING APPENDIX SUBMITTED ON A COMPACT DISK

[0002] This application includes a Sequence Listing as a text file named "97382-925619 (00110PC) Sequence Listing.txt," created December 16, 2014, and containing 66,887 bytes. The material contained in this text file is incorporated by reference in its entirety for all purposes.

15 STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

[0003] This invention was made with government support under grant 1R43DA031516, awarded by National Institute on Drug Abuse. The government has certain rights in the invention.

20 FIELD OF THE INVENTION

[0004] This disclosure relates to TRPA1-modulating compounds useful for treating pain as well as compositions and methods that include the compounds. In some embodiments, the compounds of the present invention have applications in preventing, reducing or inhibiting acute or chronic pain in a variety of operative and interventional procedures, including
25 surgical, diagnostic and therapeutic procedures.

BACKGROUND OF THE INVENTION

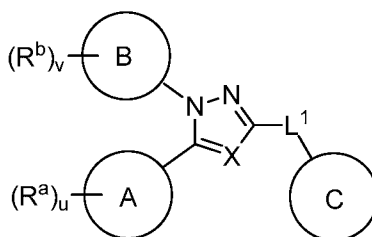
[0005] More than 100 million Americans suffer from chronic pain. Furthermore, problems with use of illicit drugs include pain-reliever misuse, abuse, and addiction. Because of this, it is increasingly difficult for patients with legitimate medical needs for opioid-containing
30 drugs, like Vicodin, to obtain prescriptions. The U.S. Substance Abuse and Mental Health Services Administration estimated 20.1 million Americans were illicit-drug users and an

estimated 4.7 million of those persons used pain relievers non-medically in 2008. Thus, an effective treatment for chronic pain that has less addictive potential and abuse liability is a major unmet need in medicine today.

[0006] Transient receptor potential cation channel, subfamily A, member 1, ("TRPA1"; wild-type, SEQ ID NO:1; variants, SEQ ID NOS:2-7) is a non-selective cation channel present in mammalian cells. TRPA1-receptor/channels play a highly specific function in sensory nerves that transmit the sensations of pain and hyperalgesia in response to inflammation as well as nerve injury, particularly in chronic conditions. Recent progress in understanding the function and identification of endogenous ligands for TRPA1 channels suggests that TRPA1 is relevant to detecting nociceptive signals.

BRIEF SUMMARY OF THE INVENTION

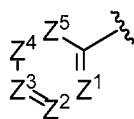
[0007] In one aspect, the invention provides a compound of Formula I:



or a pharmaceutically acceptable salt thereof;

wherein:

A is a cyclic group of Formula Ia:



Ia

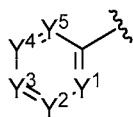
wherein Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are each a member selected from the group consisting of N, CH, and CR^a ; or, alternatively for Z^1 , the member Z^1 and X, together with atoms in the rings to which they are attached, form an additional fused, five- to eight-membered cycloalkyl or heterocyclyl ring with from 0 to 4 R^z substituents;

with the proviso that at least one member selected from the group consisting of Z^2 , Z^3 , and Z^4 is N;

each R^z is a member independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; or, alternatively, two R^z

substituents, together with the carbon atom to which they are attached, join to form an oxo, spirocycloalkyl, or spiroheterocyclyl group;

B is a cyclic group of Formula Ib:



Ib

wherein Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are each a member independently selected from the group consisting of N, CH, and CR^b ; or, alternatively, the members

$-Y^2=Y^3-$ or $-Y^4=Y^5-$ are combined into a single member selected from the group consisting of NH, NR^c , O, and S;

each R^a and R^b is a member independently selected from the group consisting of cyano, carboxyl, C_1 - C_4 alkyl, C_1 - C_4 hydroxyalkyl, C_3 - C_8 cycloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, halo, C_0 - C_6 amino, C_1 - C_6 amido, C_1 - C_4 alkyloxycarbonyl, C_1 - C_6 alkylsulfonyl, and hydroxyl; or, alternatively, two adjacent R^a or R^b , together with the atoms in groups A or B to which they are attached, form an additional fused aryl, heteroaryl, cycloalkyl, or heterocyclyl ring with from 0 to 4 R^z substituents;

each R^c is a member independently selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_3 - C_6 cycloalkyl, $(C_3$ - C_6 cycloalkyl) C_1 - C_3 alkyl, and C_1 - C_7 acyl;

each u is an integer independently selected from 0 to 4;

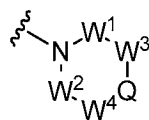
v is an integer from 0 to 5;

X is N or CR^d ; or, alternatively, X is CR^d , wherein X and the member Z^1 , together with atoms in the rings in which they are included, form the additional fused, five- to eight-membered cycloalkyl or heterocyclyl ring with from 0 to 4 R^z substituents;

each R^d is a member independently selected from the group consisting of halo, cyano, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, C_3 - C_6 cycloalkyl, and C_3 - C_6 cycloalkoxy;

each L^1 , L^2 , and L^3 , if present, is a member independently selected from the group consisting of $C=O$, $C=S$, $C=NH$, and $C=NR^c$;

C is a cyclic group of Formula Ic:

**Ic**

wherein Q is a member selected from the group consisting of C(R^e)(D), N(E), F, and G; or, alternatively, the members -W³-Q- or -W⁴-Q- join to form a member H; and

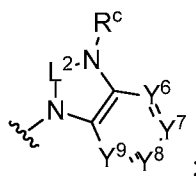
wherein W¹, W², W³, and W⁴ are each an independently selected C(R^f)₂; or, alternatively, the members -W³-Q- or -W⁴-Q- join to form a member H;

R^e is a member selected from the group consisting of hydrogen, C₁-C₃ alkyl, and C₁-C₃ fluoroalkyl; or, alternatively, R^e and an R^f substituent of W¹, W², W³, or W⁴ join to form a -(C(R^z)₂)_t- bridge, wherein t is an integer selected from 2 or 3;

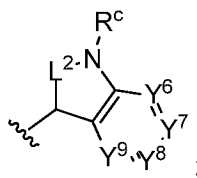
each R^f is a member independently selected from the group consisting of hydrogen, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, and halo; or, alternatively, two adjacent R^f, together with the atoms in group C to which they are attached, form an additional aryl, heteroaryl, cycloalkyl, or heterocyclyl fused ring with from 0 to 4 R^z substituents; or, alternatively, two geminal R^f, together with the atom in group C to which they are attached, form a spirocycloalkyl or spiroheterocyclyl ring with from 0 to 4 R^z substituents; or, alternatively, two axial R^f substituents of a pair of Wⁿ selected from the group consisting of (W¹ and W²), (W² and W³), and (W³ and W⁴) join to form a -(C(R^z)₂)_t- bridge; or, alternatively, R^e and an R^f substituent of W¹, W², W³, or W⁴ join to form a -(C(R^z)₂)_t- bridge;

each t is an integer selected from 2 or 3;

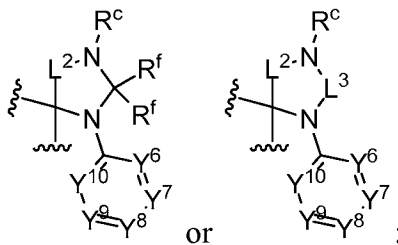
D is a bicyclic group of Formula Id:

**Id**

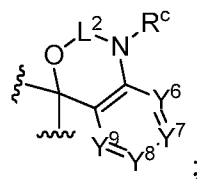
E is a bicyclic group of Formula Ic:

**Ie**

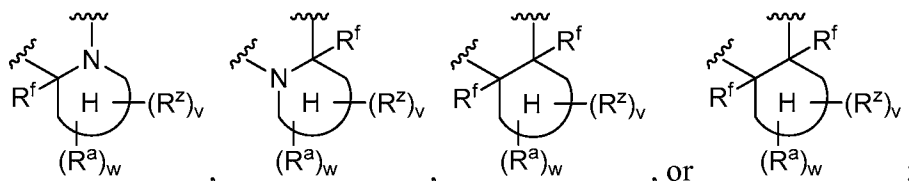
F is a spirocyclic group of Formula If:

**If**

G is a bicyclic spirocyclic group of Formula Ig:

**Ig**

H is a fused group of Formula Ih:

**Ih**

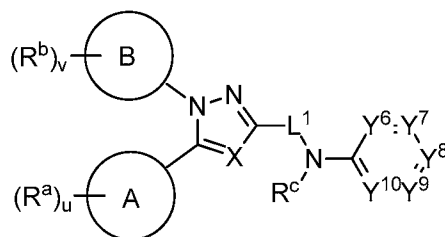
wherein the H ring is a fused, five- to eight-membered cycloalkyl or heterocyclyl ring;

wherein v is an integer from 0 to 4; and

wherein w is an integer from 0 to 2; and

Y^6 , Y^7 , Y^8 , Y^9 , and Y^{10} , if present, are each a member independently selected from the group consisting of N, CH, and CR^b ; or, alternatively for Y^8 and Y^9 , the members $-Y^6=Y^7-$ or $-Y^8=Y^9-$ are combined into a single member selected from the group consisting of NR^c , O, and S.

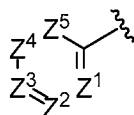
[0008] In one aspect, the invention provides a compound of Formula II:



or a pharmaceutically acceptable salt thereof;

wherein:

A is a cyclic group of Formula IIa:



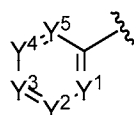
IIa

wherein Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are each a member selected from the group consisting of N, CH, and CR^a ; or, alternatively for Z^1 , the member Z^1 and X, together with atoms in the rings to which they are attached, form an additional fused, five- to eight-membered cycloalkyl or heterocyclyl ring with from 0 to 5 R^z substituents;

with the proviso that at least one member selected from the group consisting of Z^2 , Z^3 , and Z^4 is N;

each R^z is a member independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; or, alternatively, two R^z substituents, together with the carbon atom to which they are attached, join to form an oxo, spirocycloalkyl, or spiroheterocyclyl group;

B is a cyclic group of Formula IIb:



IIb

wherein Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are each a member independently selected from the group consisting of N, CH, and CR^b ; or, alternatively, the members $-Y^2=Y^3-$ or $-Y^4=Y^5-$ are combined into a single member selected from the group consisting of NH, NR^c , O, and S;

each R^a and R^b is a member independently selected from the group consisting of cyano, carboxyl, C_1 - C_4 alkyl, C_1 - C_4 hydroxyalkyl, C_3 - C_8 cycloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, halo, C_0 - C_6 amino, C_1 - C_6 amido,

C₁-C₄ alkyloxycarbonyl, C₁-C₆ alkylsulfonyl, and hydroxyl; or, alternatively, two adjacent R^a or R^b, together with the atoms in groups A or B to which they are attached, form an additional fused aryl, heteroaryl, cycloalkyl, or heterocyclyl ring with from 0 to 5 R^z substituents;

each R^c is a member independently selected from the group consisting of C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₃-C₆ cycloalkyl, (C₃-C₆ cycloalkyl)C₁-C₃alkyl, and C₁-C₇ acyl;

each u is an integer independently selected from 0 to 4;

v is an integer from 0 to 5;

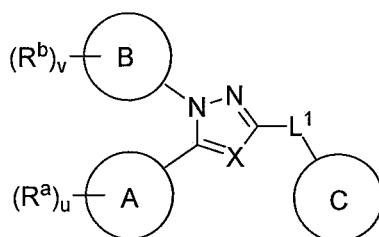
X is N or CR^d; or, alternatively, X is CR^d, wherein X and the member Z¹, together with atoms in the rings in which they are included, form the additional fused, five- to eight-membered cycloalkyl or heterocyclyl ring with from 0 to 5 R^z substituents;

each R^d is a member independently selected from the group consisting of halo, cyano, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₃-C₆ cycloalkyl, and C₃-C₆ cycloalkoxy;

L¹ is a member selected from the group consisting of C=O, C=S, C=NH, and C=NR^c;

Y⁶, Y⁷, Y⁸, Y⁹, and Y¹⁰, if present, are each a member independently selected from the group consisting of N, CH, and CR^b; or, alternatively for Y⁸ and Y⁹, the members -Y⁶=Y⁷- or -Y⁸=Y⁹- are combined into a single member selected from the group consisting of NR^c, O, and S.

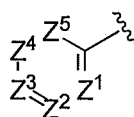
[0008a] In another aspect, the invention provides a compound of Formula I:



or a pharmaceutically acceptable salt thereof;

wherein:

A is a cyclic group of Formula Ia:



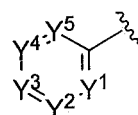
Ia

wherein Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are each a member selected from the group consisting of N, CH, and CR^a ; or, alternatively for Z^1 , the member Z^1 and X, together with atoms in the rings to which they are attached, form an additional fused, five- to eight-membered cycloalkyl or heterocyclyl ring with from 0 to 4 R^z substituents;

with the proviso that at least one member selected from the group consisting of Z^2 , Z^3 , and Z^4 is N;

each R^z is a member independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; or, alternatively, two R^z substituents, together with the carbon atom to which they are attached, join to form an oxo, spirocycloalkyl, or spiroheterocyclyl group;

B is a cyclic group of Formula Ib:



Ib

wherein Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are each a member independently selected from the group consisting of N, CH, and CR^b ; or, alternatively, the members

$-Y^2=Y^3-$ or $-Y^4=Y^5-$ are combined into a single member selected from the group consisting of NH, NR^c , O, and S;

each R^a and R^b is a member independently selected from the group consisting of cyano, carboxyl, C_1 - C_4 alkyl, C_1 - C_4 hydroxyalkyl, C_3 - C_8 cycloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, halo, C_0 - C_6 amino, C_1 - C_6 amido, C_1 - C_4 alkyloxycarbonyl, C_1 - C_6 alkylsulfonyl, and hydroxyl; or, alternatively, two adjacent R^a or R^b , together with the atoms in groups A or B to which they are attached, form an additional fused aryl, heteroaryl, cycloalkyl, or heterocyclyl ring with from 0 to 4 R^z substituents;

each R^c is a member independently selected from the group consisting of hydrogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_3 - C_6 cycloalkyl, $(C_3$ - C_6 cycloalkyl) C_1 - C_3 alkyl, and C_1 - C_7 acyl;

each u is an integer independently selected from 0 to 4;

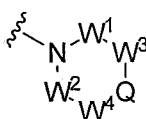
v is an integer from 0 to 5;

X is N or CR^d; or, alternatively, X is CR^d, wherein X and the member Z¹, together with atoms in the rings in which they are included, form the additional fused, five- to eight-membered cycloalkyl or heterocyclyl ring with from 0 to 4 R^z substituents;

each R^d is a member independently selected from the group consisting of hydrogen, halo, cyano, C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₃-C₆ cycloalkyl, and C₃-C₆ cycloalkoxy;

each L¹, L², and L³, if present, is a member independently selected from the group consisting of C=O, C=S, C=NH, and C=NR^e;

C is a cyclic group of Formula Ic:



Ic

wherein Q is a member selected from the group consisting of C(R^e)(D), N(E), F, and G; or, alternatively, the members -W³-Q- or -W⁴-Q- join to form a member H; and

wherein W¹, W², W³, and W⁴ are each an independently selected C(R^f)₂; or, alternatively, the members -W³-Q- or -W⁴-Q- join to form a member H;

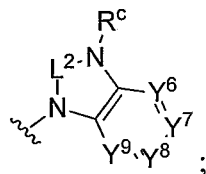
R^e is a member selected from the group consisting of hydrogen, C₁-C₃ alkyl, and C₁-C₃ fluoroalkyl; or, alternatively, R^e and an R^f substituent of W¹, W², W³, or W⁴ join to form a -(C(R^z)₂)_t- bridge or a -(CH₂)_t- bridge, wherein t is an integer selected from 2 or 3;

each R^f is a member independently selected from the group consisting of hydrogen, C₁-C₃ alkyl, C₁-C₃ fluoroalkyl, and halo; or, alternatively, two adjacent R^f, together with the atoms in group C to which they are attached, form an additional aryl, heteroaryl, cycloalkyl, or heterocyclyl fused ring with from 0 to 4 R^z substituents; or, alternatively, two geminal R^f, together with the atom in group C to which they are attached, form a spirocycloalkyl or spiroheterocyclyl ring with from 0 to 4 R^z substituents; or, alternatively, two axial R^f substituents of a pair of Wⁿ selected from the group consisting of (W¹ and W²), (W² and W³), and (W³ and W⁴) join to form a -(C(R^z)₂)_t- bridge or a

$-(CH_2)_t-$; or, alternatively, R^c and an R^f substituent of W^1 , W^2 , W^3 , or W^4 join to form a $-(C(R^Z)_2)_t-$ bridge or a $-(CH_2)_t-$ bridge;

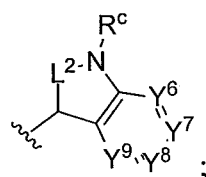
each t is an integer selected from 2 or 3;

D is a bicyclic group of Formula Id:



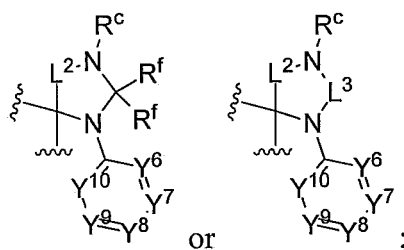
Id

E is a bicyclic group of Formula Ie:



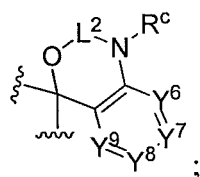
Ie

F is a spirocyclic group of Formula If:



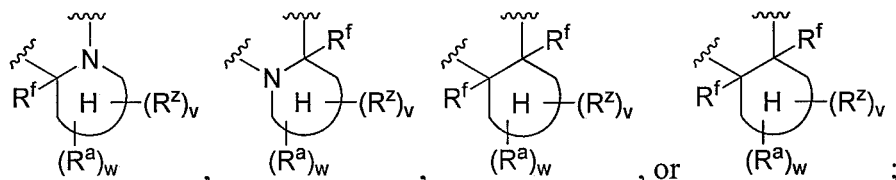
If

G is a bicyclic spirocyclic group of Formula Ig:



Ig

H is a fused group of Formula Ih:



Ih

wherein the H ring is a fused, five- to eight-membered cycloalkyl or heterocyclyl ring;

wherein v is an integer from 0 to 4; and
wherein w is an integer from 0 to 2; and
 Y^6 , Y^7 , Y^8 , Y^9 , and Y^{10} , if present, are each a member independently selected from the group consisting of N, CH, and CR^b ; or, alternatively for Y^8 and Y^9 , the members $-Y^6=Y^7-$ or $-Y^8=Y^9-$ are combined into a single member selected from the group consisting of NR^c , O, and S.

[0009] In another aspect, the invention provides a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula I or II and at least one pharmaceutically acceptable carrier, excipient, or diluent.

[0010] In another aspect, the invention provides a method of treating or preventing pain comprising administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a compound of Formula I or II.

[0010a] In another aspect, there is provided the use of a therapeutically effective amount, or a prophylactically effective amount, of a compound as described herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing pain.

[0010b] In another aspect, there is provided the use of a therapeutically effective amount, or a prophylactically effective amount, of a compound as described herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prevention of pain before, during or after surgical procedure.

[0010c] In another aspect, there is provided the use of a therapeutically effective amount, or a prophylactically effective amount, of a compound as described herein, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prevention of pain associated with an interventional procedure, wherein the medicament is to be periprocedurally administered.

[0011] Certain other aspects and embodiments of the present invention are set forth herein and will be apparent to those of skill in the art.

BRIEF DESCRIPTION OF THE DRAWINGS

[0012] Figure 1 shows the paw withdrawal threshold (PWT in g) observed in rats treated with a compound of the invention after spinal nerve ligation.

[0013] Figure 2 shows the percentage of maximal possible effect (%MPE) of a compound of the invention in reducing neuropathic pain, as observed in rats treated with the compound after spinal nerve ligation.

DETAILED DESCRIPTION OF THE INVENTION

5 I. Definitions

[0014] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below. Definition of standard chemistry terms may be found in reference works, including Carey and Sundberg (2007) *Advanced Organic Chemistry 5th Ed.* Vols. A and B, Springer Science+Business Media LLC, New
10 York.

[0015] It must be noted that, as used in the specification and the appended claims, the singular forms “a,” “an” and “the” include plural referents unless the context clearly dictates otherwise. For example, an embodiment including “a TRPA1-modulating compound and an excipient” should be understood to present certain aspects with at least a second TRPA1-
15 modulating compound, at least a second excipient, or both.

[0016] The practice of the present invention will employ, unless otherwise indicated, conventional methods of synthetic organic chemistry, mass spectroscopy, preparative and analytical methods of chromatography, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology. Conventional methods of organic chemistry include those
20 included in *March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, 6th Edition*, M.B. Smith and J. March, John Wiley & Sons, Inc., Hoboken, NJ, 2007. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, suitable methods and materials are described below. The materials, methods, and examples are illustrative only and not intended
25 to be limiting.

[0017] The term “about” as used herein to modify a numerical value indicates a defined range around that value. If “X” were the value, “about X” would generally indicate a value from 0.95X to 1.05X. Any reference to “about X” specifically indicates at least the values X, 0.95X, 0.96X, 0.97X, 0.98X, 0.99X, 1.01X, 1.02X, 1.03X, 1.04X, and 1.05X. Thus, “about
30 X” is intended to teach and provide written description support for a claim limitation of, e.g., “0.98X.” When the quantity “X” only includes whole-integer values (e.g., “X carbons”),

“about X” indicates from (X-1) to (X+1). In this case, “about X” as used herein specifically indicates at least the values X, X-1, and X+1.

[0018] When “about” is applied to the beginning of a numerical range, it applies to both ends of the range. Thus, “from about 5 to 20%” is equivalent to “from about 5% to about 20%.” When “about” is applied to the first value of a set of values, it applies to all values in that set. Thus, “about 7, 9, or 11%” is equivalent to “about 7%, about 9%, or about 11%.”

[0019] The term “acyl” as used herein includes an alkanoyl, aroyl, heterocycloyl, or heteroaroyl group as defined herein. Examples of acyl groups include, but are not limited to, acetyl, benzoyl, and nicotinoyl.

[0020] The term “agonist” embraces agents that, *e.g.*, increase, hasten, or activate the expression of a described target protein or bind to, stimulate, increase, open, activate, enhance, increase activation, sensitize or up-regulate the activity of one or more proteins (or encoding polynucleotide(s)). As used herein, “agonist” generally includes partial agonists, full agonists, and superagonists (*i.e.*, greater than full agonism). Assays for determining whether a compound “agonizes” or “does not agonize” a protein include, *e.g.*, contacting the protein(s) with the compound and then determining the functional effects on the protein activity or contacting cells expressing protein(s) with the compound and then determining the functional effects on the described target protein activity. One of skill in the art will be able to determine whether an assay is suitable for determining whether a compound agonizes or does not agonize a protein. Samples or assays comprising a TRPA1 target are treated with a test compound and are compared to control samples without the test compound (and to positive control samples activated by exposure to a known TRPA1 agonist) to measure the extent of effect on TRPA1 activity. Control samples (untreated with agonists) are used to establish a baseline activity value. Agonism of the TRPA1 protein or channel is achieved when the activity value increases relative to the untreated control (*e.g.*, increases by 20%, 30%, 40%, 50%, 75%, or 100%, or even more).

[0021] The term “antagonist” embraces agents that, *e.g.*, slow or reduce the expression of a described target protein or block, destimulate, decrease, close, deactivate, interfere with, reduce activation, desensitize or down-regulate the activity of one or more proteins (or encoding polynucleotide(s)). As used herein, “antagonist” generally includes partial antagonists and full antagonists. Assays for determining whether a compound “antagonizes” or “does not antagonize” a protein include, *e.g.*, contacting the protein(s) with the test

compound and then determining the functional effects on the protein activity or contacting cells expressing protein(s) with the test compound and then determining the functional effects on the described target protein activity. One of skill in the art will be able to determine whether an assay is suitable for determining whether a compound antagonizes or does not antagonize a protein. Samples or assays comprising a TRPA1 target are treated with a putative antagonist and are compared to control samples without the compound (and to control samples activated by a known agonist) to measure the extent of effect on TRPA1 activity. Agonist-activated control samples (untreated with antagonists) are assigned a relative activity value of 100%. Antagonism of the TRPA1 protein or channel activity is achieved when the activity value relative to the agonist-activated control is less than 100% (*e.g.*, 80%, 50%, 40%, 30%, 20%, or 10%, or even lower).

[0022] Cells used to determine the agonist or antagonist activity of a compound of the present invention can be cells or cell lines transiently or permanently transfected or transformed with the appropriate nucleic acid encoding TRPA1 or can be cells or cell lines that express TRPA1 from endogenous genes. Typically, the TRPA1 receptor-channel is expressed on the surface of a recombinant host cell such as human embryonic kidney (HEK), CHO, SH-SY5Y or COS-7 cells. Alternatively, cells endogenously expressing TRPA1, such as dorsal root ganglion neurons can be isolated from an animal, cultured and used to determine antagonist activity. Examples of cell lines that endogenously express TRPA1 that are suitable for use also include, but are not limited to the human WI-38 cell line, the differentiated human neuroblastoma IMR-32 cell line and the differentiated rat PC12 cell line. The assays described herein can also be performed with cells that express variant TRPA1 proteins. Methods for performing assays to determine if a compound is an agonist or antagonist of the TRPA1 channel are well known in the art. One non-limiting example involves a spectrofluorimetric assay in which cells loaded with a fluorescent dye which is sensitive to intracellular calcium concentrations are subsequently contacted with the compounds of interest to determine their ability to alter intracellular calcium levels. Another method involves testing compounds using an electrophysiological assay, such as patch clamping.

[0023] The term “alkanoyl” as used herein embraces an alkyl-C(O)- group wherein the alkyl group is as defined herein. Examples of alkanoyl groups include, but are not limited to, acetyl and propanoyl.

[0024] The term “alkyl,” either alone or within other terms such as “haloalkyl” and “alkylamino,” embraces linear or branched radicals having one to about twelve carbon atoms. “Lower alkyl” radicals have one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, *tert*-butyl, pentyl, isoamyl, hexyl and the like. The term “alkylene” embraces bridging divalent linear and branched alkyl radicals. Examples include methylene, ethylene, propylene, isopropylene and the like.

[0025] The term “alkenyl” embraces linear or branched radicals having at least one carbon-carbon double bond of two to about twelve carbon atoms. “Lower alkenyl” embraces radicals having two to about six carbon atoms. Examples of alkenyl radicals include ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms “alkenyl” and “lower alkenyl,” embrace radicals having “cis” and “trans” orientations, or alternatively, “E” and “Z” orientations.

[0026] The term “alkoxy” as used herein contemplates an oxygen with a lower alkyl group as a substituent and includes methoxy, ethoxy, butoxy, and the like.

[0027] The term “alkynyl” denotes linear or branched radicals having at least one carbon-carbon triple bond and having two to about twelve carbon atoms. “Lower alkynyl” radicals have two to about six carbon atoms. Examples of such radicals include propargyl, butynyl, and the like.

[0028] The term “aroyl” as used herein embraces an aryl-CO- group wherein aryl is as defined herein. Examples include, but are not limited to, benzoyl, naphth-1-oyl and naphth-2-oyl.

[0029] The term “aryl”, alone or in combination, means a carbocyclic aromatic system containing one or two rings wherein such rings may be attached together in a fused manner. The term “aryl” embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, and indanyl.

[0030] The term “comprising” is meant to be open ended, including the indicated component, but not excluding other elements.

[0031] “Conservatively modified variants” embrace both amino acid and nucleic acid sequences. With respect to particular nucleic acid sequences, conservatively modified variants refers to those nucleic acids which encode identical or essentially identical amino

acid sequences, or where the nucleic acid does not encode an amino acid sequence, to essentially identical sequences. Because of the degeneracy of the genetic code, a large number of functionally identical nucleic acids encode any given protein. For instance, the codons GCA, GCC, GCG and GCU all encode the amino acid alanine. Thus, at every position where an alanine is specified by a codon, the codon can be altered to any of the corresponding codons described without altering the encoded polypeptide. Such nucleic acid variations are “silent variations,” which are one species of conservatively modified variations. Every nucleic acid sequence herein which encodes a polypeptide also describes every possible silent variation of the nucleic acid. One of skill will recognize that each codon in a nucleic acid (except AUG, which is ordinarily the only codon for methionine) can be modified to yield a functionally identical molecule. Accordingly, each silent variation of a nucleic acid which encodes a polypeptide is implicit in each described sequence.

[0032] As to amino acid sequences, one of skill will recognize that individual substitutions, in a nucleic acid, peptide, polypeptide, or protein sequence which alters a single amino acid or a small percentage of amino acids in the encoded sequence is a “conservatively modified variant” where the alteration results in the substitution of an amino acid with a chemically similar amino acid. Conservative substitution tables providing functionally similar amino acids are well known in the art.

[0033] The following six groups each contain amino acids that are conservative substitutions for one another:

- 1) Alanine (A), Serine (S), Threonine (T);
 - 2) Aspartic acid (D), Glutamic acid (E);
 - 3) Asparagine (N), Glutamine (Q);
 - 4) Arginine (R), Lysine (K);
 - 5) Isoleucine (I), Leucine (L), Methionine (M), Valine (V); and
 - 6) Phenylalanine (F), Tyrosine (Y), Tryptophan (W).
- (see, e.g., Creighton, *Proteins* (1984)).

[0034] The term “cyclic group” means a cycloalkyl, heterocyclyl, aryl, or heteroaryl.

[0035] The term “cycloalkyl” includes saturated carbocyclic groups of 3 to 10 carbons.

Lower cycloalkyl groups include C₃-C₆ rings. Examples include cyclopentyl, cyclopropyl, and cyclohexyl.

[0036] As used herein, “cycloalkylalkyl” embraces an alkyl group wherein the alkyl group includes one or more cycloalkyl substituents (typically one). Examples include, but are not limited to, cyclohexylmethyl, cyclopentylmethyl, and cyclopropylmethyl.

[0037] The term “geminal” embraces two or more substituents that are directly attached to the same atom. An example is 3,3-dimethyl substitution on a cyclohexyl or spirocyclohexyl ring.

[0038] The term “halo” means halogens such as fluorine, chlorine, bromine or iodine atoms (i.e., fluoro, chloro, bromo, or iodo).

[0039] The term “haloalkyl” embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more halo as defined above. Examples include monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals including perhaloalkyl. A monohaloalkyl radical, for one example, may have an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. “Lower haloalkyl” embraces radicals having 1-6 carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. “Perfluoroalkyl” means an alkyl radical having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

[0040] The term “haloalkoxy” means alkoxy radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more halo as defined above. Examples include monohaloalkoxy, dihaloalkoxy and polyhaloalkoxy radicals including perhaloalkoxy. Examples further include difluoromethoxy, trifluoromethoxy and trifluoroethoxy.

[0041] The term “heteroaryl” denotes aryl ring systems that contain one or more heteroatoms selected from the group O, N and S, wherein the ring nitrogen and sulfur atom(s) are optionally oxidized, and nitrogen atom(s) are optionally quaternized. Examples include unsaturated 5 to 6 membered heteromonocyclyl group containing 1 to 4 nitrogen atoms, for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen atom, for example, pyranyl, 2-furyl, 3-furyl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered

heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

[0042] The term “heteroaroyl” embraces a heteroaryl-C(O)- group wherein heteroaryl is as defined herein. Heteroaroyl groups include, but are not limited to, thiophenoyl, nicotinoyl, pyrrol-2-ylcarbonyl, and pyridinoyl.

[0043] The term “heterocyclyl” (or “heterocyclo”) embraces saturated, and partially saturated, heteroatom-containing ring radicals, where the heteroatoms may be selected from nitrogen, sulfur and oxygen. Heterocyclic rings comprise monocyclic 6-8 membered rings, as well as 5-16 membered bicyclic ring systems (which can include bridged fused and spiro-fused bicyclic ring systems). It does not include rings containing -O-O-, -O-S- or -S-S- portions.

[0044] Examples of saturated heterocyclo groups include saturated 3- to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl radicals include dihydrothienyl, dihydropyranyl, dihydrofuryl, dihydrothiazolyl, and the like.

[0045] Particular examples of partially saturated and saturated heterocyclo groups include pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl, dihydrothienyl, 2,3-dihydro-benzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofuryl, isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4- tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7- trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3- dihydro-1H-1λ'-benzo[d]isothiazol-6-yl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl, and the like.

[0046] Heterocyclo groups also includes radicals where heterocyclic radicals are fused/condensed with aryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen

atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl and dihydrobenzofuryl].

[0047] The term “heterocycloyl” embraces a heterocyclyl-C(O)- group wherein heterocyclyl is as defined herein. Examples include, but are not limited to, N-methyl prolinoyl and tetrahydrofuranoyl.

[0048] The term “hydroxy” or “hydroxyl” embraces -OH.

[0049] The term “hydroxyalkyl” embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with one or more hydroxy groups. Examples include hydroxymethyl, 2-hydroxyethyl, and (*R*)- or (*S*)-1-hydroxyethyl.

[0050] When any two substituent groups or any two instances of the same substituent group are “independently selected” from a list of alternatives, the groups may be the same or different. For example, if R^a and R^b are independently selected from alkyl, fluoro, amino, and hydroxyalkyl, then a molecule with two R^a groups and two R^b groups could have all groups be an alkyl group (e.g., four different alkyl groups). Alternatively, the first R^a could be alkyl, the second R^a could be fluoro, the first R^b could be hydroxyalkyl, and the second R^b could be amino (or any other substituents taken from the group). Alternatively, both R^a and the first R^b could be fluoro, while the second R^b could be alkyl (i.e., some pairs of substituent groups may be the same, while other pairs may be different). In some embodiments, multiple instances of variables that may be selected from a list of alternatives are independently selected.

[0051] The term “interventional procedure” embraces any medical procedure used for diagnosis or treatment that involves incision, puncture, entry into a body cavity, or the use of ionizing, electromagnetic or acoustic energy.

[0052] As used herein, “or” should in general be construed non-exclusively. For example, an embodiment of “a composition comprising A or B” would typically present an aspect with a composition comprising both A and B, and an embodiment of “a method to treat or to prevent” could treat, prevent, or do a combination of both. “Or” should, however, be

construed to exclude those aspects presented that cannot be combined without contradiction (*e.g.*, a composition pH that is between 9 and 10 or between 7 and 8).

[0053] The term “oxo” as used herein contemplates an oxygen atom attached with a double bond.

5 [0054] The term “periprocedurally” embraces administration of the compound during (intraprocedurally), before (preprocedurally), or after an medical procedure (postprocedurally). In one embodiment, a compound of the present invention is administered (i) preprocedurally or postprocedurally; and (ii) intraprocedurally. The compounds of the present invention are administered to a surgical, diagnostic, or therapeutic procedure site by
10 techniques well known to those of ordinary skill in the art. The compound may be administered periprocedurally, which may include perioperatively (*i.e.*, before, during or after a surgical procedure).

[0055] “Pharmaceutically acceptable” means approved or approvable by a regulatory agency of the Federal or state government or listed in the U.S. Pharmacopoeia or other
15 generally recognized pharmacopoeia for use in animals, and more particularly in humans. It can be material which is not biologically or otherwise undesirable, *i.e.*, the material can be administered to an individual without causing any undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

20 [0056] The term “pharmaceutically acceptable salt” of a compound means a salt that is pharmaceutically acceptable (*i.e.*, non-toxic at the therapeutic dosage) and that possesses the desired pharmacological activity of the parent compound. Such salts include, for example, acid addition salts and base addition salts. Examples of pharmaceutically acceptable salts include inorganic acid addition salts, such as chloride, bromide, sulfate, phosphate, and
25 nitrate; organic acid addition salts, such as acetate, galactarate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate, fumarate, methanesulfonate, *p*-toluenesulfonate, and ascorbate; salts with acidic amino acid, such as aspartate and glutamate; alkali metal salts, such as sodium salt and potassium salt; alkaline earth metal salts, such as magnesium salt and calcium salt; ammonium salt; organic base salts, such as trimethylamine salt,
30 triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, and N,N'-dibenzylethylenediamine salt; and salts with a basic amino acid, such as lysine salt and arginine salt. The salts may be in some cases hydrates or ethanol solvates.

[0057] As used herein, a reference to a composition of formula A, B, C, or a salt thereof embraces A, a salt of A, B, a salt of B, C, or a salt of C.

[0058] The term “spirocycloalkyl” embraces a cycloalkyl in which geminal substituents on a carbon atom are replaced to join in forming a 1,1-substituted ring. For example, but without limitation, for a $-C(R^1)(R^2)-$ group that was part of a longer carbon chain, if R^1 and R^2 joined to form a cyclopropyl ring incorporating the carbon to which R^1 and R^2 were bonded, this would be a spirocycloalkyl group (*i.e.*, spirocyclopropyl).

[0059] The term “spiroheterocyclyl” embraces a heterocycloalkyl in which geminal substituents on a carbon atom are replaced to join in forming a 1,1-substituted ring. For example, but without limitation, for a $-C(R^1)(R^2)-$ group that was part of a longer carbon chain, if R^1 and R^2 joined to form a pyrrolidine ring incorporating the carbon to which R^1 and R^2 were bonded, this would be a spiroheterocyclyl group.

[0060] The term “TRPA1 modulator” is a composition that measurably increases or decreases the activity of TRPA1.

[0061] Compounds of the present disclosure can exist as stereoisomers, wherein asymmetric or chiral centers are present. Stereoisomers are designated (*R*) or (*S*) depending on the configuration of substituents around the chiral carbon atom. The terms (*R*) and (*S*) used herein are configurations as defined in IUPAC 1974 *Recommendations for Section E, Fundamental Stereochemistry, Pure Appl. Chem.*, (1976), 45: 13-30, hereby incorporated by reference. The present disclosure contemplates various stereoisomers and mixtures thereof, and these isomers (*e.g.*, a substantially pure (*R*) or (*S*) enantiomer of a chiral compound of the present invention) are specifically included within the scope of the present disclosure. Stereoisomers include enantiomers, diastereomers, and mixtures of enantiomers or diastereomers. Individual stereoisomers of compounds of the present disclosure can be prepared synthetically from commercially available starting materials which contain asymmetric or chiral centers or by preparation of racemic mixtures followed by resolution well-known to those of ordinary skill in the art. These methods of resolution are exemplified by (1) attachment of a mixture of enantiomers to a chiral auxiliary, separation of the resulting mixture of diastereomers by recrystallization or chromatography and liberation of the optically pure product from the auxiliary or (2) direct separation of the mixture of optical enantiomers on chiral chromatographic columns.

[0062] In certain embodiments, the compounds of the invention can be obtained as *N*-oxides. Conversion of a tertiary amine group (*i.e.*, a compound having the formula R_3N) in a compound of the invention to the corresponding *N*-oxide (*i.e.*, a compound having the formula $R_3N^{\oplus}-O^{\ominus}$) can be conducted chemically according to methods that are known in the art. Conversion of a compound to the *N*-oxide can also occur after administration to a subject or patient. In certain cases, such conversion is catalyzed enzymatically (*e.g.*, by a cytochrome P450 enzyme). In some instances, the *N*-oxide can be a metabolite of a tertiary amine present in a compound of the invention. The *N*-oxide can be an intermediate between the tertiary amine and its *N*-dealkylated analogs. Depending on the particular compound, an *N*-oxide can be more active or less active than its parent amine.

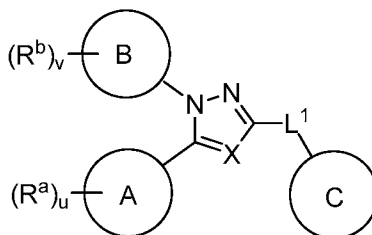
[0063] Where compounds of the present disclosure include F, I, C or H, the disclosure is not limited to the most common isotopes of these elements. Compounds containing for example ^{18}F , ^{19}F , ^{11}C , ^{13}C , ^{14}C , ^{123}I , ^{125}I , 3H and 2H are specifically contemplated as being included in the disclosure. A compound of the invention can be radiolabeled according to a number of known techniques. A compound can be radiolabeled, for example, by appending one or more radioisotopes of a halogen (*e.g.*, ^{125}I) to an aromatic ring, or by alkylating a nitrogen of a compound of the invention with a group comprising a radioisotope.

Radiolabeled compounds can be used to measure binding of the compounds to TRPA1; to detect the compounds in cells, tissues, or organs of a subject to whom the compounds are administered; to enable analysis of compound metabolism; or for radiotherapeutic techniques. Radiolabeled compounds of the invention can also be used as competitive binders in studies for characterizing natural TRPA1 ligands. Isotopes of still other elements can be used in conjunction with the compounds and methods of the invention.

[0064] In the Summary of the Invention above, Detailed Description, and the claims below, reference is made to particular features and aspects of the invention, including method steps. The disclosure of the invention in this specification includes all possible combinations of such particular features within the embodiments of the invention disclosed, at least to the extent that such combinations are non-contradictory. For example, if the Detailed Description presents aspects A, B, and C of an embodiment, it is understood that this also discloses particular embodiments including both aspects A and B, both aspects B and C, and both aspects A and C, as well as an embodiment with aspects A, B, and C.

II. Compounds of the Invention

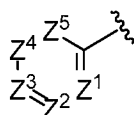
[0065] In one aspect, the invention sets forth a compound of Formula I:



or a pharmaceutically acceptable salt thereof;

5 wherein:

A is a cyclic group of Formula Ia:



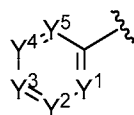
Ia

wherein Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are each a member selected from the group consisting of N, CH, and CR^a ; or, alternatively for Z^1 , the member Z^1 and X, together with atoms in the rings to which they are attached, form an additional fused, five- to eight-membered cycloalkyl or heterocyclyl ring with from 0 to 4 R^z substituents;

with the proviso that at least one member selected from the group consisting of Z^2 , Z^3 , and Z^4 is N;

each R^z is a member independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; or, alternatively, two R^z substituents, together with the carbon atom to which they are attached, join to form an oxo, spirocycloalkyl, or spiroheterocyclyl group;

B is a cyclic group of Formula Ib:



Ib

wherein Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are each a member independently selected from the group consisting of N, CH, and CR^b ; or, alternatively, the members $-Y^2=Y^3-$ or $-Y^4=Y^5-$ are combined into a single member selected from the group consisting of NH, NR^c , O, and S;

each R^a and R^b is a member independently selected from the group consisting of cyano, carboxyl, C_1 - C_4 alkyl, C_3 - C_8 cycloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, halo, C_0 - C_6 amino, C_1 - C_6 amido, C_1 - C_4 alkyloxycarbonyl, C_1 - C_6 alkylsulfonyl, and hydroxyl; or, alternatively, two adjacent R^a or R^b , together with the atoms in groups A or B to which they are attached, form an additional fused aryl, heteroaryl, cycloalkyl, or heterocyclyl ring with from 0 to 4 R^z substituents;

each R^c is a member independently selected from the group consisting of C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_3 - C_6 cycloalkyl, $(C_3$ - C_6 cycloalkyl) C_1 - C_3 alkyl, and C_1 - C_7 acyl;

each u is an integer independently selected from 0 to 4;

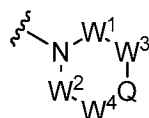
v is an integer from 0 to 5;

X is N or CR^d ; or, alternatively, X is CR^d , wherein X and the member Z^1 , together with atoms in the rings in which they are included, form the additional fused, five- to eight-membered cycloalkyl or heterocyclyl ring with from 0 to 4 R^z substituents;

each R^d is a member independently selected from the group consisting of halo, cyano, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, C_3 - C_6 cycloalkyl, and C_3 - C_6 cycloalkoxy;

each L^1 , L^2 , and L^3 , if present, is a member independently selected from the group consisting of $C=O$, $C=S$, $C=NH$, and $C=NR^c$;

C is a cyclic group of Formula Ic:



Ic

wherein Q is a member selected from the group consisting of $C(R^e)(D)$, $N(E)$, F , and G ; or, alternatively, the members $-W^3-Q-$ or $-W^4-Q-$ join to form a member H ; and

wherein W^1 , W^2 , W^3 , and W^4 are each an independently selected $C(R^f)_2$; or, alternatively, the members $-W^3-Q-$ or $-W^4-Q-$ join to form a member H ;

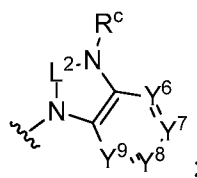
R^e is a member selected from the group consisting of hydrogen, C_1 - C_3 alkyl, and C_1 - C_3 fluoroalkyl; or, alternatively, R^e and an R^f substituent of W^1 , W^2 , W^3 , or

W^4 join to form a $-(C(R^Z)_2)_t-$ bridge, wherein t is an integer selected from 2 or 3;

each R^f is a member independently selected from the group consisting of hydrogen, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, and halo; or, alternatively, two adjacent R^f , together with the atoms in group C to which they are attached, form an additional aryl, heteroaryl, cycloalkyl, or heterocyclcyl fused ring with from 0 to 4 R^Z substituents; or, alternatively, two geminal R^f , together with the atom in group C to which they are attached, form a spirocycloalkyl or spiroheterocyclcyl ring with from 0 to 4 R^Z substituents; or, alternatively, two axial R^f substituents of a pair of W^n selected from the group consisting of (W^1 and W^2), (W^2 and W^3), and (W^3 and W^4) join to form a $-(C(R^Z)_2)_t-$ bridge; or, alternatively, R^e and an R^f substituent of W^1 , W^2 , W^3 , or W^4 join to form a $-(C(R^Z)_2)_t-$ bridge;

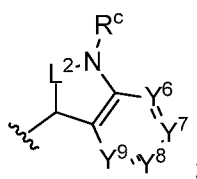
each t is an integer selected from 2 or 3;

D is a bicyclic group of Formula Id:



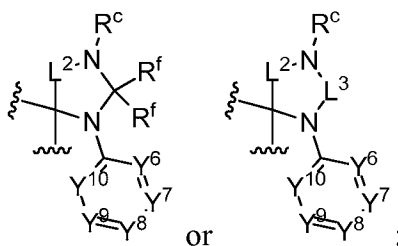
Id

E is a bicyclic group of Formula Ie:



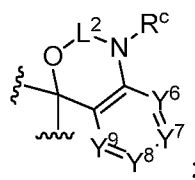
Ie

F is a spirocyclic group of Formula If:

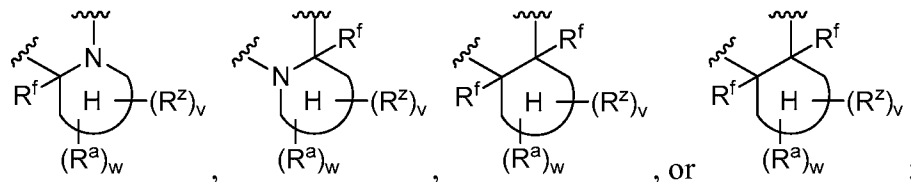


If

G is a bicyclic spirocyclic group of Formula Ig:

**Ig**

H is a fused group of Formula Ih:

**Ih**

wherein the H ring is a fused, five- to eight-membered cycloalkyl or heterocyclyl ring;

wherein v is an integer from 0 to 4; and

wherein w is an integer from 0 to 2; and

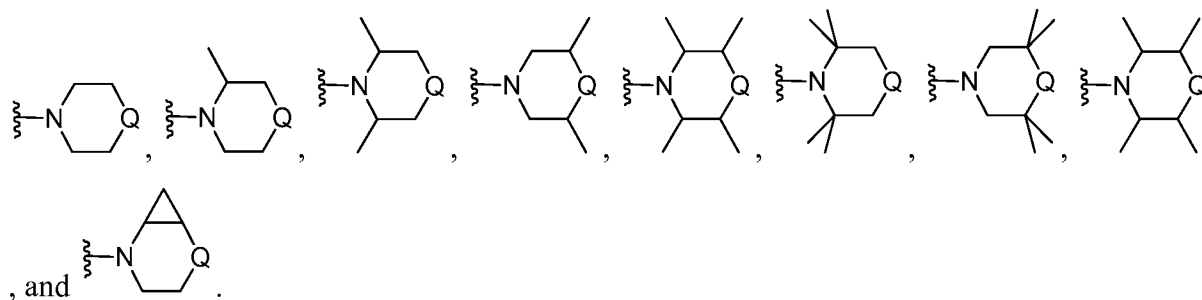
- 10 Y⁶, Y⁷, Y⁸, Y⁹, and Y¹⁰, if present, are each a member independently selected from the group consisting of N, CH, and CR^b; or, alternatively for Y⁸ and Y⁹, the members -Y⁶=Y⁷- or -Y⁸=Y⁹- are combined into a single member selected from the group consisting of NR^c, O, and S.

- [0066] In some embodiments, Q is C(R^c)(D). In some embodiments, Q is N(E). In some
15 embodiments, Q is F. In some embodiments, Q is G. In some embodiments, the members -W³-Q- or -W⁴-Q- join to form a member H.

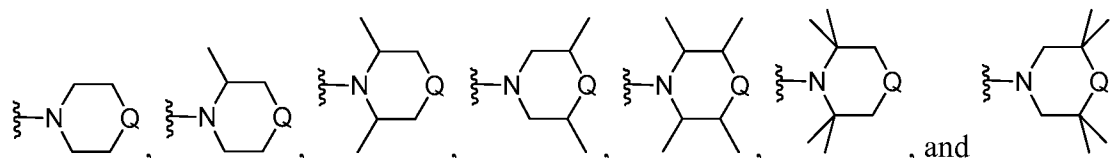
[0067] In some embodiments, W¹, W², W³, and W⁴ comprise from 1 to 4 independently selected R^f groups other than hydrogen. In some embodiments, W¹, W², W³, and W⁴ comprise from 1 to 4 independently selected R^f alkyl groups.

- 20 [0068] In some embodiments, W¹ and W² are combined into a single moiety W² (e.g., to form a pyrrolidine-based five-membered C ring rather than a piperidine- or piperazine-based six-membered C ring).

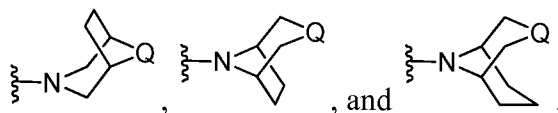
[0069] In some embodiments, C is a member selected from the group consisting of:



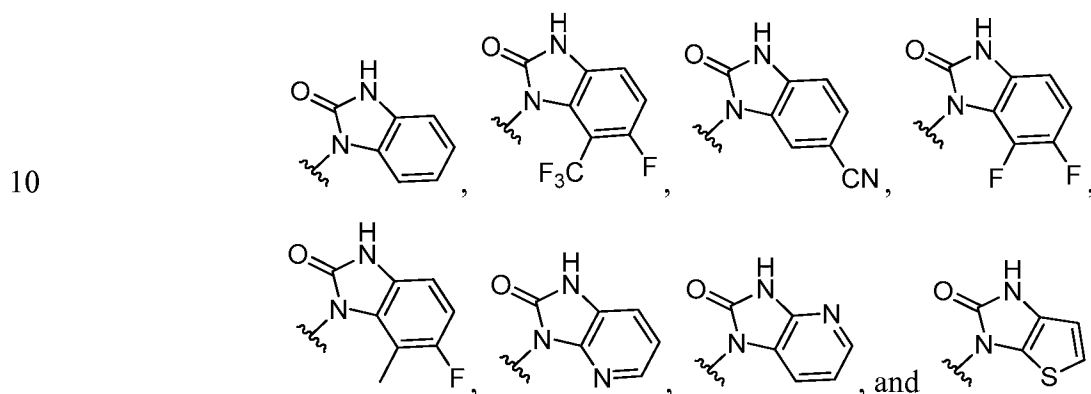
[0070] In some embodiments, C is a member selected from the group consisting of:



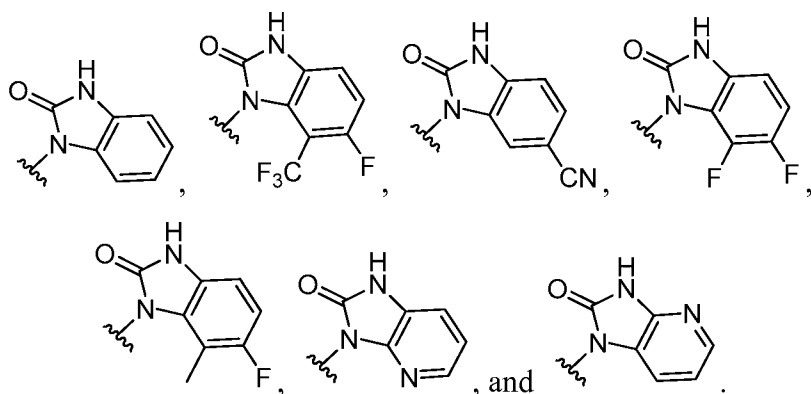
- 5 [0071] In some embodiments, the pair of W^n is selected from the group consisting of (W^1 and W^2) and (W^3 and W^4). In some embodiments, C is a member selected from the group consisting of:



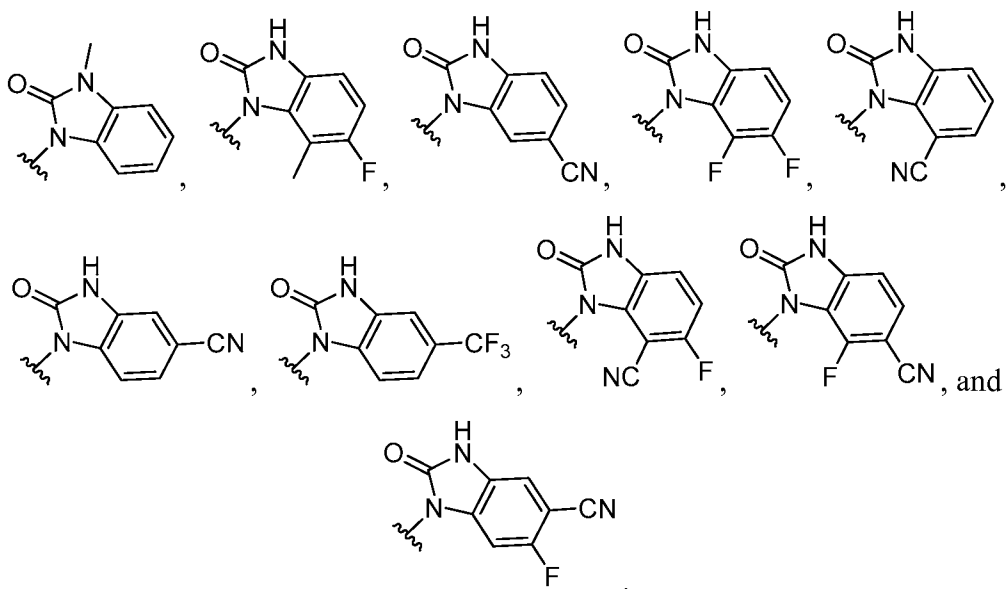
[0072] In some embodiments, D is a member selected from the group consisting of:



[0073] In some embodiments, D is a member selected from the group consisting of:



[0074] In some embodiments, D is a member selected from the group consisting of:



[0075] In some embodiments, L^1 is C=O. In some embodiments, L^2 is C=O. In some embodiments, L^3 is C=O.

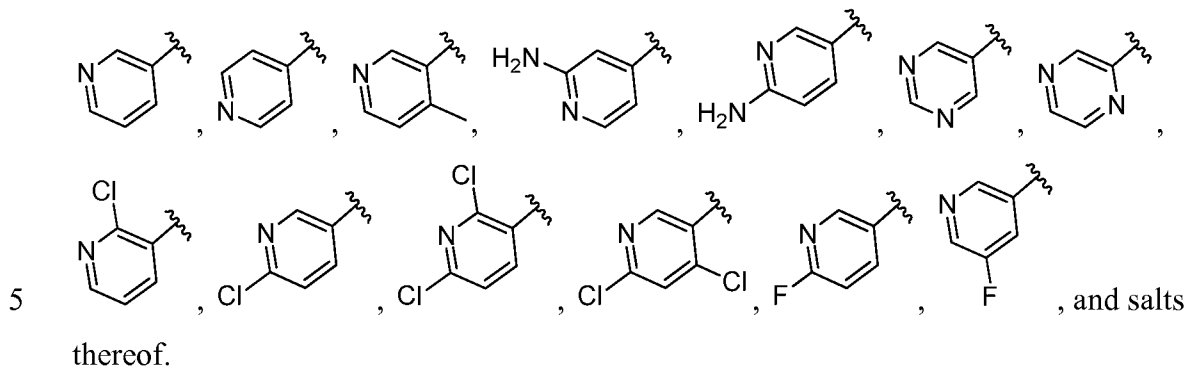
[0076] In some embodiments, the compound is selected from the group consisting of the compounds listed in Table 7. In some embodiments, the compound is selected from the group consisting of the compounds listed in Table 7 as having “A”-level activity. In some embodiments, the compound is selected from compound 49, 55, 77, 99, 175, and 177.

[0077] In some embodiments, Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are each a member selected from the group consisting of N, CH, and CR^a .

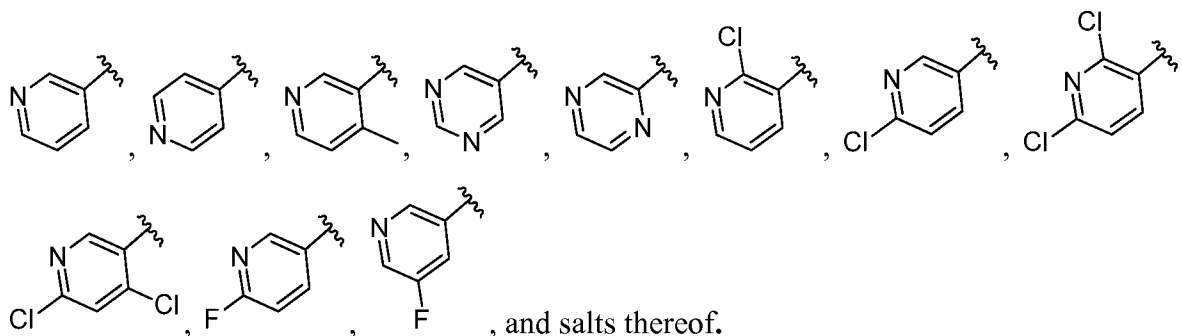
[0078] In some embodiments, Z^1 and X, together with atoms in the rings to which they are attached, form an additional fused, five- to eight-membered cycloalkyl or heterocyclyl ring with from 0 to 4 R^z substituents.

[0079] In some embodiments, Z^2 is N. In some preferred embodiments, Z^3 or Z^4 is N. In some embodiments, Z^3 is N. In some embodiments, Z^4 is N.

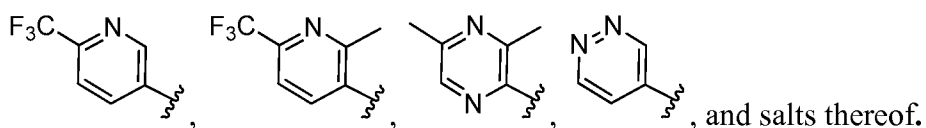
[0080] In some embodiments, A is a member selected from the group consisting of:



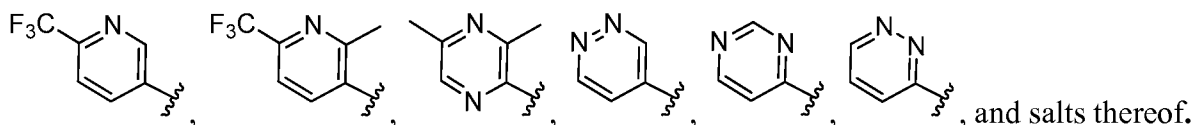
[0081] In some embodiments, A is a member selected from the group consisting of:



10 [0082] In some embodiments, A is a member selected from the group consisting of:



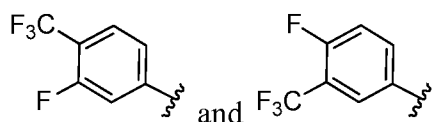
[0083] In some embodiments, A is a member selected from the group consisting of:



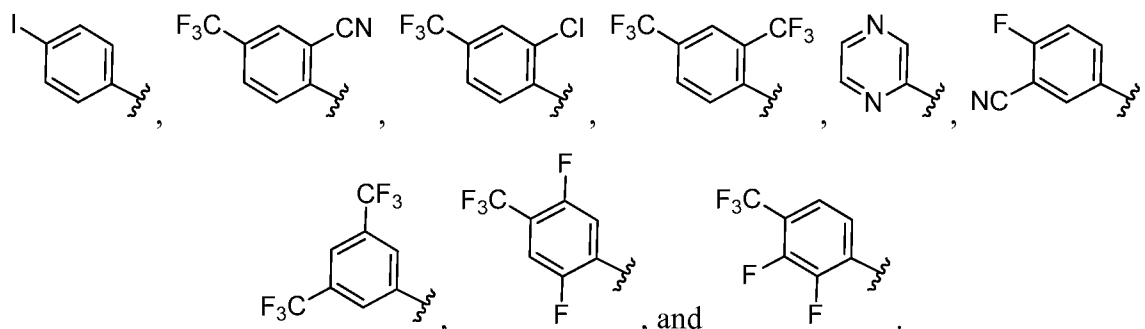
15 [0084] In some embodiments, Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are each a member independently selected from the group consisting of N, CH, and CR^b .

[0085] In some embodiments, Y^1 is N. In some embodiments, Y^1 is CH.

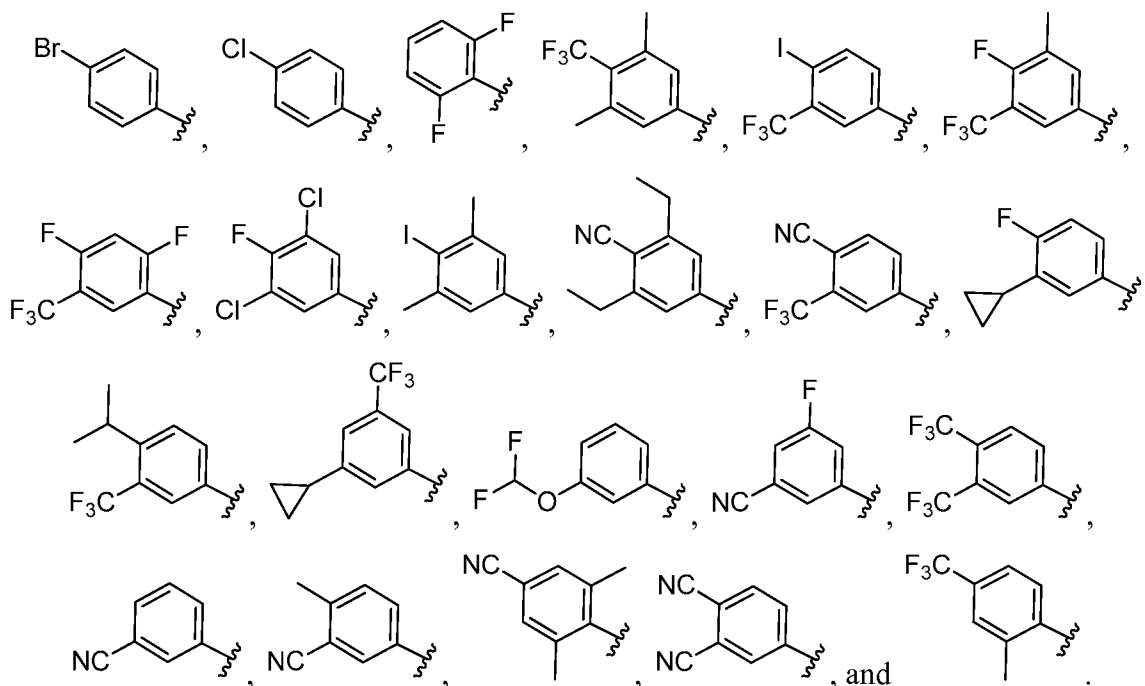
[0086] In some embodiments, Y^1 is CR^b . In some embodiments, the $Y^1 R^b$ is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, and trifluoromethoxy.



[0097] In some embodiments, B is a member selected from the group consisting of:



5 **[0098]** In some embodiments, B is a member selected from the group consisting of:



10 **[0099]** In some embodiments, each R^a and R^b is a member independently selected from the group consisting of cyano, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, halo, C₀-C₆ amino, C₁-C₆ amido, and hydroxyl. In some embodiments, each R^a and R^b is a member independently selected from the group consisting of cyano, C₁-C₄ alkyl, C₁-C₄ alkoxy, C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, and halo.

15 **[0100]** In some embodiments, u is an integer independently selected from 0 to 3 (e.g., 0, 1, 2, or 3). In some embodiments, u is an integer independently selected from 0 to 4 (e.g., 0, 1,

2, 3, or 4). In some embodiments, u is an integer independently selected from 0 to 5 (*e.g.*, 0, 1, 2, 3, 4, or 5).

[0101] In some embodiments, v is an integer independently selected from 0 to 3 (*e.g.*, 0, 1, 2, or 3). In some embodiments, v is an integer independently selected from 0 to 4 (*e.g.*, 0, 1, 2, 3, or 4). In some embodiments, v is an integer independently selected from 0 to 5 (*e.g.*, 0, 1, 2, 3, 4, or 5).

[0102] In some embodiments, X is N.

[0103] In some embodiments, each R^c is independently selected from the group consisting of hydrogen, cyano, C₁-C₃ alkyl, trifluoromethyl, cycloalkyl, trifluoromethoxy, and C₁-C₃ alkoxy. In some embodiments, each R^c is independently selected from the group consisting of hydrogen, cyano, C₁-C₃ alkyl, trifluoromethyl, cyclopropyl, trifluoromethoxy, and C₁-C₃ alkoxy. In some embodiments, each R^c is independently selected from the group consisting of hydrogen, methyl, bromo, chloro, trifluoromethyl, ethyl, isopropyl, isobutyl, cyclopropyl, cyclobutyl, and cyclopropylmethyl.

[0104] In some embodiments, Y⁶ is N. In some embodiments, Y⁶ is CH.

[0105] In some embodiments, Y⁶ is CR^b. In some embodiments, the Y⁶ R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, and trifluoromethoxy. In some embodiments, the Y⁶ R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, trifluoromethoxy, -C(O)N(H)Me, -NMe₂, and -SO₂Me.

[0106] In some embodiments, Y⁷ is N. In some embodiments, Y⁷ is CH.

[0107] In some embodiments, Y⁷ is CR^b. In some embodiments, the Y⁷ R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, and trifluoromethoxy. In some embodiments, the Y⁷ R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, trifluoromethoxy, -C(O)N(H)Me, -NMe₂, and -SO₂Me.

[0108] In some embodiments, Y⁸ is N. In some embodiments, Y⁸ is CH.

[0109] In some embodiments, Y⁸ is CR^b. In some embodiments, the Y⁸ R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, and trifluoromethoxy. In some embodiments, the Y⁸ R^b is a member selected from the group

consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, trifluoromethoxy, -C(O)N(H)Me, -NMe₂, and -SO₂Me.

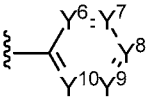
[0110] In some embodiments, Y⁹ is N. In some embodiments, Y⁹ is CH.

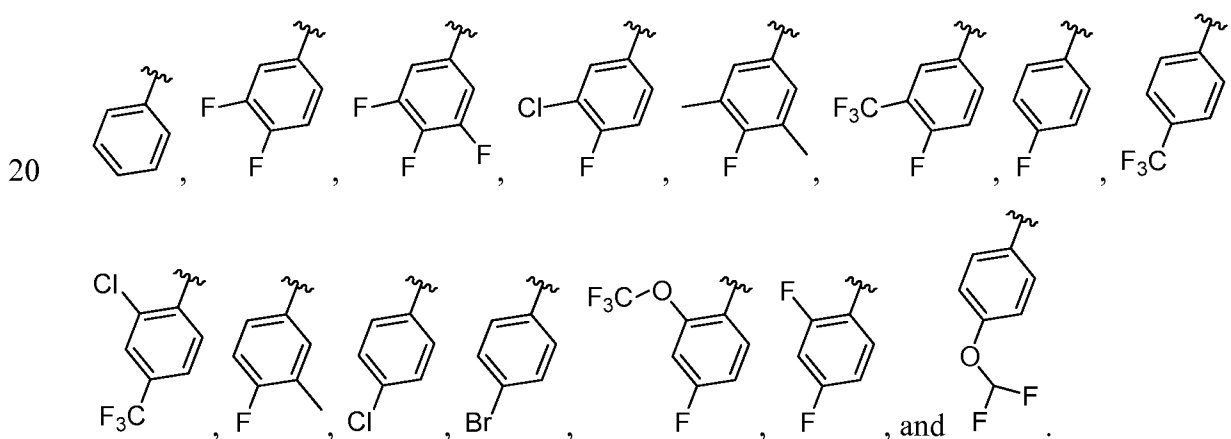
[0111] In some embodiments, Y⁹ is CR^b. In some embodiments, the Y⁹ R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, and trifluoromethoxy. In some embodiments, the Y⁹ R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, trifluoromethoxy, -C(O)N(H)Me, -NMe₂, and -SO₂Me.

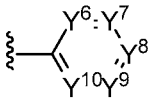
[0112] In some embodiments, Y¹⁰ is N. In some embodiments, Y¹⁰ is CH.

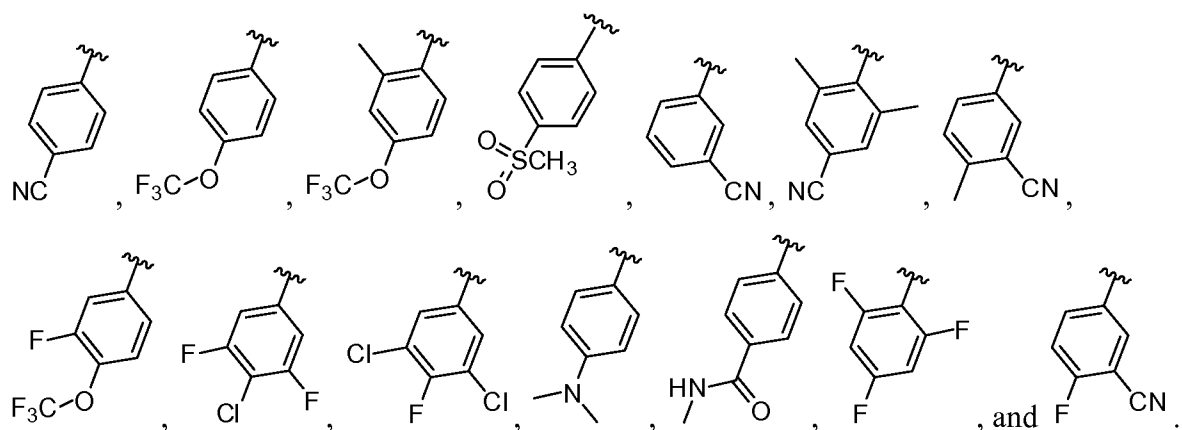
[0113] In some embodiments, Y¹⁰ is CR^b. In some embodiments, the Y¹⁰ R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, and trifluoromethoxy. In some embodiments, the Y¹⁰ R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, trifluoromethoxy, -C(O)N(H)Me, -NMe₂, and -SO₂Me.

[0114] In aspects or embodiments directed to Markush groups, in some further embodiments, the present invention is directed only to a single member of the Markush group.

[0115] In some embodiments,  is a member selected from the group consisting of:

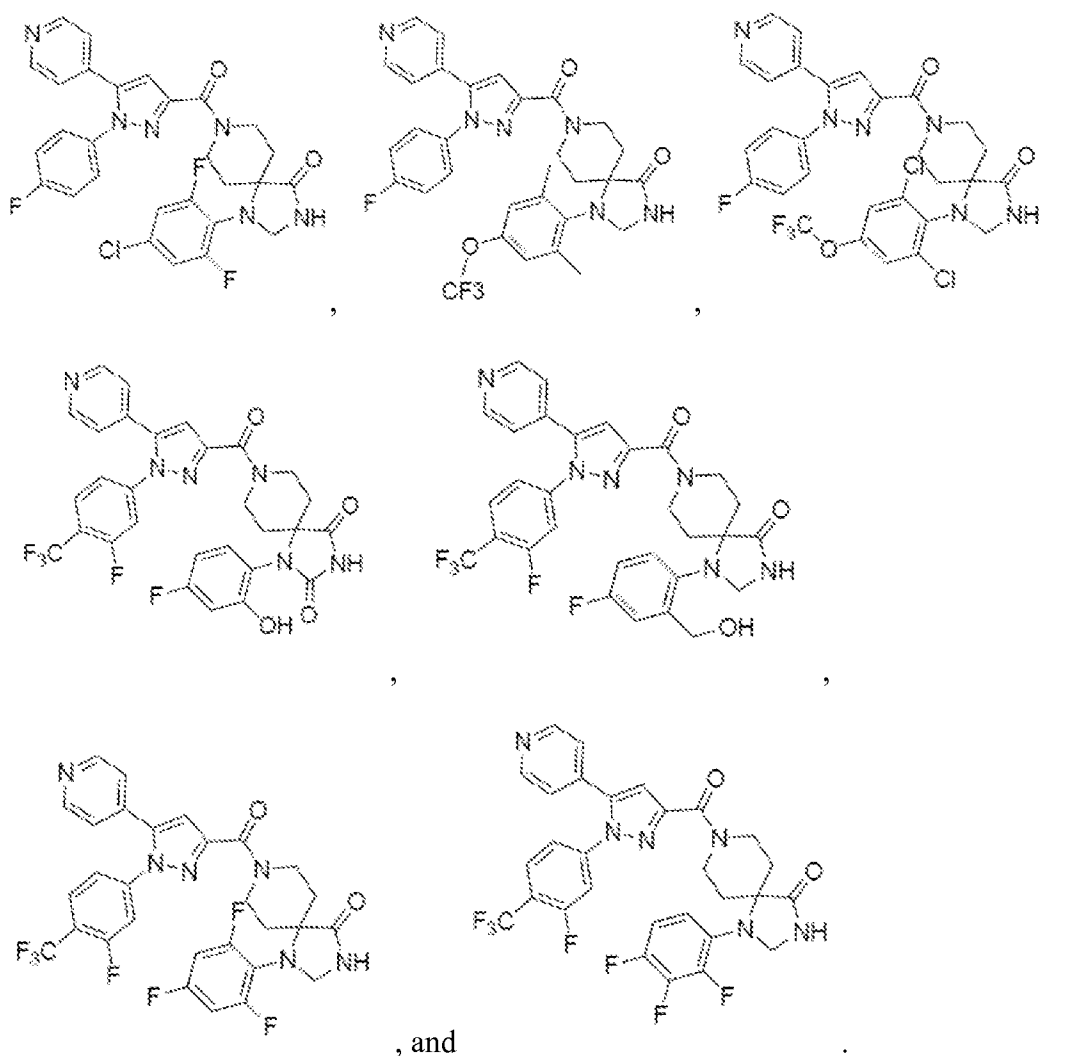


[0116] In some embodiments,  is a member selected from the group consisting of:

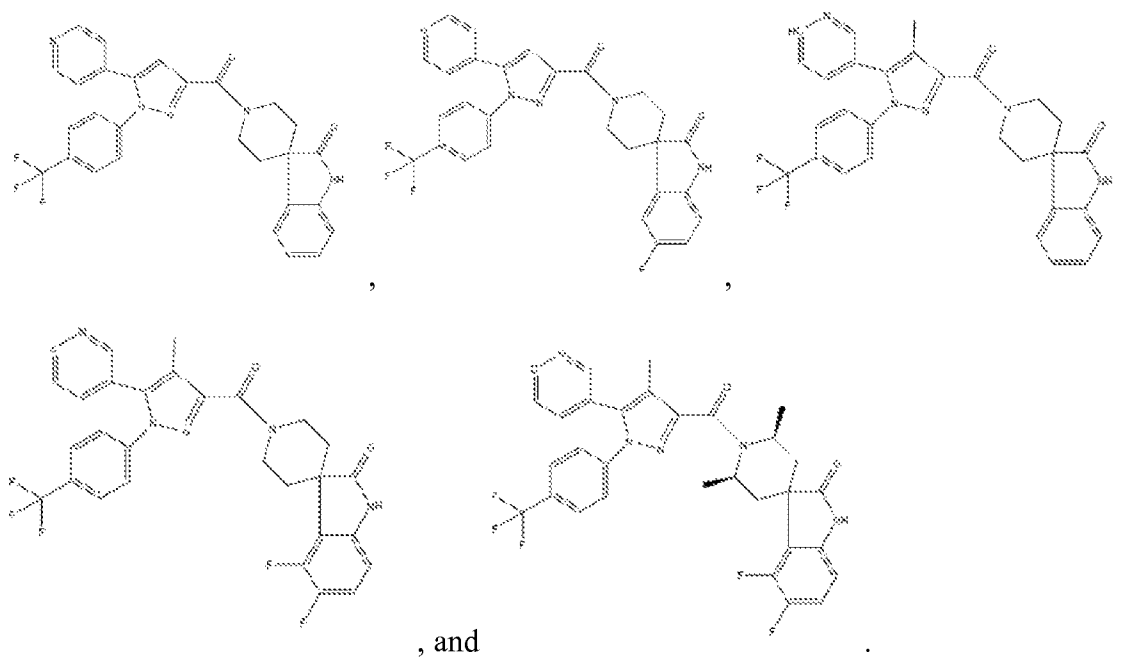


[0117] In aspects or embodiments directed to Markush groups, in some further embodiments, the present invention is directed only to a single member of the Markush group.

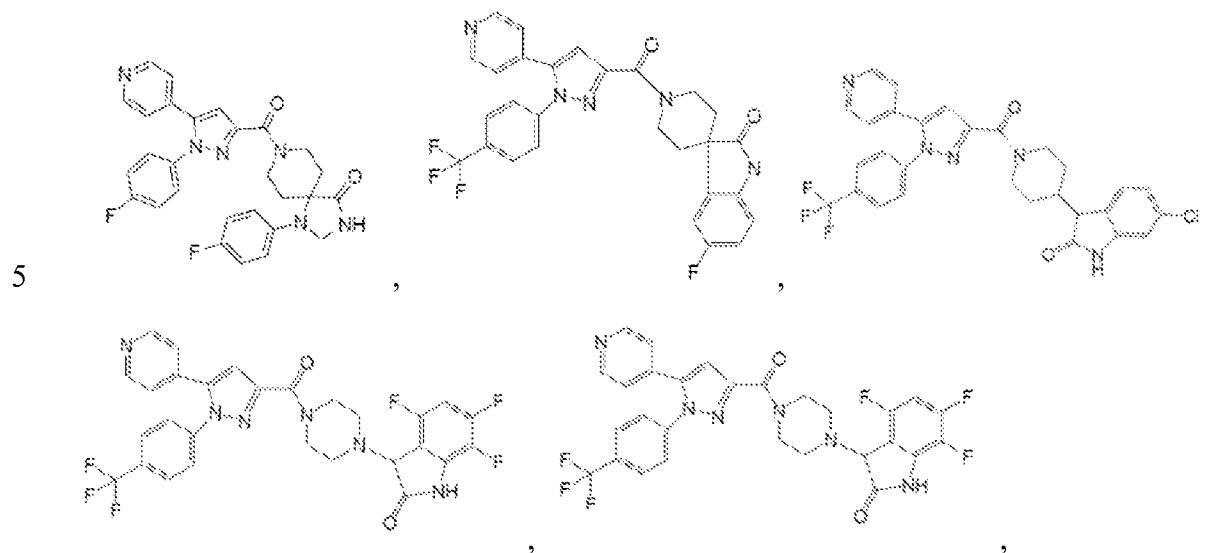
[0118] In some embodiments, the compound is selected from the group consisting of:

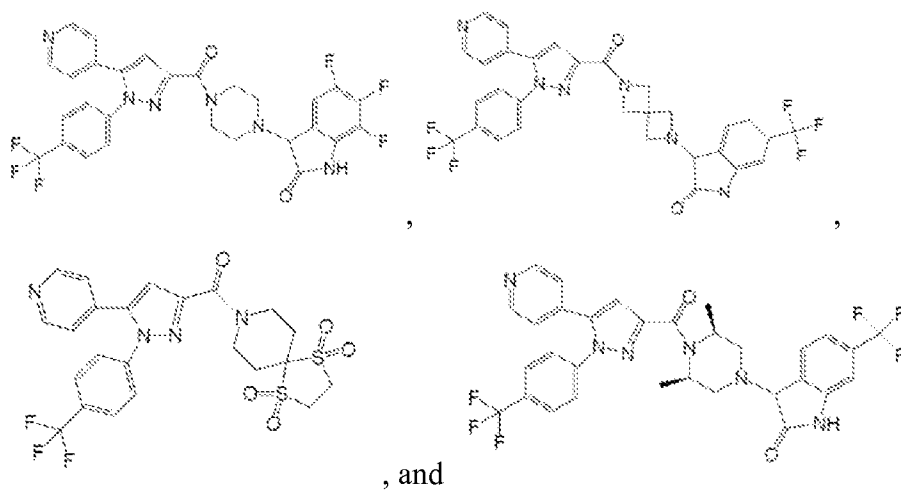


[0119] In some embodiments, the compound is selected from the group consisting of:

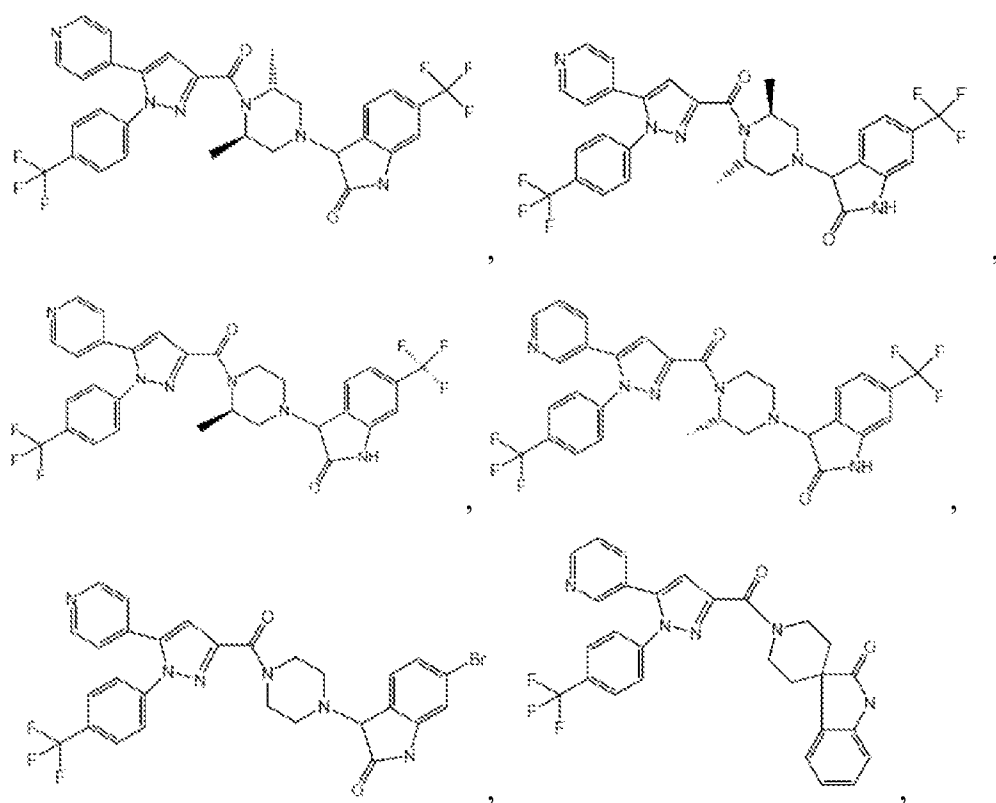


[0120] In some embodiments, the compound is selected from the group consisting of:

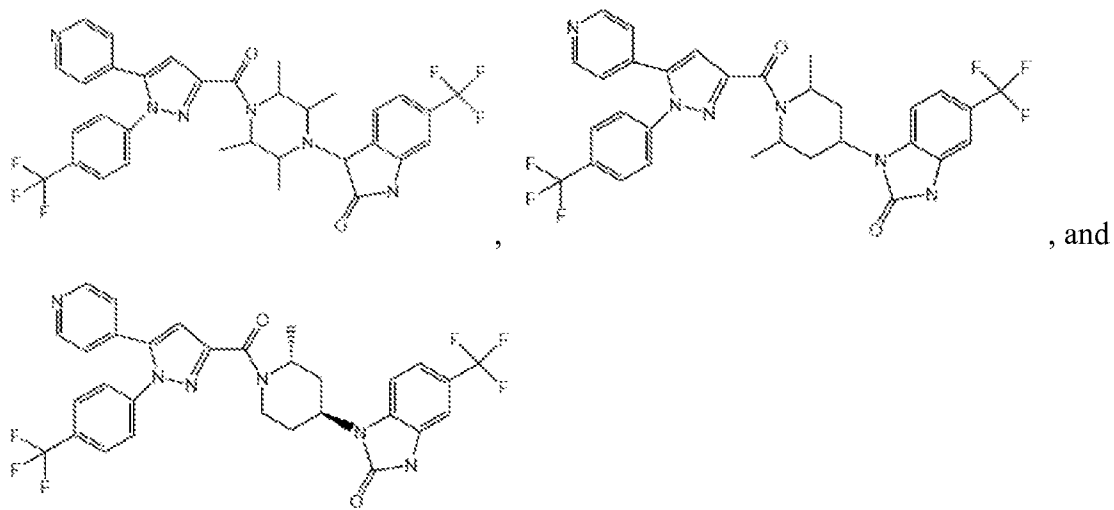




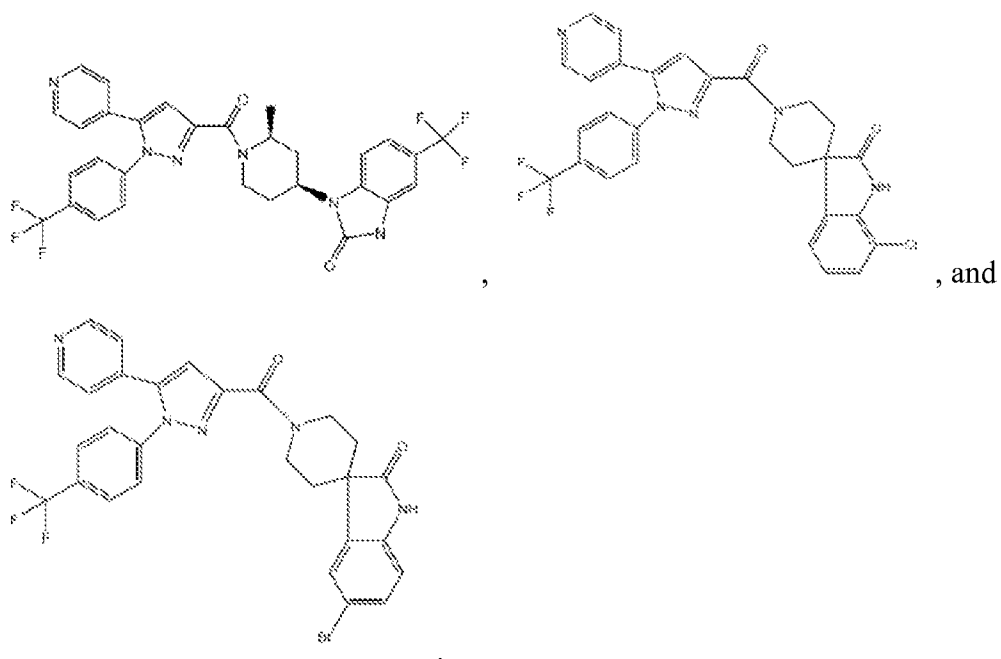
[0121] In some embodiments, the compound is selected from the group consisting of:



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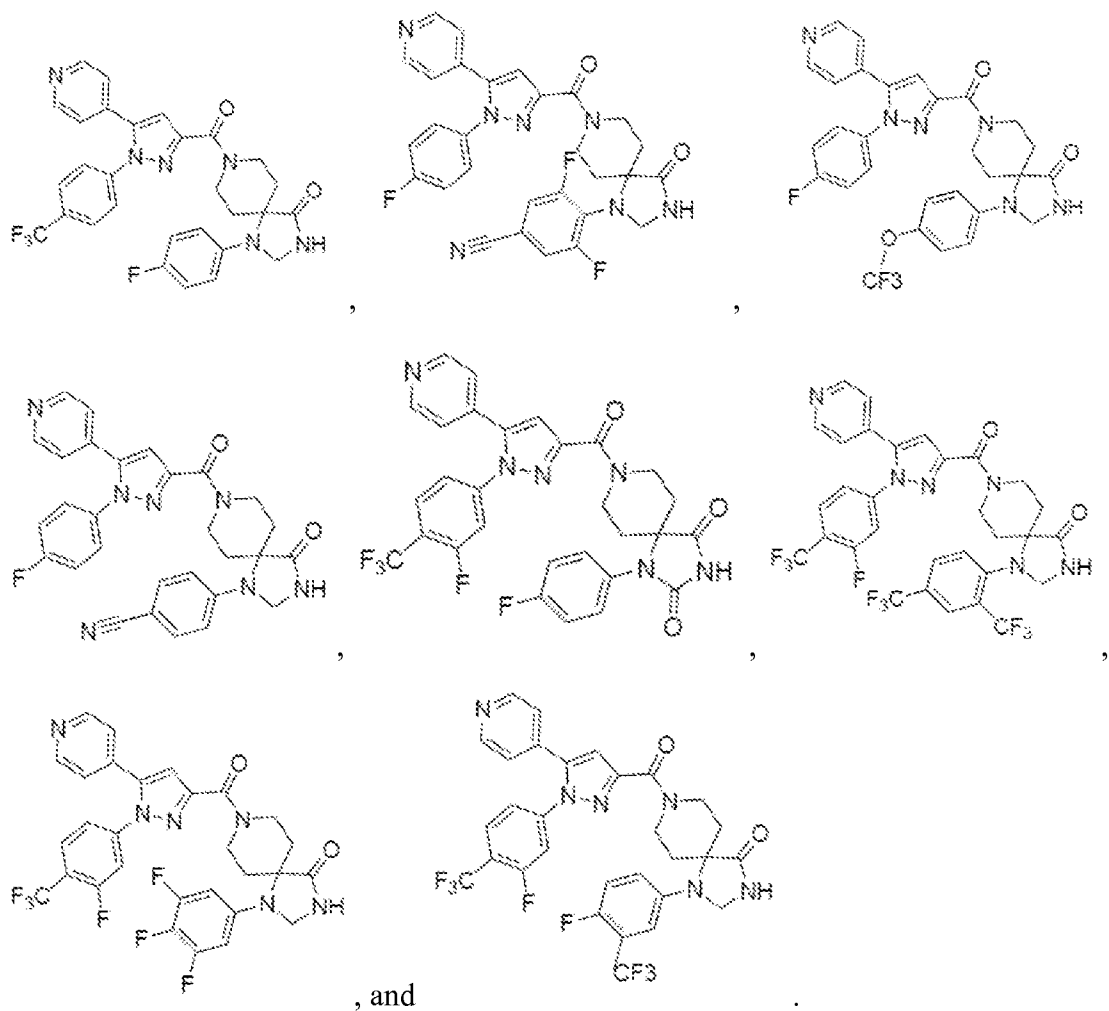


[0122] In some embodiments, the compound is selected from the group consisting of:

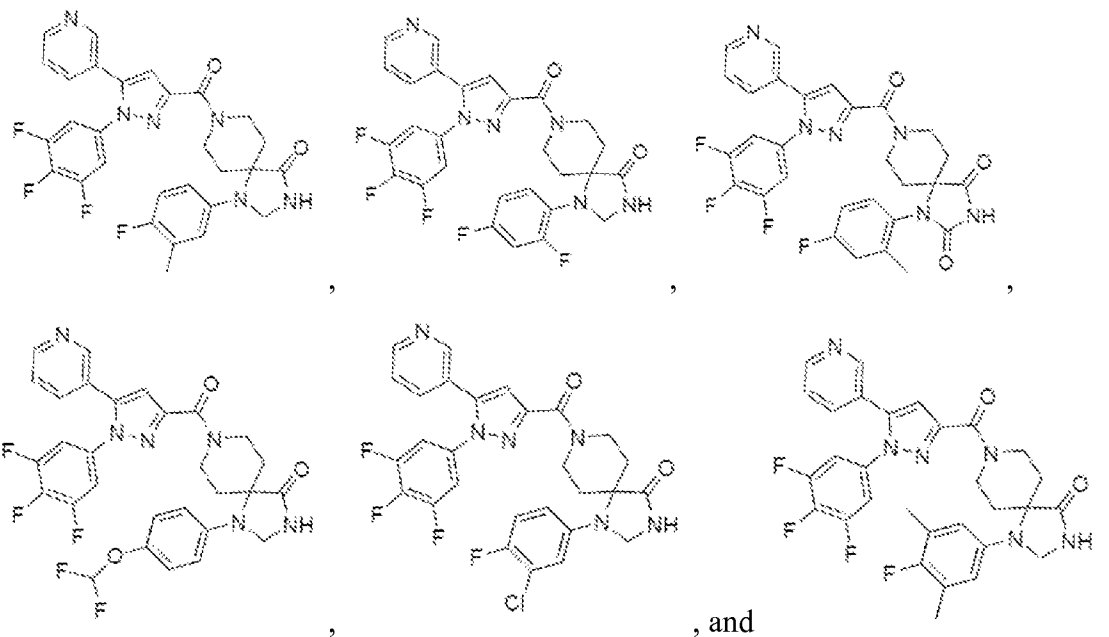


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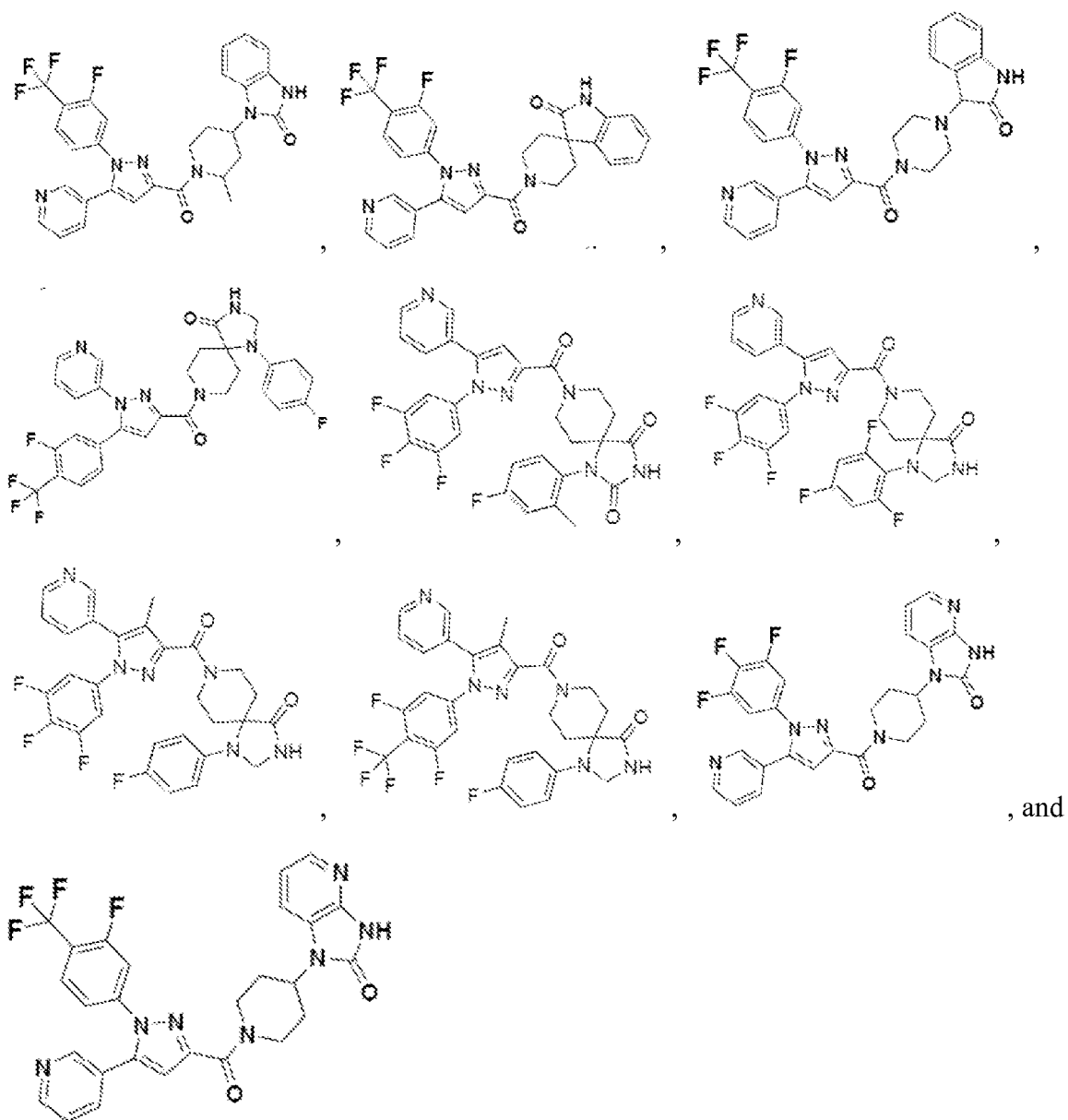
[0123] In some embodiments, the compound is selected from the group consisting of:



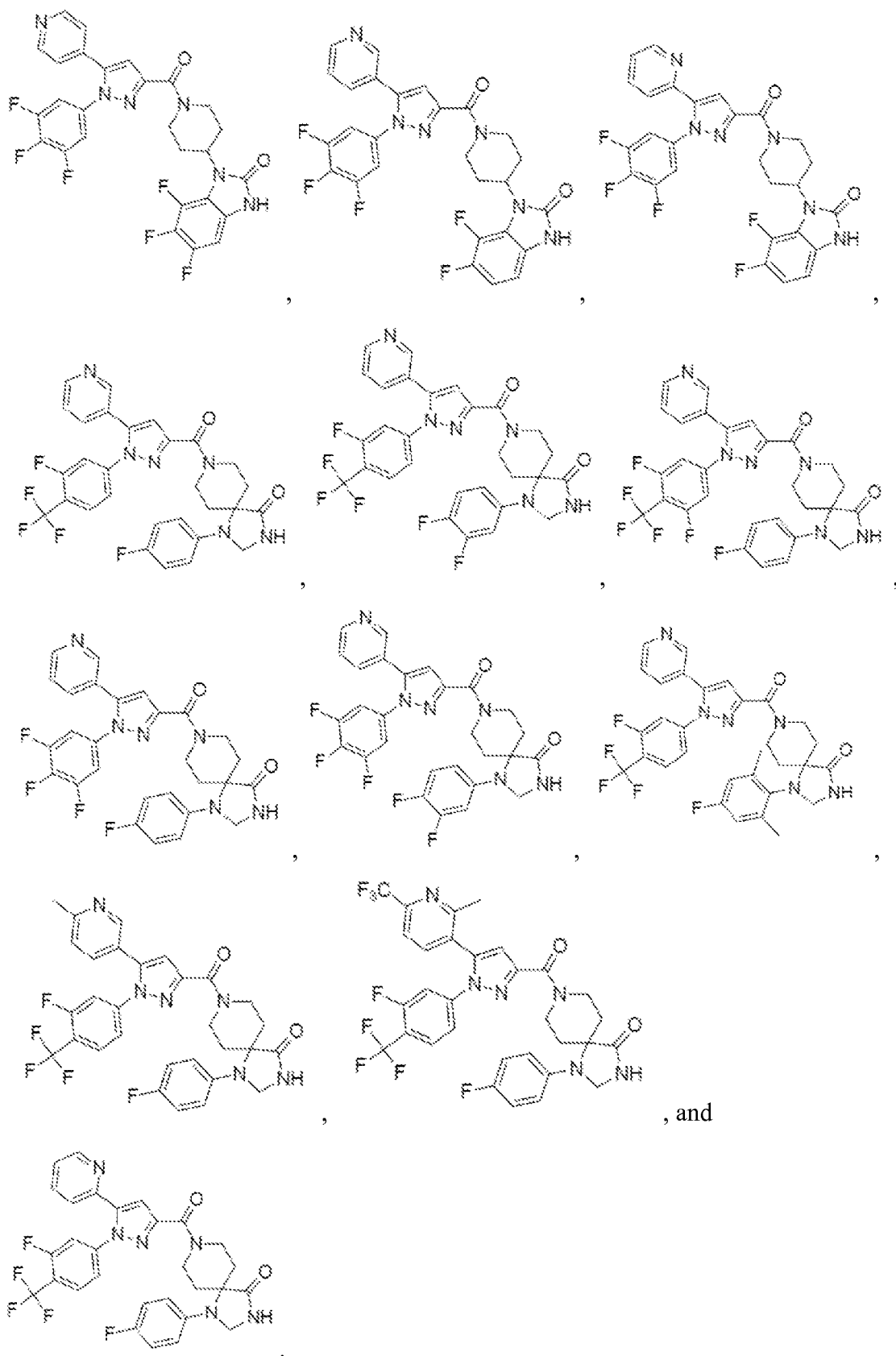
[0124] In some embodiments, the compound is selected from the group consisting of:



[0125] In some embodiments, the compound is selected from the group consisting of:

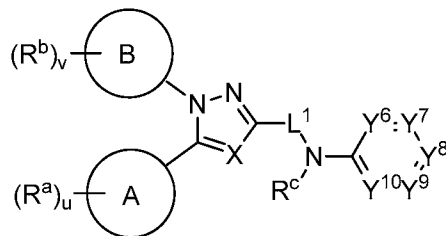


5 [0126] In some embodiments, the compound is selected from the group consisting of:



[0127] In some embodiments, the compound incorporates the features of one or more of the structural features of embodiments set forth for Formula II or Formula III. In some embodiments, the compound combines the features of two (or more) embodiments.

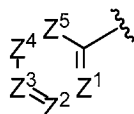
[0128] In one aspect, the invention provides a compound of Formula II:



or a pharmaceutically acceptable salt thereof;

wherein:

A is a cyclic group of Formula IIa:



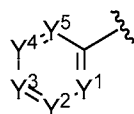
IIa

wherein Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are each a member selected from the group consisting of N, CH, and CR^a ; or, alternatively for Z^1 , the member Z^1 and X, together with atoms in the rings to which they are attached, form an additional fused, five- to eight-membered cycloalkyl or heterocyclyl ring with from 0 to 5 R^Z substituents;

with the proviso that at least one member selected from the group consisting of Z^2 , Z^3 , and Z^4 is N;

each R^Z is a member independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; or, alternatively, two R^Z substituents, together with the carbon atom to which they are attached, join to form an oxo, spirocycloalkyl, or spiroheterocyclyl group;

B is a cyclic group of Formula Ib:



Ib

wherein Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are each a member independently selected from the group consisting of N, CH, and CR^b ; or, alternatively, the

members $-Y^2=Y^3-$ or $-Y^4=Y^5-$ are combined into a single member selected from the group consisting of NH, NR^c , O, and S;

each R^a and R^b is a member independently selected from the group consisting of cyano, carboxyl, C_1-C_4 alkyl, C_1-C_4 hydroxyalkyl, C_3-C_8 cycloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, halo, C_0-C_6 amino, C_1-C_6 amido, C_1-C_4 alkyloxycarbonyl, C_1-C_6 alkylsulfonyl, and hydroxyl; or, alternatively, two adjacent R^a or R^b , together with the atoms in groups A or B to which they are attached, form an additional fused aryl, heteroaryl, cycloalkyl, or heterocyclyl ring with from 0 to 5 R^z substituents;

each R^c is a member independently selected from the group consisting of C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_6 cycloalkyl, $(C_3-C_6$ cycloalkyl) C_1-C_3 alkyl, and C_1-C_7 acyl;

each u is an integer independently selected from 0 to 4;

v is an integer from 0 to 5;

X is N or CR^d ; or, alternatively, X is CR^d , wherein X and the member Z^1 , together with atoms in the rings in which they are included, form the additional fused, five- to eight-membered cycloalkyl or heterocyclyl ring with from 0 to 5 R^z substituents;

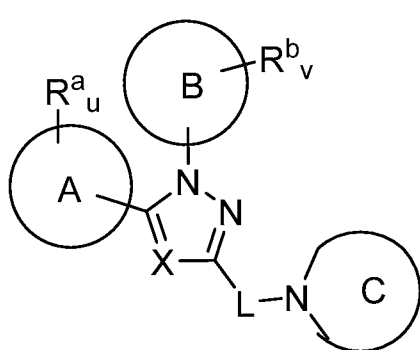
each R^d is a member independently selected from the group consisting of halo, cyano, C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy, C_1-C_4 haloalkoxy, C_3-C_6 cycloalkyl, and C_3-C_6 cycloalkoxy;

L^1 is a member selected from the group consisting of $C=O$, $C=S$, $C=NH$, and $C=NR^c$;

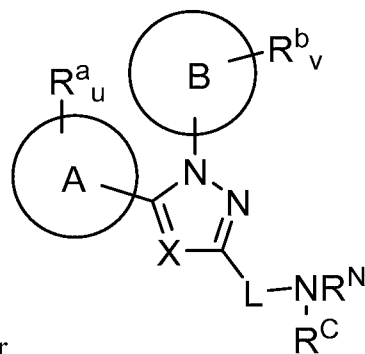
Y^6 , Y^7 , Y^8 , Y^9 , and Y^{10} , if present, are each a member independently selected from the group consisting of N, CH, and CR^b ; or, alternatively for Y^8 and Y^9 , the members $-Y^6=Y^7-$ or $-Y^8=Y^9-$ are combined into a single member selected from the group consisting of NR^c , O, and S.

[0129] In some embodiments, the compound incorporates the features of one or more of the structural features of embodiments set forth for Formula I or Formula III. In some embodiments, the compound combines the features of two (or more) embodiments.

[0130] In one aspect, the invention provides compounds according to Formula III or a pharmaceutically acceptable salt thereof:



IIIa or



IIIb, wherein:

Ring A and Ring B are each independently:

a 5- or 6-membered cyclic group with the proviso that Ring A and Ring B are not both unsubstituted phenyl; or

5 a 9-10-membered fused aromatic bicyclic ring with optionally 1, 2, 3, or 4 heteroatoms selected from N, O or S as part of the 9-10 members ;

R^a and R^b are each independently selected from the group consisting of -CN, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, halogen, and hydroxy;

10 optionally, two R^a , together with the atoms in Ring A to which they are attached, join to form a ring;

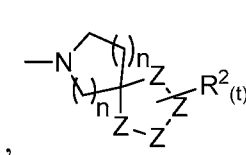
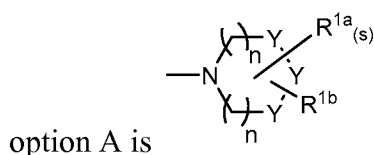
optionally, two R^b , together with the atoms in Ring B to which they are attached, join to form a ring;

u and v are each independently 0, 1, 2, or 3;

15 X is CR^x or N, wherein R^x is selected from H, -CN, C_1 - C_3 alkyl, -CF₃ cyclopropyl, and C_1 - C_3 alkoxy;

L is $-[C(O)]_{0,1}-(CH_2)_{0,1,2}-$

Ring C is option A, option B, or option C wherein:



or a fused 8-14 member bi- or

tri-cyclic cyclic group optionally having 1-4 heteroatoms selected from N and O and

20 optionally substituted with 1-4 R^3 wherein:

Y is a bond, $-\text{CH}_2-$, $-\text{S}(\text{O})_2-$, $-\text{S}(\text{O})-$, $-\text{C}(\text{O})-$, $-\text{NH}-$, or $-\text{O}-$; with the proviso that if two Y are bonds, the third Y is $-\text{CH}_2-$;

each Z is independently $-\text{CH}_2-$, $-\text{NH}-$, $-\text{S}-$, or $-\text{O}-$ with the proviso that at least 2 of Z are $-\text{CH}_2-$;

5 each n is independently 0, 1 or 2 provided that if one n is 0, the other n is not 0;

s is 0, 1, 2, 3, or 4;

t is 1, 2, 3, or 4;

10 each R^{1a} is independently C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, C_1 - C_4 haloalkyl, $-\text{CN}$, or halogen;

R^{1b} is:

an 8- to 9-membered bicyclic cyclic group having 0, 1, or 2 heteroatoms selected from S, N, and O, substituted by one or more oxo or (=S) and optionally substituted by one or more substituents selected from the group consisting of halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkoxy, and C_1 - C_4 haloalkyl, or

$-\text{R}^4-\text{R}^5$ wherein each of R^4 and R^5 are a 5- to 6-membered cyclic group having 0, 1, or 2 heteroatoms selected from N and O and each optionally substituted with oxo, halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkoxy, and C_1 - C_4 haloalkyl;

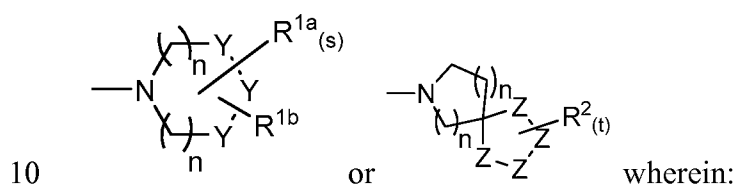
20 each R^2 is independently selected from the group consisting of $-\text{CN}$, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, $-(\text{C}_1$ - C_4 alkyl)-OH, C_1 - C_4 haloalkyl, halogen, oxo, hydroxy, and 5- to 9-membered mono- or bicyclic cyclic group having 0, 1, or 2 heteroatoms selected from N and O, and wherein:

if one R^2 is oxo, t is 2 or 3 and one R^2 is other than oxo,

25 if R^2 is a cyclic group, it is optionally substituted by one or more substituents selected from the group consisting of $-\text{CN}$, halogen, C_1 - C_4 alkyl, and C_1 - C_4 haloalkyl, and optionally, two R^2 , together with the atoms to which they are attached, join to form a 5- or 6-membered cyclic group optionally substituted with 1-4 substituents selected from the group consisting of $-\text{CN}$, halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkoxy, and C_1 - C_4 haloalkyl;

one R^3 is oxo and any remaining R^3 is independently selected from the group consisting of 5- to 9-membered mono- or bicyclic cyclic group having 0, 1, or 2 heteroatoms selected from N and O, -CN, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, C_1 - C_4 haloalkyl, halogen, oxo, and hydroxyl, and if R^3 is a cyclic group, it is optionally substituted by one or more substituents selected from the group consisting of halogen, C_1 - C_4 alkyl and C_1 - C_4 haloalkyl;

option B is if Ring A is a 6-membered cyclic group, Ring C is selected from the group consisting of a fused 8-14 member bi- or tri-cyclic cyclic group optionally having 1-4 heteroatoms selected from N and O and optionally substituted by 1-3 R^3 ,



Y is a bond, $-CH_2-$, $-S(O)_2-$, $-S(O)-$, $-C(O)-$, $-NH-$, or $-O-$ with the proviso that if two Y are bonds, the third Y is $-CH_2-$;

each n is independently 0, 1 or 2 provided that if one n is 0, the other n is not 0;

15 each Z is independently $-CH_2-$, $-NH-$, $-S-$ or $-O-$, with the proviso that at least 2 of Z are $-CH_2-$;

each R^{1a} is independently C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, C_1 - C_4 haloalkyl, -CN, or halogen;

R^{1b} is:

20 a 5- to 9-membered mono- or bicyclic cyclic group having 0, 1, or 2 heteroatoms selected from S, N and O optionally substituted by one or more substituents selected from the group consisting of (=S), oxo, halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkoxy and

C_1 - C_4 haloalkyl and wherein if Ring C is

, each n is 1 and s is 0, then R^{1b} is not phenyl, pyridine, or pyrimidine, or

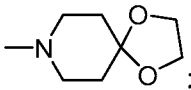
$-R^4-R^5$ wherein each of R^4 and R^5 are a 5- to 6-membered cyclic group having 0, 1 or 2 heteroatoms selected from N and O and each optionally substituted with oxo, halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkoxy and C_1 - C_4 haloalkyl;

each R^2 and R^3 is independently selected from the group consisting of 5- to 9-membered mono- or bicyclic cyclic group having 0, 1 or 2 heteroatoms selected from N and O, -CN, C_1 - C_4 alkyl, $-(C_1-C_4 \text{ alkyl})-OH$, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, C_1 - C_4 haloalkyl, halogen, oxo, and hydroxy and if R^2 is a cyclic group, it is optionally substituted by one or more substituents selected from the group consisting of -CN, halogen, C_1 - C_4 alkyl, and C_1 - C_4 haloalkyl;

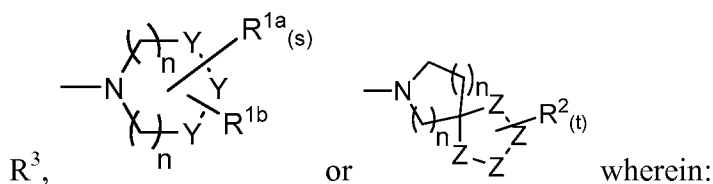
optionally, two R^2 , together with the atoms to which they are attached, join to form a 5- or 6-membered cyclic group optionally substituted with 1-4 substituents selected from the group consisting of -CN, halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkoxy, and C_1 - C_4 haloalkyl;

s is 0, 1, 2, 3 or 4; and

t is 0, 1, 2, 3 or 4;

with the proviso that, in option B, if X is N, Ring C is not ; or

option C is if Ring A is a 6-membered cyclic group other than pyridine, Ring C is selected from the group consisting of a fused 8-14 member bi- or tri-cyclic cyclic group optionally having 1-4 heteroatoms selected from N and O and optionally substituted by 1-3



Y is a bond, $-CH_2-$, $-S(O)_2-$, $-S(O)-$, $-C(O)-$, $-NH-$, or $-O-$ with the proviso that if two Y are bonds, the third Y is $-CH_2-$;

each n is independently 0, 1 or 2 provided that if one n is 0, the other n is not 0;

each Z is independently $-CH_2-$, $-NH-$, $-S-$, or $-O-$ with the proviso that at least 2 of Z are $-CH_2-$;

each R^{1a} is independently C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, C_1 - C_4 haloalkyl, -CN, or halogen;

R^{1b} is:

a 5- to 9-membered mono- or bicyclic cyclic group having 0, 1 or 2 heteroatoms selected from S, N and O optionally substituted by one or more substituents selected from the group consisting of (=S), oxo, halogen, C₁-C₄ alkyl, C₁-C₄ haloalkoxy, and C₁-C₄ haloalkyl, or

5 -R⁴-R⁵ wherein each of R⁴ and R⁵ are a 5- to 6-membered cyclic group having 0, 1, or 2 heteroatoms selected from N and O and each optionally substituted with oxo, halogen, C₁-C₄ alkyl, C₁-C₄ haloalkoxy and C₁-C₄ haloalkyl;

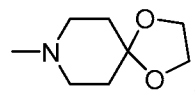
each R² and R³ is independently selected from the group consisting of 5- to 9-membered mono- or bicyclic cyclic group having 0, 1 or 2 heteroatoms selected from N and
10 O, -CN, -C₁-C₄ alkyl, -(C₁-C₄ alkyl)-OH, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl, halogen, oxo and hydroxy and if R² is a cyclic group, it is optionally substituted by one or more substituents selected from the group consisting of -CN, halogen, C₁-C₄ alkyl and C₁-C₄ haloalkyl;

optionally, two R², together with the atoms to which they are attached, join to
15 form a 5- or 6-membered cyclic group optionally substituted with 1-4 substituents selected from the group consisting of -CN, halogen, C₁-C₄ alkyl, C₁-C₄ haloalkoxy, and C₁-C₄ haloalkyl;

s is 0, 1, 2, 3, or 4; and

t is 0, 1, 2, 3, or 4;

20 with the proviso that, in option C, if X is N, Ring C is not



R^N is H or C₁-C₄ alkyl; and

R^C is:

a 5-6 membered heteroaryl optionally substituted by 1-4 R⁴;

a fused 8-10 member cyclic group having 0, 1, or 2 heteroatoms selected from
25 N and O and optionally substituted by 1-3 R⁴ if R^N is other than H; or

if Ring A is a 6-membered cyclic group, R^C is a fused 8-10 member cyclic group having 0, 1, or 2 heteroatoms selected from N and O and optionally substituted by 1-3 R⁴ wherein:

each R⁴ is independently selected from the group consisting of 5- to 9-
30 membered mono- or bicyclic cyclic group having 0, 1 or 2 heteroatoms selected from N and

O, -CN, -C₁-C₄ alkyl, -(C₁-C₄ alkyl)-OH, C₁-C₄ alkoxy, C₁-C₄ haloalkoxy, C₁-C₄ haloalkyl, halogen, oxo, and hydroxy; and

if R⁴ is a cyclic group, it is optionally substituted by one or more substituents selected from the group consisting of -CN, halogen, C₁-C₄ alkyl, and C₁-C₄ haloalkyl.

5 [0131] In some embodiments two R², together with the atoms to which they are attached, join to form a 5- or 6-membered aryl or heteroaryl group optionally substituted with 1-4 substituents selected from the group consisting of -CN, halogen, C₁-C₄ alkyl, C₁-C₄ haloalkoxy, and C₁-C₄ haloalkyl.

10 [0132] In some embodiments two R², together with the atoms to which they are attached, join to form a 5- or 6-membered aryl or heteroaryl group optionally substituted with 1-4 substituents selected from the group consisting of halogen, C₁-C₄ alkyl, C₁-C₄ haloalkoxy, and C₁-C₄ haloalkyl.

[0133] In some embodiments at least one of Ring A or Ring B is an aryl or heteroaryl group.

15 [0134] In some embodiments at least one of Ring A or Ring B is a 6-membered aryl or 6-membered heteroaryl group.

[0135] In some embodiments both of Ring A and Ring B are either a 6-membered aryl or a 6-membered heteroaryl group.

[0136] In some embodiments both of Ring A and Ring B are not phenyl.

20 [0137] In some embodiments at least one of Ring A and Ring B is a 5-membered cyclic group having two heteroatoms.

[0138] In some embodiments Ring A is a 6-membered cyclic group or a 5- membered cyclic group wherein the 5-membered cyclic group includes 0, 2, or 3 heteroatoms.

25 [0139] In some embodiments Ring B is a 6-membered cyclic group or a 5- membered cyclic group wherein the 5-membered cyclic group includes 0, 2 or 3 heteroatoms.

[0140] In some embodiments each R^a is independently -CN, halogen, a C₁-C₄ haloalkoxy, a C₁-C₄ haloalkyl, or C₁-C₄ alkyl; independently halogen, a C₁-C₄ haloalkoxy, a C₁-C₄ haloalkyl or C₁-C₄ alkyl; independently -CN, F, Cl, -OCF₃, -OCHF₂, -CF₃ or -CH₃; or independently F, Cl, -OCF₃, -OCHF₂, -CF₃, or -CH₃.

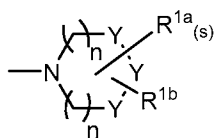
[0141] In some embodiments u is 1, 2, or 3, and each R^a is independently F or –CF₃.

[0142] In some embodiments each R^b is independently –CN, halogen, a C₁-C₄ haloalkoxy, a C₁-C₄ haloalkyl, or C₁-C₄ alkyl; independently halogen, a C₁-C₄ haloalkoxy, a C₁-C₄ haloalkyl or C₁-C₄ alkyl; independently –CN, F, Cl, –OCF₃, –OCHF₂, –CF₃ or –CH₃; or
5 independently F, Cl, –OCF₃, –OCHF₂, –CF₃, or –CH₃.

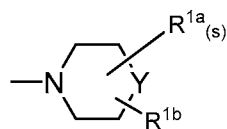
[0143] In some embodiments each R^b is independently –CN, halogen, a C₁-C₄ haloalkoxy, a C₁-C₄ haloalkyl, or C₁-C₄ alkyl.

[0144] In some embodiments each R^b is independently –CN, F, Cl, –OCF₃, –OCHF₂, –CF₃, or –CH₃.

10 [0145] In some embodiments v is 1, 2 or 3 and each R^b is independently F or –CF₃.



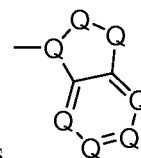
[0146] In a first aspect Ring C is



[0147] In a second aspect Ring C is

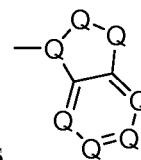
[0148] In some embodiments of the first or second aspects Y is –CH₂–.

15 [0149] In some embodiments of the first or second aspects R^{1b} is a 5- to 9-membered mono- or bicyclic cyclic group having 0, 1, 2, or 3 heteroatoms selected from S, N and O and substituted by one or more substituents selected from the group consisting of oxo, halogen, C₁-C₄ alkyl, C₁-C₄ haloalkoxy, and C₁-C₄ haloalkyl.

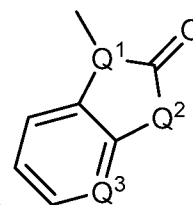


[0150] In some embodiments of the first or second aspects R^{1b} is

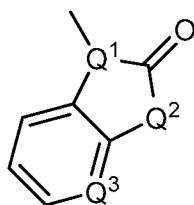
20 optionally substituted by one or more substituents selected from the group consisting of (=S), oxo, halogen, C₁-C₄ alkyl, C₁-C₄ haloalkoxy and C₁-C₄ haloalkyl and wherein each Q is independently selected from –N–, –NH–, –CH– and –CH₂– provided that not more than three Q



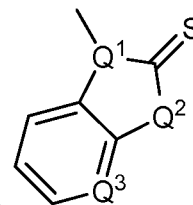
are -N-or -NH-. In some embodiments of the first or second aspects R^{1b} is which is optionally substituted by one or more substituents selected from the group consisting of oxo, halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkoxy and C_1 - C_4 haloalkyl and wherein each Q is independently selected from -N-, -NH-, -CH-, and -CH₂- provided that not more than three Q are -N-or -NH-.



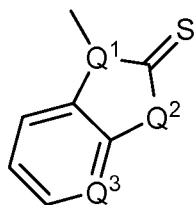
[0151] In some embodiments of the first or second aspects R^{1b} is which is optionally substituted by one or more substituents selected from the group consisting of (=S), oxo, halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkoxy, and C_1 - C_4 haloalkyl; and wherein Q^1 is -C- or -N-; Q^2 is -CH₂-, -NH-, -O-, or -S-; and Q^3 is -CH- or -N-. In some embodiments of the first



10 or second aspects R^{1b} is which is optionally substituted by one or more substituents selected from the group consisting of halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkoxy and C_1 - C_4 haloalkyl and wherein Q^1 is -C- or -N-; Q^2 is -CH₂-, -NH-, -O-, or -S-; and Q^3 is -CH- or -N-.



15 [0152] In some embodiments of the first or second aspects R^{1b} is which is optionally substituted by one or more substituents selected from the group consisting of (=S), oxo, halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkoxy, and C_1 - C_4 haloalkyl; and wherein Q^1 is -C- or -N-; Q^2 is -CH₂-, -NH-, -O-, or -S-; and Q^3 is -CH- or -N-. In some embodiments of the first



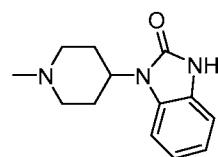
or second aspects R^{1b} is which is optionally substituted by one or more

substituents selected from the group consisting of halogen, C₁-C₄ alkyl, C₁-C₄ haloalkoxy and C₁-C₄ haloalkyl and wherein Q¹ is -C- or -N-; Q² is -CH₂-, -NH-, -O-, or -S-; and Q³ is -CH- or -N-.

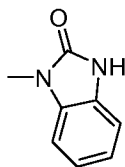
5 [0153] In some embodiments of the first or second aspects R^{1b} is substituted with F, Cl, Br, I, -CF₃, -OCF₃, -OH, or C₁-C₄ alkyl.

[0154] In some embodiments of the first or second aspects R^{1b} is a 9-membered bicyclic cyclic group substituted by oxo and optionally substituted by one or more substituents selected from the group consisting of halogen, C₁-C₄ alkyl, C₁-C₄ haloalkoxy, and C₁-C₄ haloalkyl.

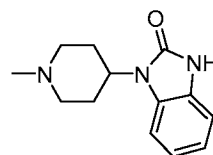
10 [0155] In some embodiments of the first or second aspects R^{1b} is



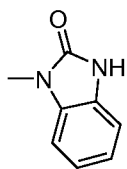
and



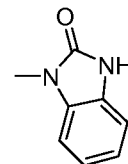
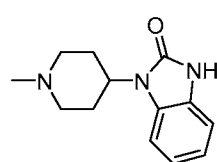
wherein is optionally substituted by one or more substituents selected from the group consisting of (=S), oxo, halogen, C₁-C₄ alkyl, C₁-C₄ haloalkoxy, and C₁-C₄ haloalkyl.



In some embodiments of the first or second aspects R^{1b} is and wherein



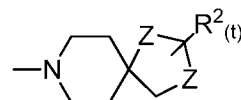
15 is optionally substituted by one or more substituents selected from the group consisting of oxo, halogen, C₁-C₄ alkyl, C₁-C₄ haloalkoxy, and C₁-C₄ haloalkyl. In some



embodiments of the first or second aspects R^{1b} is ; and wherein is optionally substituted by one or more substituents selected from the group consisting of halogen, C₁-C₄ alkyl, C₁-C₄ haloalkoxy, and C₁-C₄ haloalkyl.



[0156] In a third aspect, Ring C is

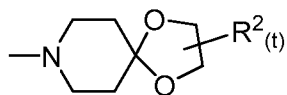


[0157] In some embodiments of the third aspect Ring C is wherein each Z is independently CH₂, NH, or O; t is 1 or 2 and at least one R² is oxo.

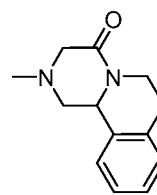
[0158] In some embodiments of the third aspect t is 2 and the two R² are oxo and phenyl, which is optionally substituted with a fluorine, 1-3 halogens or 2-3 halogens of which one is fluorine.

[0159] In some embodiments of the third aspect one Z is O and one Z is -CH₂-; t is 2 and both R² are halogens.

[0160] In some embodiments of the third aspect X is -CR^x- and Ring C is



[0161] In a fourth aspect, Ring C is a fused tricyclic cyclic group optionally substituted with 1-4 R³.



[0162] In some embodiments of the fourth aspect Ring C is optionally substituted with 1-4 R³.

[0163] Also provided is a pharmaceutical composition comprising a therapeutically effective amount of a compound as claimed in any of the aspects or embodiments herein; and a pharmaceutically acceptable carrier, excipient, diluent or a mixture thereof.

[0164] In some embodiments, the pharmaceutical composition comprises a second therapeutic agent selected from the group consisting of: i) opioid receptor agonists, ii) opioid receptor antagonists, iii) calcium channel antagonists, iv) 5-HT receptor agonists, v) 5-HT receptor antagonists vi) sodium channel antagonists, vii) NMDA receptor agonists, viii) NMDA receptor antagonists, ix) COX-2 selective inhibitors, x) neurokinin receptor antagonists, including NK1 antagonists, xi) non-steroidal anti-inflammatory drugs, xii)

selective serotonin reuptake inhibitors , xiii) selective serotonin and norepinephrine reuptake inhibitors, xiv) tricyclic antidepressant drugs, xv) norepinephrine modulators, xvi) 5-lipoxygenase inhibitors, xvii) cannabinoid receptor agonists, xviii) inhibitors of fatty acid amide hydrolase, ix) beta-adrenergic receptor agonists, x) prostanoid receptor antagonists, xxi) leukotriene receptor antagonists, xxii) histamine receptor antagonists, xxiii) steroids, xxiv) CGRP antagonists, xxv) peroxisome proliferator-activated receptor (PPAR) agonists, and xxvi) acetaminophen.

[0165] Also provided is a method of treating or preventing pain comprising administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a disclosed compound. In some embodiments the pain treated comprises acute pain, nociceptive pain, inflammatory pain, neuropathic pain, and periprocedural pain (*e.g.*, post-surgical). In some embodiments the method of treating further comprises administering a second therapeutic agent selected from the group consisting of: i) opioid receptor agonists, ii) opioid receptor antagonists, iii) calcium channel antagonists, iv) 5-HT receptor agonists, v) 5-HT receptor antagonists vi) sodium channel antagonists, vii) NMDA receptor agonists, viii) NMDA receptor antagonists, ix) COX-2 selective inhibitors, x) neurokinin receptor antagonists, including NK1 antagonists, xi) non-steroidal anti-inflammatory drugs, xii) selective serotonin reuptake inhibitors , xiii) selective serotonin and norepinephrine reuptake inhibitors, xiv) tricyclic antidepressant drugs, xv) antiepileptic drugs, xvi) 5-lipoxygenase inhibitors, xvii) cannabinoid receptor agonists, xviii) inhibitors of fatty acid amide hydrolase (FAAH), ix) beta-adrenergic receptor agonists, xx) prostanoid receptor antagonists, xxi) leukotriene receptor antagonists, xxii) histamine receptor antagonists, xxiii) steroids, xxiv) CGRP antagonists, xxv) peroxisome proliferator-activated receptor (PPAR) agonists, and xxvi) acetaminophen.

[0166] In some embodiments the 5-HT receptor agonist is a 5-HT_{1B} receptor agonist or a 5HT_{1D} receptor agonist. In some embodiments the 5-HT receptor agonist is a triptan. In some embodiments the triptan is sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, or frovatriptan.

[0167] In some embodiments the opioid receptor agonist is morphine, codeine, oxycodone, pentazocine, fentanyl, sufentanil, tramadol, meperidine, methadone, or etorphine.

[0168] In some embodiments the NSAID is aspirin, ibuprofen, naproxen, ketoprofen, loxoprofen, meloxicam, or diclofenac.

[0169] In some embodiments the COX-2 inhibitor is celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, or valdecoxib.

- 5 [0170] Also provided is a method of treating or preventing pain before, during or after surgical procedure, comprising the step of administering to a patient in need thereof a therapeutically effective amount, or a prophylactically effective amount, of a disclosed compound.

III. Pharmaceutical Compositions

- 10 [0171] Pharmaceutical compositions comprising the disclosed compounds are also provided. In a first embodiment, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients or vehicles, and optionally other therapeutic and/or prophylactic ingredients. Such excipients are known to those of skill in the art. A thorough discussion of pharmaceutically acceptable excipients and salts is available in
15 *Remington's Pharmaceutical Sciences*, 18th Edition (Easton, Pennsylvania: Mack Publishing Company, 1990). The compositions can be administered orally, mucosally, parenterally, topically, transdermally, intranasally, intravenously or by inhalation.

- [0172] Depending on the intended mode of administration, the pharmaceutical compositions may be in the form of solid, semi-solid or liquid dosage forms, such as, for
20 example, tablets, suppositories, pills, capsules, powders, liquids, suspensions, creams, ointments, lotions or the like, preferably in unit dosage form suitable for single administration of a precise dosage. The compositions will include an effective amount of the selected drug in combination with a pharmaceutically acceptable carrier and, in addition, may include other pharmaceutical agents, adjuvants, diluents, buffers, etc.

- 25 [0173] Pharmaceutical compositions comprise a disclosed compound including isomers, racemic or non-racemic mixtures of isomers, or pharmaceutically acceptable salts or solvates thereof together with one or more pharmaceutically acceptable carriers and optionally other therapeutic and/or prophylactic ingredients.

- [0174] For solid compositions, conventional nontoxic solid carriers include, for example,
30 pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talc, cellulose, glucose, sucrose, magnesium carbonate and the like.

[0175] For oral administration, the composition will generally take the form of a tablet, capsule, a softgel capsule nonaqueous solution, suspension or syrup. Tablets and capsules are preferred oral administration forms. Tablets and capsules for oral use will generally include one or more commonly used carriers such as lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. When liquid suspensions are used, the active agent may be combined with emulsifying and suspending agents. If desired, flavoring, coloring and/or sweetening agents may be added as well. Other optional components for incorporation into an oral formulation herein include, but are not limited to, preservatives, suspending agents, thickening agents and the like.

[0176] Parenteral administration includes intraarticular, intravesical, intravenous, intramuscular, intradermal, intraperitoneal, intraocular, intravitreal, intrathecal and subcutaneous administration. The compositions for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the physiological fluids of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives.

[0177] Another mode of administration of a compound of the present invention is for use in regional analgesia. Epidural analgesia and spinal analgesia are commonly employed techniques of providing pain relief during labor, surgical procedures and diagnostic procedures. Epidural analgesia can be administered by injection into the epidural space or an indwelling catheter can be directed into the epidural space and the patient receives a continuous infusion or multiple injections of the compound of the present invention. Administration may also encompass a combination of epidural and spinal analgesia. In addition, administration may include wound infiltration or injection to create a plexus block.

[0178] Compositions for topical, inhalation and transdermal routes of administration include powders, sprays, ointments, pastes, creams, gels, lotions, solutions, patches and inhalants. The ointments, pastes, creams and gels may contain, in addition to an a disclosed composition, excipients, such as animal and vegetable fats, oils, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures thereof. A dry powder formulation or aerosol formulation of the disclosed compound is useful for pulmonary delivery.

[0179] Powders, aerosols and sprays can contain, in addition to a disclosed compound, excipients such as lactose, talc, silicic acid, aluminum hydroxide, calcium silicates and polyamide powder, or mixtures of these substances. Sprays can additionally contain customary propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane. Transdermal patches have the added advantage of providing controlled delivery of a disclosed compound to the body. Such dosage forms can be made by dissolving or dispersing the compound in the proper medium. Absorption enhancers can also be used to increase the flux of the compound across the skin. The rate of such flux can be controlled by either providing a rate controlling membrane or dispersing the compound in a polymer matrix or gel.

[0180] Ophthalmic formulations, eye ointments, powders, solutions and the like, are also contemplated as within the scope of the disclosure. Formulations for ophthalmic administration include are generally formulated as sterile aqueous solutions and to be compatible with the eye. The ophthalmic formulations intended for direct application to the eye are formulated so as to have a pH and tonicity that are compatible with the eye. Example pH ranges are 4 to 9, more preferably 5.5 to 8.5, and most preferably 7 to 8. The osmolality of one or more of the disclosed compounds in the solution is 200 to 350 milliosmoles per kilogram (mOsm/kg), or 250 to 330 mOsm/kg. The use of nonionic osmolality-adjusting agents is preferred. Examples include propylene glycol, glycerol, xylitol or combinations thereof. Boric acid may also be utilized as an osmolality-adjusting agent in the ophthalmic formulations. Boric acid, if utilized, will be present in the compositions as a mixture of ionic and nonionic species. The ophthalmic formulations may contain various types of pharmaceutical excipients, such as surfactants, viscosity-modifying agents such as carboxymethylcellulose, glycerin, polyvinylpyrrolidone, polyethylene glycol and so on, provided that such excipients are non-ionic. One or more conventional antimicrobial preservatives, such as benzalkonium chloride, polyquaternium-1 or EDTA can be present in the ophthalmic formulations. The overall composition may include sufficient antimicrobial activity to satisfy USP/FDA/ISO preservative efficacy requirements. Ophthalmic formulations can be made for single or multi-dose packaging.

[0181] The pharmaceutical compositions can be prepared by any of the methods well known in the art of pharmacy and drug delivery. In general, methods of preparing the compositions include the step of bringing the active ingredient into association with a carrier containing one or more accessory ingredients. The pharmaceutical compositions are typically

prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation.

IV. Methods of Treating Pain

5 [0182] Provided are methods of treating pain by the disclosed compounds. Exemplary types of pain treated by the provided compounds include (1) acute, chronic, visceral, inflammatory and/or neuropathic pain syndromes; (2) pain resulting from, or associated with, traumatic nerve injury, nerve compression or entrapment, acute herpetic and postherpetic neuralgia, trigeminal neuralgia, fibromyalgia, diabetic neuropathy, cancer and/or
10 chemotherapy; (3) lower back pain; (4) phantom limb pain; (5) pain resulting from inflammatory disease, including osteoarthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, gout, neuropathic arthropathy, psoriatic arthritis, ankylosing spondylitis, other spondyloarthropathies, crystalline arthropathies or systemic lupus erythematosus (SLE); (6) headache pain, migraine pain and cluster headache pain; (7) HIV- and HIV treatment-induced
15 neuropathy, chronic pelvic pain, neuroma pain, complex regional pain syndrome; or (8) stroke or neural trauma.

[0183] The compounds of the present invention have applications in preventing, reducing or inhibiting acute and/or chronic pain in a variety of operative and interventional procedures, including surgical, diagnostic and therapeutic procedures. An interventional procedure is
20 defined as any procedure used for diagnosis or treatment that involves incision; puncture; entry into a body cavity; or the use of ionizing, electromagnetic or acoustic energy.

[0184] In some embodiments, the compound is administered periprocedurally, which may include perioperatively. In some embodiments, the compound of the present invention is administered preprocedurally or postprocedurally as well as intraprocedurally. In some
25 embodiments, the compounds of the present invention are administered to a surgical, diagnostic or therapeutic procedure site by techniques well known to those of ordinary skill in the art. In some embodiments, post-surgical pain is treated by the methods of the invention.

[0185] The methods of treating pain generally comprise administering a compound of the invention to a subject in need thereof. In some embodiments, the method of treating pain
30 comprises modulating the activity of TRPA1 (SEQ ID NO:1) or a variant thereof (*e.g.*, a variant selected from SEQ ID NOS:2-7) in the subject. Modulating the activity of TRPA1

can include activating TRPA1 or inhibiting TRPA1. In some embodiments, the method of treating pain comprises administering a compound of the invention to a subject and modulating the activity of TRPA1 (SEQ ID NO:1) in the subject. In some embodiments, the method of treating pain comprises administering a compound of the invention to a subject and inhibiting the activity of TRPA1 (SEQ ID NO:1) in the subject.

[0186] In some embodiments, the treatment of pain comprises administering a disclosed compound and a second compound selected from one or more of the following classes: i) opioid receptor agonists, ii) opioid receptor antagonists, iii) calcium channel antagonists, iv) serotonin (5-HT) receptor agonists, v) 5-HT receptor antagonist vi) sodium channel antagonists, vii) NMDA receptor agonists, viii) NMDA receptor antagonists, ix) COX-2 selective inhibitors, x) neurokinin receptor antagonists, including NK1 antagonists, xi) non-steroidal anti-inflammatory drugs (NSAIDs), xii) selective serotonin reuptake inhibitors, xiii) selective serotonin and norepinephrine reuptake inhibitors, xiv) tricyclic antidepressant drugs, xv) norepinephrine modulators, xvi) 5-lipoxygenase inhibitors, xvii) cannabinoid receptor agonists, xviii) inhibitor of fatty acid amide hydrolases, xix) beta-adrenergic receptor agonists, x) prostanoid receptor antagonists, xxi) leukotriene receptor antagonists, xxii) histamine receptor antagonists, xxiii) steroids, xxiv) CGRP antagonists, xxv) peroxisome proliferator-activated receptor (PPAR) agonists, and xxvi) acetaminophen.

[0187] Examples of 5-HT receptor agonists include 5-HT_{1B} receptor agonists and 5-HT_{1D} receptor agonists. Examples of 5-HT_{1B} and 5-HT_{1D} receptor agonists include triptans such as sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, and frovatriptan. Example opioid receptor agonists include morphine, codeine, hydrocodone, oxycodone, pentazocine, nalbuphine, fentanyl, sufentanil, tramadol, meperidine, methadone, and etorphine. Examples of NSAIDs include aspirin, ibuprofen, naproxen, ketoprofen, flurbiprofen, loxoprofen, indomethacin, etodolac, diflunisal, ketorolac, nabumetone, oxaprozin, piroxicam, meloxicam, and diclofenac. Examples of COX-2 inhibitors include celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, and valdecoxib. Examples of PPAR agonists include PPAR- γ subtypes such as thiazolidinediones, examples of which include rosiglitazone, pioglitazone and troglitazone. Useful PPAR agonists also include PPAR- α subtype agonists. Examples of sodium channel antagonists include lidocaine, bupivacaine, etidocaine, ropivacaine, mepivacaine, procaine, 2-chloroprocaine, pramoxine, prilocaine, proparacaine and tetracaine.

[0188] In some embodiments, the method of treating pain further comprises administering an analgesic, antidepressant, anxiolytic, antiemetic, anti-epileptic or anticonvulsant.

[0189] The compounds can be administered at any suitable dose in the methods of the invention. In general, compounds of the invention are administered at doses ranging from about 0.01 milligrams to about 100 milligrams per kilogram of a subject's body weight (*i.e.*, about 0.01-100 mg/kg). The dose of a compound can be, for example, about 0.01-100 mg/kg, or about 0.5-50 mg/kg, or about 1-25 mg/kg, or about 2-10 mg/kg. The dose of the compound can be about 0.01, 0.05, 0.1, 0.25, 0.50, 0.75, 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 85, 90, 95, or 100 mg/kg. The dosages can be varied depending upon the particular compound used, the requirements of the patient, the type and severity of the pain being treated, and the particular formulation being administered. In general, the dose administered to a patient is sufficient to result in a beneficial therapeutic response in the patient. The size of the dose will also be determined by the existence, nature, and extent of any adverse side-effects that accompany the administration of the drug in a particular patient. Determination of the proper dosage for a particular situation is within the skill of the typical practitioner. The total dosage can be divided and administered in portions over a period of time suitable to treat to the pain.

[0190] In some embodiments, the invention sets forth a compound or formulation as set forth in one of the embodiments herein for use in a medicament. In some embodiments, the invention sets forth the use of a compound or formulation as set forth in one of the embodiments herein for the manufacture of a medicament for the treatment of pain (*e.g.*, for one of the disorders set forth in the method embodiments herein).

[0191] Compounds of the invention can be administered using any of the pharmaceutical compositions described herein. One of skill in the art will appreciate that type of composition and route of administration will depend, in part, on factors such as the type and severity of pain being treated. In some embodiments, acute pain is treated by parenteral injection of a solution or suspension of a compound of the invention. In certain other embodiments, chronic pain is treated by oral administration of a compound of the invention in a form such as a tablet, pill, or capsule.

[0192] Administration of compounds of the invention can be conducted for a period of time which will vary depending upon the type of pain being treated, its severity, and the overall condition of the patient. Administration can be conducted, for example, hourly, every 2

hours, three hours, four hours, six hours, eight hours, or twice daily including every 12 hours, or any intervening interval thereof. Administration can be conducted once daily, or once every 36 hours or 48 hours, or at other intervals. Following treatment, a patient can be monitored for changes in his or her condition and for pain alleviation. The dosage of the compounds can either be increased in the event the patient does not respond significantly to a particular dosage level, or the dose can be decreased if an alleviation or absence of pain is observed, or if unacceptable side effects are seen with a particular dosage.

[0193] A therapeutically effective amount of a compound of the invention can be administered to the subject in a treatment regimen comprising intervals of at least 1 hour, or 6 hours, or 12 hours, or 24 hours, or 36 hours, or 48 hours between dosages. Administration can be conducted at intervals of at least 72, 96, 120, 168, 192, 216, or 240 hours, or the equivalent amount of days. The dosage regimen can consist of two or more different interval sets. For example, a first part of the dosage regimen can be administered to a subject multiple times daily, daily, every other day, or every third day. The dosing regimen can start with dosing the subject every other day, every third day, weekly, biweekly, or monthly. The first part of the dosing regimen can be administered, for example, for up to 30 days, such as 7, 14, 21, or 30 days. A subsequent second part of the dosing regimen with a different interval administration administered weekly, every 14 days, or monthly can optionally follow, continuing for 4 weeks up to two years or longer, such as 4, 6, 8, 12, 16, 26, 32, 40, 52, 63, 68, 78, or 104 weeks. Alternatively, if pain subsides or generally improves in the patient, the dosage may be maintained or kept at lower than maximum amount. If the pain recurs, the first dosage regimen can be resumed until an improvement is seen, and the second dosing regimen can be implemented again. This cycle can be repeated multiple times as necessary.

Animal Pain Models for *In Vivo* Testing

[0194] Animal models are useful for understanding the mechanism of pain and development of effective therapy for its optimal management. Numerous pain models have been developed to simulate clinical pain conditions with diverse etiology. Development of these models has contributed immensely in understanding acute and chronic pain and underlying peripheral mechanisms. This includes the role of TRPA1 in acute and chronic pain models. Based on these animal pain models, research has resulted in the development of new therapeutic agents for pain management, and the preclinical data obtained using these animal models have been successively translated to effective pain management in clinical

studies. Each animal model has been created with specific methodology. Data from each different model is interpreted in the context of the specific pain model.

Data Analysis for Pain Models

[0195] Compounds are evaluated in well characterized *in vivo* models to assess acute, inflammatory, neuropathic pain and periprocedural (*e.g.*, post-surgical) pain. Animals are randomly assigned to each treatment group. Results are presented as mean + S.E.M. Percent Reversal is calculated as (post-dose – pre-dose)/(pre-injury-pre-dose)x100 for each rat or mouse. 100% corresponds to complete reversal of hyperalgesia or allodynia, equivalent to non-injured values, and 0% corresponds to values not different from baseline post-injury. As appropriate, results are analyzed using either 1-way ANOVA or 2-way ANOVA (for dose and time post-dose) test followed by Bonferroni post-tests for multiple comparisons (Prism, Graph Pad, San Diego, CA). ED₅₀ are calculated as doses corresponding to a 50% effect (100% effect corresponding to recovery to baseline values in the absence of injury). In general, experimental and control groups contain at least six animals per group.

V. Examples

Example 1. Synthesis of compounds of the Invention

[0196] Analytical TLC was performed on Merck silica gel 60 F₂₅₄ aluminium-backed plates. Compounds were visualised by UV light and/or stained with either I₂ or potassium permanganate solution followed by heating. Flash column chromatography was performed on silica gel. ¹H-NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer with a BBO (Broad Band Observe) and BBFO (Broad Band Fluorine Observe) probe. Chemical shifts (δ) are expressed in parts per million (ppm) downfield by reference to tetramethylsilane as the internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br s (broad singlet). Coupling constants (*J*) are given in hertz (Hz). LCMS analyses were performed either on an Acquity BEH C-18 column (2.10 × 100 mm, 1.70 μ m) or Acquity HSS-T3 (2.1 × 100 mm, 1.8 μ m) using the Electrospray Ionisation (ESI) technique.

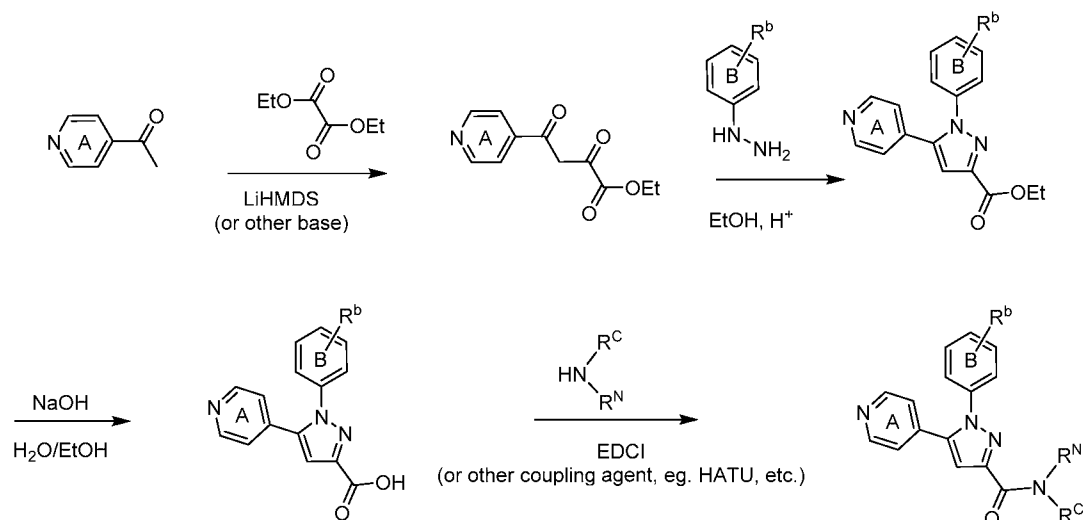
[0197] The following solvents, reagents or scientific terminology may be referred to by their abbreviations:

	TLC	Thin Layer Chromatography
	CDCl_3	Deuterated chloroform
	DCM	Dichloromethane
	THF	Tetrahydrofuran
5	MeOH	Methanol
	EtOH	Ethanol
	IPA	Isopropanol
	EtOAc	Ethyl acetate
	Et_2O	Diethyl ether
10	DMF	N,N-Dimethylformamide
	TEA/ Et_3N	Triethylamine
	DIPEA	Diisopropylethylamine (Hunig's base)
	LiHMDS	Lithium bis(trimethylsilyl)amide
	HATU	N,N,N,N-Tetramethyl-O-(7-azabenzotriazol-1-yl)uroniumhexafluorophosphate
15	AcOH	Acetic acid
	TFA	Trifluoroacetic acid
	mL	milliliters
	mmol	millimoles
	h	hour or hours
20	min	minute or minutes
	g	grams
	mg	milligrams
	μL	Microlitres
	M	Molar concentration
25	μM	micromolar concentration
	μm	micrometer or micron
	N	Normal concentration
	eq	Equivalents
	rt or RT	Room temperature, ambient, about 27°C
30	MS	Mass spectrometry
	Hz	Hertz

[0198] In the below schemes like-numbered compounds are not necessarily the same. Numbering restarts with each scheme.

[0199] The disclosed compounds can be made by the following general scheme A.

Scheme A



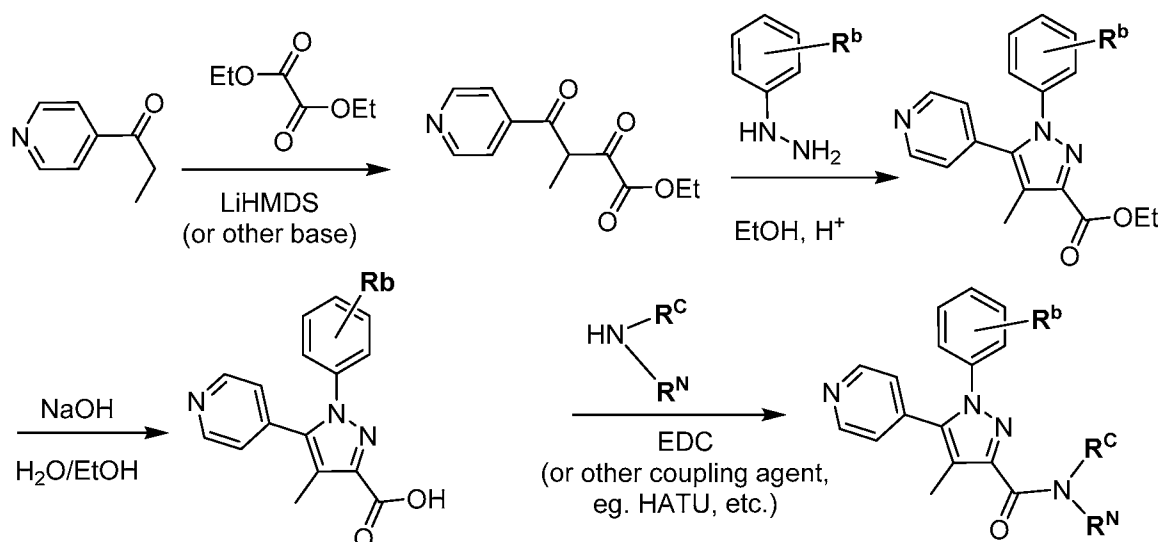
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[0200] This scheme may be modified to provide the various rings A and B as well as ring C or $-N(R^N)(R^C)$ of the disclosed compounds by replacing the various starting materials with those that provide the desired rings or $-N(R^N)(R^C)$. Using the below Scheme A-1 in place of A, compositions with a substitution on the 4-position of the pyrazole (such as $-CH_3$) as shown here, can be made.

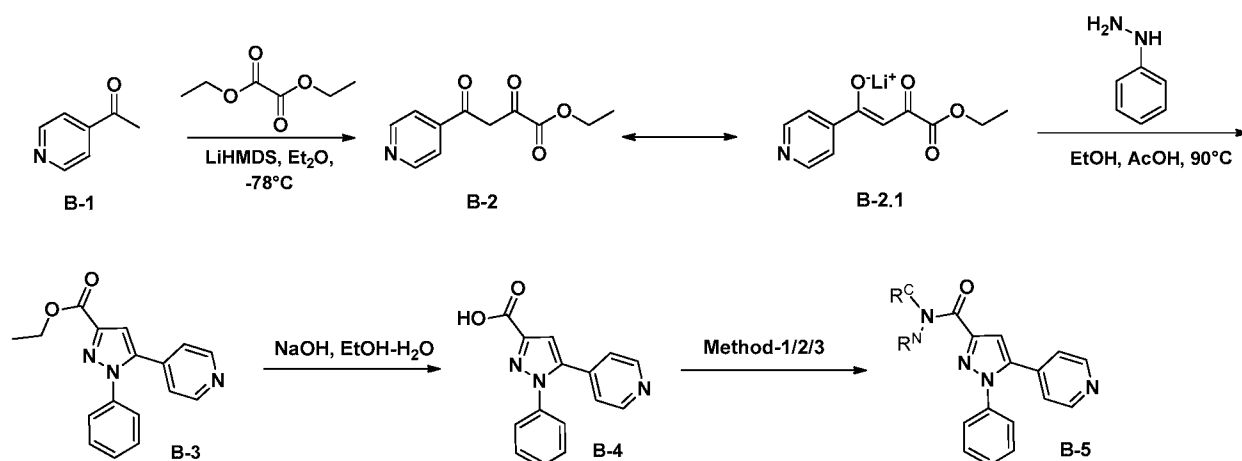
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Scheme A-1



[0201] In one embodiment, compounds can be prepared according to Scheme B.

Scheme B



- 5 [0202] **Preparation of ethyl 2,4-dioxo-4-(pyridin-4-yl)butanoate (B-2):** A solution of 4-acetyl pyridine (10.0 g, 82.55 mmol) in diethyl ether (160 mL) was cooled to -78°C followed by addition of LiHMDS (15.16 g, 90.80 mmol). The resulting reaction mixture was stirred at -78°C for 45 min followed by drop wise addition of diethyl oxalate in about 30min. The reaction mixture was then left to stir at room temperature for 16 h. After completion of the reaction (TLC and MS monitoring), the solution was then cooled 0°C and the resulting precipitate was filtered to get the desired product as an off-white solid (18.0 g, 98%), which was carried forward to the next step without purification.
- 10

[0203] ¹H-NMR (400 MHz, DMSO-d₆): δ 8.66 (d, *J*= 4.80 Hz, 2H), 7.70 (d, *J*= 5.20 Hz, 2H), 6.43 (s, 1H), 4.15 (q, *J*= 7.20 Hz, 2H) and 1.25 (t, *J*= 7.20 Hz, 3H).

- 15 [0204] **Preparation of ethyl 1-phenyl-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylate (B-3):** To a solution of ethyl 2,4-dioxo-4-(pyridin-4-yl)butanoate B-2 (18 g, 81.45 mmol) in EtOH (500 mL) was added phenyl hydrazine hydrochloride (9.68 g, 89.59 mmol) and acetic acid (140.0 mL). The resulting reaction mixture was stirred at 90°C for 3-4 h. After completion the reaction (TLC monitoring) the solvent was evaporated and the residue was directly purified over silica gel (100-200 Mesh, 10% EtOAc-hexane) to get the desired product (8.0 g, 33%).
- 20

[0205] ¹H-NMR (400 MHz, DMSO-d₆): δ 8.55 (d, *J*= 6.0 Hz, 2H), 7.51 (m, 3H), 7.38 (m, 3H), 7.24 (m, 2H), 4.35 (q, *J*= 7.20 Hz, 2H) and 1.32 (t, *J*= 7.20 Hz, 3H).

[0206] Preparation of 1-phenyl-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylic acid (B-4):

To an ice-cold solution of ethyl 1-phenyl-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylate B-3 (5.50 g, 18.77 mmol) in EtOH (110 mL) was added drop wise an aqueous solution of sodium hydroxide (2.25 g dissolved in 5.50 mL H₂O). The resulting solution was stirred at room temperature for 4 h. After completion of the reaction (TLC monitoring), the solvent was evaporated, added H₂O to the residue followed by extraction with EtOAc (2 x 100 mL). The organic layer was discarded and the pH of the aqueous layer was adjusted to ~4-5 by adding 1N HCl followed by extraction with EtOAc (3 x 200 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to get the desired product (3.0 g, 61%) as a white solid.

[0207] ¹H-NMR (400 MHz, DMSO-d₆): δ 13.11 (br s, 1H), 8.55 (d, *J*= 5.60 Hz, 2H), 7.50 (m, 3H), 7.38 (m, 2H), 7.31 (s, 1H) and 7.23 (d, *J*= 6.0 Hz, 2H).

Preparing Final Compounds having pyridinyl Ring A and phenyl Ring B

[0208] Method 1: To an ice cold solution of 1-phenyl-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylic acid 4 (0.10 g, 0.38 mmol, 1.0 eq), in DMF (2.0 mL) was added DIPEA (0.145 g, 1.13 mmol, 3.0 eq) and HATU (0.214 g, 0.56 mmol, 1.50 eq). The resulting mixture was stirred under nitrogen atmosphere at 0°C for 15 min followed by addition of the respective amine (2.0 eq). The reaction mixture was then stirred at room temperature for 4-6 h. After the completion of the reaction (TLC monitoring), the solution was diluted with icecold water (30 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified over silica gel (100-200 Mesh, 1-5% MeOH-DCM) to give the desired products generally in good to excellent yields (18-96%). Individual yields and solvent systems are shown in Table 1. Compounds 14, 31, 38 and 39 were directly obtained after the work-up by triturating the residue with the solvents disclosed in Table 1. Compound 40 was purified via prep-TLC using the solvent system 5%MeOH-DCM.

[0209] Method 2: To an ice cold solution of 1-phenyl-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylic acid 4 (0.10 g, 0.38 mmol, 1.0 eq) in DMA (5 mL) was added methanesulfonyl chloride (0.129 g, 1.13 mmol, 3.0 eq) and 2,6-lutidine (0.12 g, 1.13 mmol, 3.0 eq) drop wise. The resulting mixture was stirred under nitrogen atmosphere at 0°C for 15 min followed by addition of the respective amine (1.30 eq) and then left to stir at 50°C for 6 h. After completion of the reaction (TLC monitoring), the solution was then cooled to room

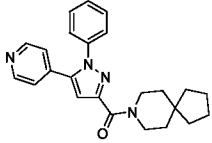
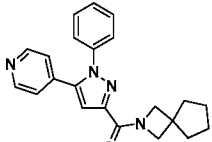
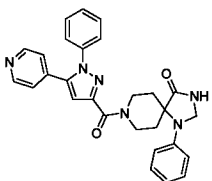
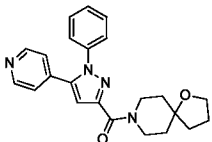
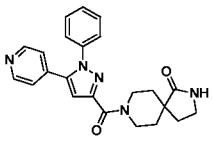
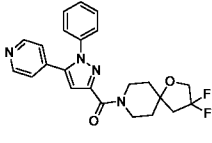
temperature, diluted with ice cold water (25-50 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified over silica gel (100-200 Mesh, 1-2% MeOH-DCM) to give the desired products in moderate yields (21-54%). Individual yields and the solvent system in which the compounds were eluted are in Table 1.

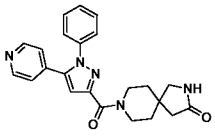
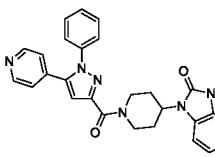
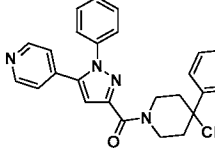
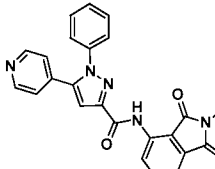
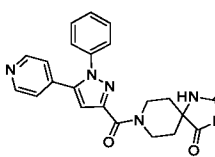
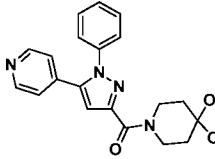
[0210] Method 3: A mixture of 1-phenyl-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylic acid 4 (0.10 g, 0.38 mmol, 1.0 eq) and SOCl₂ (0.15 g, 1.13 mmol, 3.0 eq) was heated to 90°C for 2h. After the completion of the reaction (TLC monitoring by adding MeOH to convert it to Me ester), the reaction mixture was concentrated under reduced pressure. Meanwhile in another RB flask, to an ice-cold solution of corresponding amine (1.50 eq with respect to the acid) in THF (5 mL) was added NaH (1.50 eq with respect to the acid or 1.0 eq with respect to the amine). The reaction mixture was stirred at room temperature for 1 h followed by addition of a solution of acid chloride thus generated in THF. The resulting reaction mixture was stirred at room temperature for 5-6 h. After the completion of the reaction (TLC monitoring), the reaction mass was quenched with ice-cold water and extracted with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified over silica gel (100-200 Mesh, 2-5% MeOH-DCM) to give the desired products in moderate yields (10-15%). Individual yields and the solvent system in which the compounds were eluted is provided in Table 1.

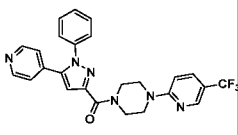
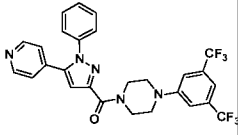
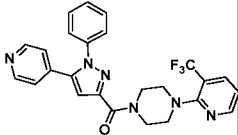
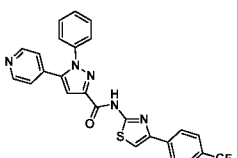
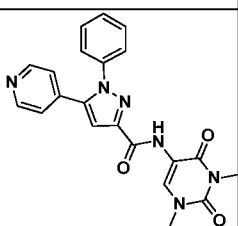
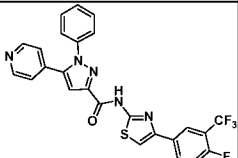
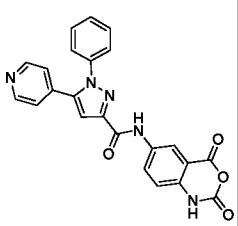
[0211] Analytical Instrument details: The ¹H-NMR spectra were obtained on Bruker 400 MHz spectrometer, while the LCMS analyses were performed on an Acquity C-18 column (2.10 mm x 100 mm, 1.70 μm) using the electrospray ionization (ESI) technique (make: Waters). Chemical shifts (δ) are expressed in parts per million (ppm) downfield by reference to tetramethylsilane as the internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br s (broad singlet). Coupling constants (*J*) are given in Hz.

[0212] Table 1 shows tabulated data of the final compounds including the method by which the final compounds were synthesized. The amines used in preparing the below compounds (via Methods 1, 2 or 3) are commercially available or can be synthesized by one of ordinary skill.

Table 1. Example compounds of the disclosure.

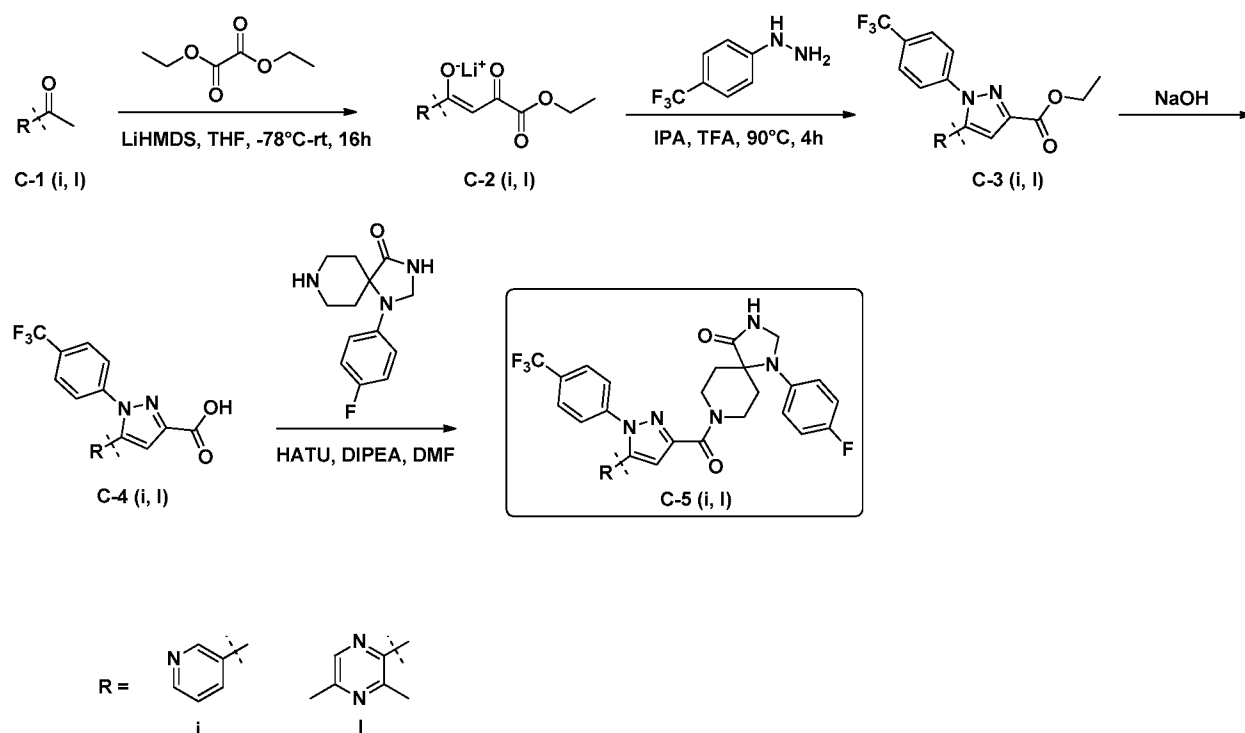
Cpd. ID	Structure	Method	Yield	Purification technique	LCMS	NMR data (DMSO-d ₆ , 400 MHz)
4		1	36%	Column chromatography (2% MeOH-DCM)	387.21 (M+H) ⁺ , 97.49%	8.50 (d, <i>J</i> = 4.80 Hz, 2H), 7.48 (m, 3H), 7.36 (m, 2H), 7.30 (d, <i>J</i> = 4.80 Hz, 2H), 7.07 (s, 1H), 3.93 (m, 2H), 3.76 (m, 2H), 1.67 (m, 4H) and 1.55-1.60 (m, 8H)
6		1	26%	Column chromatography (1-2% MeOH-DCM)	359.20 (M+H) ⁺ , 96.08%	8.55 (d, <i>J</i> = 5.20 Hz, 2H), 7.48 (m, 3H), 7.36 (m, 2H), 7.22 (m, 3H), 4.36 (s, 2H), 3.89 (s, 2H), 1.78 (br s, 4H) and 1.57 (br s, 4H)
8		1	39%	Column chromatography (2-5% MeOH-DCM)	479.23 (M+H) ⁺ , 97.60%	8.84 (br s, 1H), 8.56 (d, <i>J</i> = 5.60 Hz, 2H), 7.46 (m, 3H), 7.37 (m, 2H), 7.19-7.25 (m, 5H), 6.75 (m, 3H), 4.56-4.61 (m, 3H), 4.50 (m, 1H), 3.87 (m, 1H), 3.52 (m, 1H), 2.55 (m, 2H) and 1.75 (m, 2H)
12		1	43%	Column chromatography (1-2% MeOH-DCM)	389.22 (M+H) ⁺ , 93.94%	8.55 (d, <i>J</i> = 5.20 Hz, 2H), 7.54 (m, 3H), 7.48 (m, 2H), 7.23 (m, 2H), 7.13 (s, 1H), 4.07 (m, 1H), 3.96 (m, 1H), 3.66-3.76 (m, 3H), 3.40 (m, 1H), 1.87 (m, 2H), 1.69 (m, 2H) and 1.59 (m, 4H)
13		1	35%	Column chromatography (2-5% MeOH-DCM)	402.23 (M+H) ⁺ , 96.39%	8.55 (d, <i>J</i> = 5.20 Hz, 2H), 7.63 (br s, 1H), 7.49 (m, 3H), 7.37 (m, 2H), 7.24 (d, <i>J</i> = 5.20 Hz, 2H), 7.15 (s, 1H), 4.32-4.46 (m, 2H), 3.40 (m, 1H), 3.19 (m, 2H), 3.08 (m, 1H), 2.03 (m, 2H), 1.60-1.70 (m, 2H) and 1.40-1.48 (m, 2H)
16		1	20%	Column chromatography (2% MeOH-DCM)	425.19 (M+H) ⁺ , 97.81%	8.55 (m, 2H), 7.49 (m, 3H), 7.37 (m, 2H), 7.23 (m, 2H), 7.14 (s, 1H), 3.93-4.14 (m, 4H), 3.71 (m, 1H), 3.43 (m, 1H), 2.38 (m, 2H) and 1.76 (m, 4H)

Cpd. ID	Structure	Method	Yield	Purification technique	LCMS	NMR data (DMSO-d ₆ , 400 MHz)
18		1	96%	Column chromatography (2-5% MeOH-DCM)	402.20 (M+H) ⁺ , 97.0%	8.55 (d, <i>J</i> = 4.80 Hz, 2H), 7.57 (br s, 1H), 7.48 (m, 3H), 7.37 (m, 2H), 7.23 (d, <i>J</i> = 5.20 Hz, 2H), 7.13 (s, 1H), 3.95-3.98 (m, 1H), 3.75 (m, 2H), 3.52 (m, 1H), 3.12 (br s, 2H), 2.13 (br s, 2H) and 1.59 (br s, 4H)
25		1	61%	Column chromatography (2-5% MeOH-DCM)	465.22 (M+H) ⁺ , 95.79%	10.86 (br s, 1H), 8.56 (d, <i>J</i> = 5.60 Hz, 2H), 7.48 (m, 3H), 7.37 (m, 2H), 7.18-7.25 (m, 4H), 6.96 (m, 3H), 4.70-4.84 (m, 2H), 4.53 (m, 1H), 3.32 (m, 1H), 2.91 (m, 1H), 2.31 (m, 2H) and 1.79 (m, 2H)
28		1	55%	Column chromatography (2% MeOH-DCM)	434.23 (M+H) ⁺ , 98.27%	8.61 (d, <i>J</i> = 5.60 Hz, 2H), 7.58 (d, <i>J</i> = 7.60 Hz, 2H), 7.31-7.50 (m, 8H), 7.32 (d, <i>J</i> = 6.0 Hz, 2H), 7.26 (s, 1H), 4.89 (m, 1H), 4.77 (m, 1H), 3.49 (m, 1H), 3.10 (m, 1H), 2.25 (m, 2H) and 2.10 (m, 2H)
29		1	33%	Column chromatography (2-5% MeOH-DCM)	424.18 (M+H) ⁺ , 94.76%	10.91 (br s, 1H), 8.80 (d, <i>J</i> = 4.40 Hz, 1H), 8.58 (d, <i>J</i> = 4.80 Hz, 2H), 7.84 (t, <i>J</i> = 8.0 Hz, 1H), 7.58 (m, 4H), 7.47 (m, 3H), 7.29 (d, <i>J</i> = 5.20 Hz, 2H) and 3.02 (s, 3H)
30		1	22%	Column chromatography (2-5% MeOH-DCM)	417.18 (M+H) ⁺ , 98.45%	8.54-8.67 (m, 4H), 7.48 (m, 3H), 7.38 (m, 2H), 7.19-7.23 (m, 3H), 4.47 (d, <i>J</i> = 8.40 Hz, 1H), 4.33 (d, <i>J</i> = 8.80 Hz, 1H), 3.60 (m, 1H), 3.28 (m, 1H), 1.84 (m, 2H) and 1.69 (m, 2H)
31		1	77%	Triturating with n-pentane	391.19 (M+H) ⁺ , 98.18%	8.55 (d, <i>J</i> = 5.20 Hz, 2H), 7.48 (m, 3H), 7.37 (m, 2H), 7.23 (d, <i>J</i> = 5.20 Hz, 2H), 7.16 (s, 1H), 3.92 (m, 6H), 3.71 (m, 2H) and 1.69 (m, 4H)

Cpd. ID	Structure	Method	Yield	Purification technique	LCMS	NMR data (DMSO-d ₆ , 400 MHz)
32		1	24%	Column chromatography (2% MeOH-DCM)	479.22 (M+H) ⁺ , 99.12%	8.56 (d, <i>J</i> = 5.60 Hz, 2H), 8.43 (s, 1H), 7.84 (d, <i>J</i> = 8.40 Hz, 1H), 7.49 (m, 3H), 7.40 (m, 2H), 7.22-7.25 (m, 3H), 6.99 (d, <i>J</i> = 8.80 Hz, 1H), 4.11 (br s, 2H) and 3.72 (br s, 6H)
33		1	57%	Column chromatography (2% MeOH-DCM)	546.24 (M+H) ⁺ , 98.67%	8.56 (d, <i>J</i> = 3.60 Hz, 2H), 7.50 (m, 5H), 7.40 (m, 2H), 7.33 (s, 1H), 7.22-7.25 (m, 3H), 4.17 (br s, 2H), 3.82 (br s, 2H) and 3.46-3.49 (m, 4H)
34		1	50%	Column chromatography (2% MeOH-DCM)	479.22 (M+H) ⁺ , 92.47%	8.56 (m, 3H), 8.11 (d, <i>J</i> = 7.60 Hz, 1H), 7.50 (m, 3H), 7.40 (m, 2H), 7.24 (m, 3H), 7.19 (s, 1H), 4.08 (br s, 2H), 3.81 (br s, 2H) and 3.25 (br s, 4H)
35		3	15%	Column chromatography (2-5% MeOH-DCM)	492.09 (M+H) ⁺ , 95.88%	12.70 (br s, 1H), 8.60 (d, <i>J</i> = 5.20 Hz, 2H), 8.18 (d, <i>J</i> = 8.0 Hz, 2H), 7.97 (s, 1H), 7.83 (d, <i>J</i> = 8.0 Hz, 2H), 7.59 (s, 1H), 7.46-7.52 (m, 5H) and 7.28 (d, <i>J</i> = 5.20 Hz, 2H)
36		1	88%	Column chromatography (2-5% MeOH-DCM)	403.16 (M+H) ⁺ , 98.74%	9.13 (s, 1H), 8.56 (d, <i>J</i> = 4.80 Hz, 2H), 8.47 (s, 1H), 7.53 (m, 3H), 7.44 (m, 2H), 7.38 (s, 1H), 7.27 (d, <i>J</i> = 4.80 Hz, 2H), 3.39 (s, 3H) and 3.24 (s, 3H)
37		3	10%	Column chromatography (2-5% MeOH-DCM)	510.12 (M+H) ⁺ , 94.04%	12.67 (br s, 1H), 8.60 (d, <i>J</i> = 5.20 Hz, 2H), 8.34 (m, 2H), 7.96 (s, 1H), 7.46-7.65 (m, 7H) and 7.27 (d, <i>J</i> = 5.20 Hz, 2H)
38		1	19%	Triturating with diethyl ether-MeOH (1:1)	426.12 (M+H) ⁺ , 96.14%	11.71 (br s, 1H), 10.58 (br s, 1H), 8.57 (d, <i>J</i> = 5.60 Hz, 2H), 8.50 (s, 1H), 8.14 (d, <i>J</i> = 6.40 Hz, 1H), 7.52 (m, 3H), 7.48 (m, 2H), 7.41 (s, 1H), 7.28 (d, <i>J</i> = 5.20 Hz, 2H) and 7.16 (d, <i>J</i> = 4.80 Hz, 1H)

Cpd. ID	Structure	Method	Yield	Purification technique	LCMS	NMR data (DMSO-d ₆ , 400 MHz)
39		1	70%	Triturating with n-pentane and diethyl ether (1:1)	412.14 (M+H) ⁺ , 96.25%	10.37 (br s, 1H), 8.57 (d, J= 5.60 Hz, 2H), 7.82 (s, 1H), 7.53 (m, 4H), 7.47 (m, 2H), 7.39 (s, 1H), 7.26-7.31 (m, 3H) and 3.33 (s, 3H)
40		1	44%	Prep-TLC (5% MeOH-DCM)	424.11 (M+H) ⁺ , 99.70%	10.90 (br s, 1H), 8.57 (d, J= 6.0 Hz, 2H), 8.42 (d, J= 1.20 Hz, 1H), 8.22 (dd, J= 1.60 and 8.0 Hz respectively, 1H), 7.86 (d, J= 8.0 Hz, 1H), 7.54 (m, 3H), 7.46-7.50 (m, 3H), 7.27 (m, 2H) and 3.02 (s, 3H)

Scheme C



- 5 [0213] **General procedure for the preparation of compounds C-2 (i, l):** A solution of compound C-1 (i, l) (1 eq) in diethyl ether was cooled to -78°C followed by addition of LiHMDS (1.10 eq). The resulting reaction mixture was stirred at -78°C for 45 min followed by drop wise addition of diethyl oxalate (1.20 eq) in about 30 min. The reaction mixture was then left to stir at room temperature for 16 h. After completion of the reaction (TLC and MS
- 10 monitoring), the solution was then cooled 0°C and the resulting precipitate was filtered to get

the desired product as off-white solids C-2 (i, l), which were carried forward to the next step without purification.

[0214] 4-Ethoxy-3,4-dioxo-1-(pyridin-3-yl)but-1-en-1-olate lithium salt (C-2i): ¹H-NMR (400 MHz, DMSO-d₆): δ 8.97 (s, 1H), 7.70 (s, 1H), 8.14 (m, 1H), 7.43 (m, 1H), 6.41 (s, 1H), 4.13 (q, *J* = 6.8 Hz, 2H) and 1.23 (t, *J* = 7.2 Hz, 3H). MS: 220.12 (M-H)⁺. Yield: 88%.

[0215] 1-(3,5-Dimethylpyrazin-2-yl)-4-ethoxy-3,4-dioxobut-1-en-1-olate lithium salt (C-2l): ¹H-NMR (400 MHz, DMSO-d₆): δ 8.40 (s, 1H), 6.35 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.55 (s, 3H), 2.32 (s, 3H) and 1.21 (t, *J* = 6.8 Hz, 3H). MS: 249.09 (M-H)⁺. Yield: 96%.

[0216] General procedure for the preparation of compounds C-3 (i, l): To an ice-cold solution of compound C-2 (i, l), (1.0 eq) in IPA was added (4-(trifluoromethyl) phenyl) hydrazine (1.10 eq) and TFA (2.0 eq). The resulting reaction mixture was warmed up to room temperature and then stirred at 90°C for 4-5 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified over silica gel (100-200 Mesh, 10-15% EtOAc-hexane) to get the desired products C-3 (i, l).

[0217] Ethyl 5-(pyridin-3-yl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxylate (C-3i): LCMS: 362.14 (M+H)⁺, 90.26%. Yield: 71%.

[0218] Ethyl 5-(3,5-dimethylpyrazin-2-yl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxylate (C-3l): ¹H-NMR (400 MHz, CDCl₃): δ 8.46 (s, 1H), 7.76 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.0 Hz, 2H), 7.33 (s, 1H), 3.99 (q, *J* = 7.20 Hz, 2H), 2.43 (s, 3H), 2.26 (s, 3H) and 1.15 (t, *J* = 7.2 Hz, 3H). Yield: 26%.

[0219] General procedure for the preparation of compounds C-4 (i, l): To an ice-cold solution of compound C-3 (i, l) (1.0 eq) in EtOH, an aqueous solution of sodium hydroxide (3.0 eq) was added dropwise. The resulting solution was stirred at room temperature for 4 h. After completion of the reaction (TLC monitoring), the solvent was evaporated, H₂O added to the residue followed by extraction with EtOAc (2 x 100 mL). The organic layer was discarded and the pH of the aqueous layer was adjusted to ~6 by adding 1N HCl. The resulting precipitate was filtered and dried under vacuum to get the desired products C-4 (i, l) as white solids.

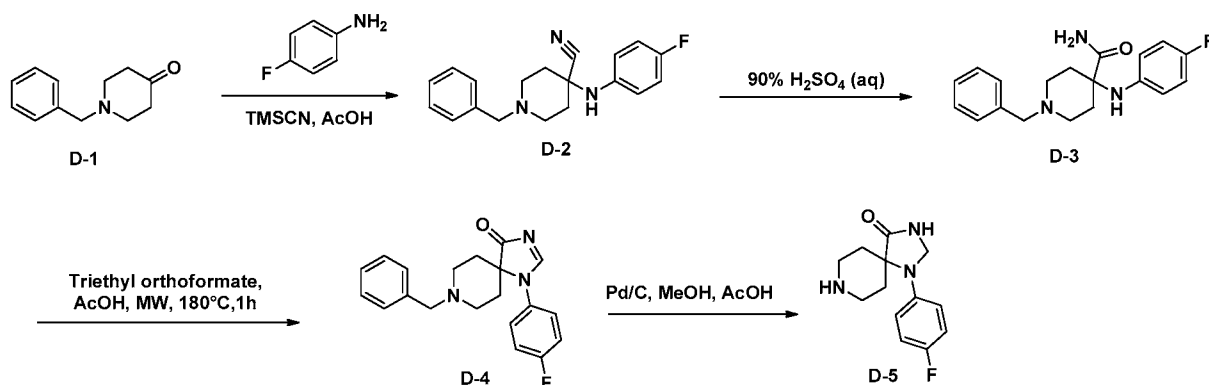
[0220] 5-(Pyridin-3-yl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxylic acid (C-4i): $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 8.56 (dd, J = 1.6 & 4.8 Hz respectively, 1H), 8.52 (d, J = 1.6 Hz, 1H), 7.82 (d, J = 8.4 Hz, 2H), 7.66 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.4 Hz, 2H), 7.40 (m, 1H) and 7.11 (s, 1H). LCMS: 334.11 ($\text{M}+\text{H}$) $^+$, 97.80%. Yield: 83%.

5 [0221] 5-(3,5-Dimethylpyrazin-2-yl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxylic acid (C-4l): $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 8.46 (s, 1H), 7.76 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.0 Hz, 2H), 7.33 (s, 1H), 2.43 (s, 3H) and 2.26 (s, 3H). LCMS: 363.16 ($\text{M}+\text{H}$) $^+$, 97.35%. Yield: 67.50%.

[0222] General procedure for the preparation of final compounds C-5 (i, l): To an ice cold solution of carboxylic acids C-4 (i, l) (1.0 eq), in DMF (2.0 mL) was added DIPEA (3.0 eq) and HATU (1.50 eq). The resulting mixture was stirred under nitrogen atmosphere at 0°C for 15 min followed by addition of the 1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (1.20 eq). The reaction mixture was then stirred at room temperature for 16 h. After the completion of the reaction (TLC monitoring), the solution was diluted with ice-cold water (30 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified via prep-TLC using the solvent system 3-5% MeOH-DCM. The final step was performed on 50-100 mg scale.

[0223] In some embodiments, 1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one is made according to Synthetic Scheme D.

Scheme D



[0224] Preparation of 1-benzyl-4-(4-fluorophenylamino)piperidine-4-carbonitrile (D-2): To an ice-cold solution of 1-benzylpiperidin-4-one D-1 (25 g, 132.10 mmol) in acetic acid (80

mL) was added 4-fluoroaniline (14.0 mL, 145.31 mmol) and trimethylsilyl cyanide (26.42 mL, 198.15 mmol). The resulting reaction mass was stirred at RT for 18 h. After completion of the reaction (TLC monitoring), the reaction mass was cooled to 0°C and the pH adjusted to ~10 using 5.0 N sodium hydroxide solution. The aqueous part was extracted with DCM (3 x 250 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was triturated with diethyl ether to get the desired product D-2 (30 g, 75%) as a pale yellow solid.

[0225] ¹H-NMR (400 MHz, CDCl₃): δ 7.32-7.34 (m, 5H), 6.91-6.94 (m, 4H), 3.55 (s, 2H), 3.47 (br s, 1H), 2.81-2.84 (m, 2H), 2.39-2.45 (m, 2H), 2.21-2.24 (m, 2H) and 1.87-1.94 (m, 2H). LC-MS: 310.13 (M+H)⁺, 96.16%.

[0226] Preparation of 1-benzyl-4-(4-fluorophenylamino)piperidine-4-carboxamide (D-3): To an ice cold solution of 1-benzyl-4-(4-fluorophenylamino)piperidine-4-carbonitrile D-2 (30 g, 97.06 mmol) was added 90% aqueous sulphuric acid (150 mL) and the resulting reaction mixture was stirred at room temperature for 16 h. After completion of the reaction (TLC monitoring), the reaction mass was cooled to 0°C and the pH adjusted to ~10 using 5.0 N sodium hydroxide solution. The aqueous part was extracted with DCM (3 x 250 mL). The combined organics were dried over anhydrous sodium sulphate, filtered and concentrated. The crude was triturated with diethyl ether to get the desired product D-3 (27 g, 87%) as an off-white solid.

[0227] ¹H-NMR (400 MHz, CDCl₃): δ 7.23-7.30 (m, 5H), 6.87-6.91 (m, 3H), 6.55-6.59 (m, 2H), 5.47 (br s, 1H), 3.93 (s, 1H), 3.48 (s, 2H), 2.72-2.75 (m, 2H), 2.28-2.35 (m, 2H), 2.04-2.10 (m, 2H) and 1.86-1.89 (m, 2H). LCMS: 328.12 (M+H)⁺, 99.60%.

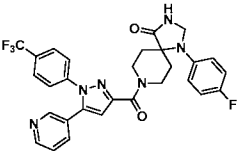
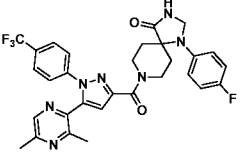
[0228] Preparation of 8-benzyl-1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (D-4): A solution of 1-benzyl-4-(4-fluorophenylamino)piperidine-4-carboxamide (2.50 g, 7.63 mmol) in triethylorthoformate (3.20 mL) and AcOH (1.20 mL) was irradiated by microwave in a sealed tube to 180°C for 30 min. The reaction mixture was diluted with water and extracted with EtOAc (3 x 100 mL). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified over silica gel (100-200 M, 4% MeOH-DCM) to get the desired product D-4 (1.20 g, 60%) as a pale yellow solid. LCMS: 338.22 (M+H)⁺, 82.22%.

[0229] Preparation of 1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (D-5): To a solution of 8-benzyl-1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (1.30 g, 3.85 mmol) in MeOH (16 mL) and AcOH (0.40 mL) were added 10% Pd-C (0.34 g) and the resulting solution was stirred under hydrogen atmosphere (1 atm) at ambient temperature for 16 h. The reaction mixture was filtered through a Celite™ bed and the filtrate was concentrated under reduced pressure to get the desired product D-5 (0.95 g, 99%) as an off-white solid, which was used as such for the next step without further purification. LCMS: 250.13 (M+H)⁺, 81.19%.

[0230] Scheme D can be modified to provide substitutions at positions other than the 4-position on the phenyl ring as well as provide substitutions other than fluorine.

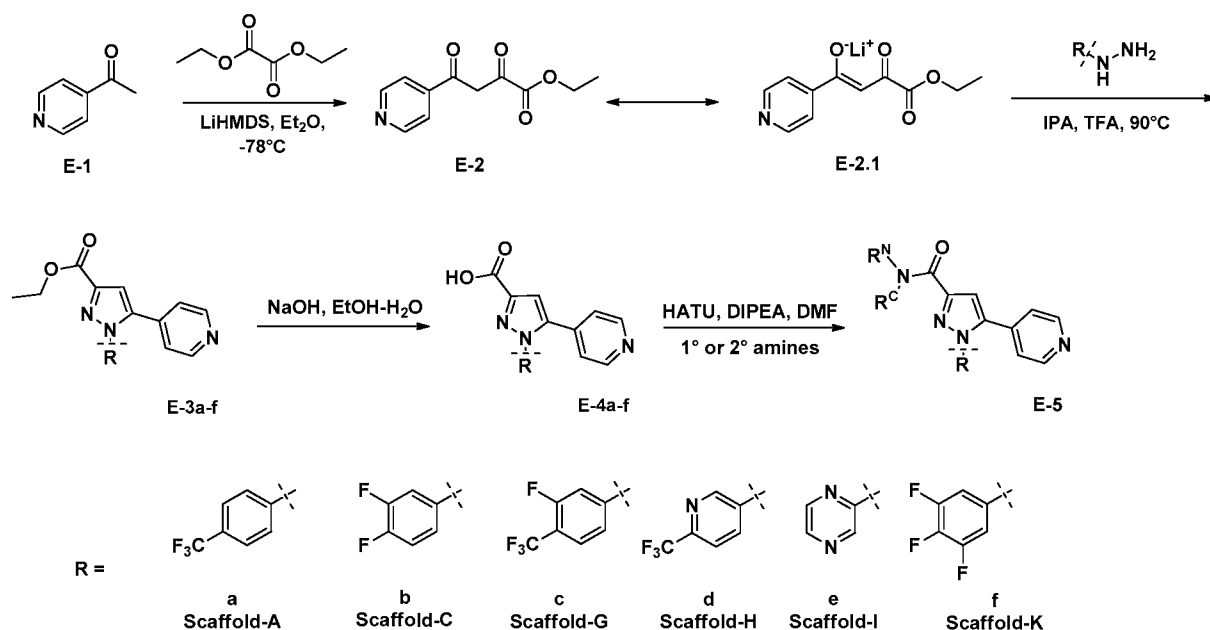
[0231] Table 2 shows individual compounds yields for compounds made according to schemes C and D:

Table 2. Example compounds of the disclosure.

Cpd. ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
49		8	565.46 (M+H) ⁺ , 95.48%	δ 8.80 (br s, 1H), 8.59 (dd, J= 1.60 and 4.80 Hz, respectively, 1H), 8.55 (d, J= 2.0 Hz, 1H), 7.83 (d, J= 8.80 Hz, 2H), 7.67-7.70 (m, 1H), 7.56 (d, J= 8.40 Hz, 2H), 7.42-7.45 (m, 1H), 7.16 (s, 1H), 7.07-7.14 (m, 2H), 6.84-6.88 (m, 2H), 4.59 (d, J= 3.20 Hz, 2H), 4.42-4.52 (m, 2H), 3.88 (m, 1H), 3.53 (m, 1H), 2.20-2.32 (m, 2H) and 1.74-1.83 (m, 2H)
52		12	594.45 (M+H) ⁺ , 99.83%	δ 8.81 (br s, 1H), 8.47 (s, 1H), 7.75 (d, J= 8.40 Hz, 2H), 7.44 (d, J= 8.40 Hz, 2H), 7.22 (s, 1H), 7.10 (t, J= 8.80 Hz, 2H), 6.85-6.88 (m, 2H), 4.59 (d, J= 3.20 Hz, 2H), 4.43-4.51 (m, 2H), 3.90 (t, J= 12.40 Hz, 1H), 3.55 (t, J= 10.40 Hz, 1H), 2.43 (s, 3H), 2.27-2.32 (m, 5H) and 1.75-1.84 (m, 2H)

[0232] In some embodiments, disclosed compounds are made according to Scheme E.

Scheme E



[0233] Preparation of ethyl 2,4-dioxo-4-(pyridin-4-yl)butanoate (E-2): A solution of 4-acetyl pyridine (10.0 g, 82.55 mmol) in di-ethyl ether (160 mL) was cooled to -78°C followed by addition of LiHMDS (15.16 g, 90.80 mmol). The resulting reaction mixture was stirred at -78°C for 45 min followed by drop wise addition of diethyl oxalate (13.5 mL, 98.92 mmol) in about 30 min. The reaction mixture was then left to stir at room temperature for 16 h. After completion of the reaction (TLC and MS monitoring), the solution was then cooled 0°C and the resulting precipitate was filtered to get the desired product as an off-white solid (18.0 g, 98%), which was carried forward to the next step without purification.

[0234] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 8.66 (d, $J=4.80$ Hz, 2H), 7.70 (d, $J=5.20$ Hz, 2H), 6.43 (s, 1H), 4.15 (q, $J=7.20$ Hz, 2H) and 1.25 (t, $J=7.20$ Hz, 3H).

[0235] General procedure for the preparation of compounds E-3a-f: To an ice-cold solution of ethyl 2,4-dioxo-4-(pyridin-4-yl)butanoate E-2 (1.0 eq) in IPA was added a respective hydrazine (1.10 eq) and TFA (2.0 eq). The resulting reaction mixture was warmed up to room temperature and then stirred at 90°C for 4-5 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified over silica gel (100-200 Mesh, 10-15% EtOAc-hexane) to get the desired product.

[0236] Ethyl 5-(pyridin-4-yl)-1-(4-(trifluoromethyl) phenyl)-1H-pyrazole-3-carboxylate (E-3a): ¹H-NMR (400 MHz, CDCl₃): δ 8.61 (d, *J*= 6.0 Hz, 2H), 7.66 (d, *J*= 8.4 Hz, 2H), 7.47 (d, *J*= 8.4 Hz, 2H), 7.17 (s, 1H), 7.11 (m, 2H), 4.44 (q, *J*= 7.20 Hz, 2H) and 1.41 (t, *J*= 7.20 Hz, 3H). LCMS: 362.21 (M+H)⁺, 99.95%. Yield: 50%.

5 [0237] Ethyl 1-(3, 4-difluorophenyl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylate (E-3b): ¹H-NMR (400 MHz, CDCl₃): δ 8.61 (d, *J*= 6.0 Hz, 2H), 7.31 (m, 1H), 7.30 (s, 1H), 7.19 (m, 1H), 7.04 (m, 2H), 7.01 (m, 1H), 4.43 (q, *J*= 7.20 Hz, 2H) and 1.39 (t, *J*= 7.20 Hz, 3H). LCMS: 330.14 (M+H)⁺, 93.07%. Yield: 55%.

10 [0238] Ethyl 1-(3-fluoro-4-(trifluoromethyl) phenyl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylate (E-3c): ¹H-NMR (400 MHz, CDCl₃): δ 8.68 (dd, *J*= 1.6 & 4.40 Hz, 2H), 7.60 (m, 1H), 7.36 (m, 1H), 7.14 (m, 4H), 4.44 (q, *J*= 7.20 Hz, 2H) and 1.39 (t, *J*= 6.80 Hz, 3H). MS: 380.0 (M+H)⁺. Yield: 45%.

15 [0239] Ethyl 5-(pyridin-4-yl)-1-(6-(trifluoromethyl) pyridin-3-yl)-1H-pyrazole-3-carboxylate (E-3d): ¹H-NMR (400 MHz, CDCl₃): δ 8.67 (m, 3H), 7.92 (dd, *J*= 2.0 & 8.40 Hz, 1H), 7.76 (s, 1H), 7.18 (m, 3H), 4.45 (q, *J*= 7.20 Hz, 2H) and 1.42 (t, *J*= 6.80 Hz, 3H). LCMS: 362.89 (M+H)⁺, 98.45%. Yield: 50%.

20 [0240] Ethyl 1-(pyrazin-2-yl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylate (E-3e): ¹H-NMR (400 MHz, CDCl₃): δ 9.21 (d, *J*= 1.20 Hz, 1H), 8.62 (m, 2H), 8.60 (m, 1H), 8.23 (dd, *J*= 1.2 & 2.40 Hz, 1H), 7.17 (d, *J*= 6.0 Hz, 2H), 7.14 (s, 1H), 4.45 (q, *J*= 7.20 Hz, 2H) and 1.42 (t, *J*= 6.80 Hz, 3H). LCMS: 296.18 (M+H)⁺, 96.22%. Yield: 30%.

[0241] Ethyl 5-(pyridin-4-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylate (E-3f): ¹H-NMR (400 MHz, CDCl₃): δ 8.72 (d, *J*= 5.60 Hz, 2H), 7.31 (m, 2H), 7.21 (s, 1H), 7.05 (m, 2H), 4.47 (q, *J*= 6.80 Hz, 2H) and 1.43 (t, *J*= 6.80 Hz, 3H). MS: 348.12 (M+H)⁺. Yield: 76%.

25 [0242] General procedure for the preparation of compounds E-4a-f: To an ice-cold solution of compound (E-3a-f) (1.0 eq) in EtOH was added drop wise an aqueous solution of sodium hydroxide (3.0 eq). The resulting solution was stirred at room temperature for 4 h. After completion of the reaction (TLC monitoring), the solvent was evaporated, H₂O added to the residue followed by extraction with EtOAc (2 x 100 mL). The organic layer was discarded and the pH of the aqueous layer was adjusted to ~6 by adding 1N HCl. The resulting
30 precipitate was filtered and dried under vacuum to get the desired product (60-80%) as a white solid.

[0243] 5-(Pyridin-4-yl)-1-(4-(trifluoromethyl) phenyl)-1H-pyrazole-3-carboxylic acid (E-4a): Scaffold A. ¹H-NMR (400 MHz, DMSO-d₆): δ 12.84 (br s, 1H), 8.58 (d, *J*= 5.60 Hz, 2H), 7.87 (d, *J*= 8.4 Hz, 2H), 7.59 (d, *J*= 8.4 Hz, 2H), 7.28 (m, 3H). LCMS: 334.13 (M+H)⁺, 97.98%. Yield: 95%.

5 [0244] 1-(3, 4-Difluorophenyl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylic acid (E-4b): Scaffold C. ¹H-NMR (400 MHz, DMSO-d₆): δ 13.17 (br s, 1H), 8.57 (d, *J*= 5.60 Hz, 2H), 7.69 (m, 1H), 7.54 (m, 1H), 7.22 (m, 4H). MS: 302.18 (M+H)⁺. Yield: 78%.

[0245] 1-(3-Fluoro-4-(trifluoromethyl) phenyl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylic acid (E-4c): Scaffold G. ¹H-NMR (400 MHz, DMSO-d₆): δ 8.60 (d, *J*= 5.6 Hz, 2H), 7.88 (m, 1H), 7.67 (s, 1H), 7.32 (m, 4H). LCMS: 352.17 (M+H)⁺, 98.60%. Yield: 92%.

[0246] 5-(Pyridin-4-yl)-1-(6-(trifluoromethyl) pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (E-4d): Scaffold H. ¹H-NMR (400 MHz, DMSO-d₆): δ 13.07 (br s, 1H), 8.81 (s, 1H), 8.60 (d, *J*= 6.0 Hz, 2H), 8.05 (m, 2H), 7.34 (m, 3H). LCMS: 335.13 (M+H)⁺, 97.97%. Yield: 75%.

15 [0247] 1-(Pyrazin-2-yl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylic acid (E-4e): Scaffold I. ¹H-NMR (400 MHz, DMSO-d₆): δ 13.40 (br s, 1H), 9.15 (s, 1H), 8.75 (d, *J*= 6.4 Hz, 1H), 8.56 (m, 2H), 8.43 (s, 1H), 7.33 (s, 3H). LCMS: 268.17 (M+H)⁺, 99.0%. Yield: 74%.

[0248] 5-(pyridin-4-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylic acid (E-4f): Scaffold K. ¹H-NMR (400 MHz, DMSO-d₆): δ 8.58 (d, *J*= 5.60 Hz, 2H), 7.58 (m, 2H), 7.29 (d, *J*= 6.0 Hz, 2H) and 7.16 (s, 1H). LCMS: 320.09 (M+H)⁺, 94.66%. Yield: 91%.

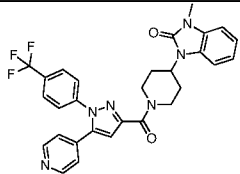
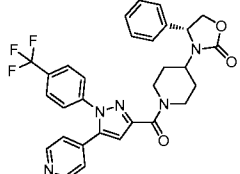
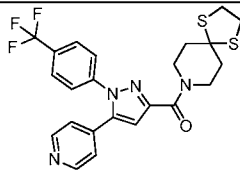
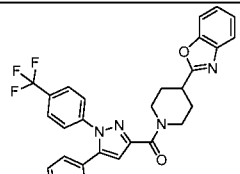
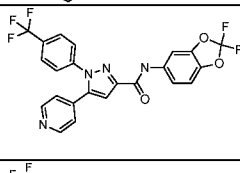
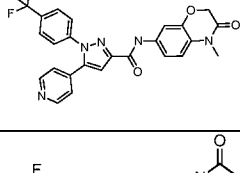
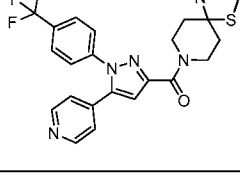
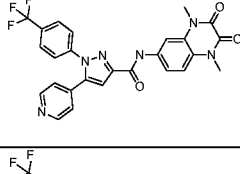
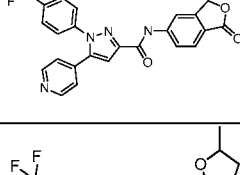
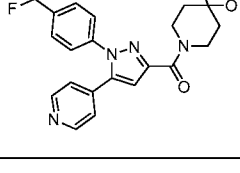
20 [0249] General procedure for the preparation of final compounds (E-5): To an ice cold solution of carboxylic acids E-4 (a-f) (1.0 eq), in DMF (2.0 mL) was added DIPEA (3.0 eq) and HATU (1.50 eq). The resulting mixture was stirred under nitrogen atmosphere at 0°C for 15 min followed by addition of the respective amine (1.20 eq). The reaction mixture was then stirred at room temperature for 16 h. After the completion of the reaction (TLC monitoring),
25 the solution was diluted with ice cold water (30 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified via prep-TLC using the solvent systems 3-5%MeOH-DCM. The final step was performed on 50-100 mg scale.

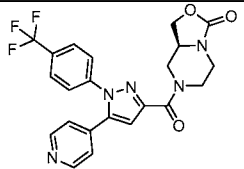
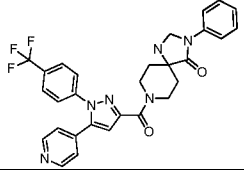
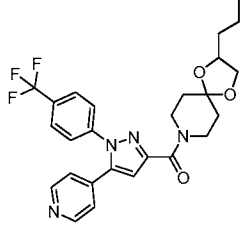
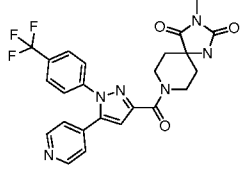
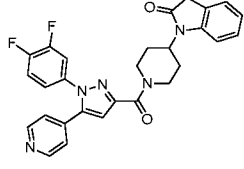
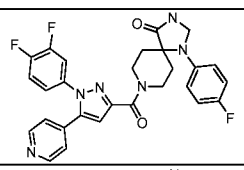
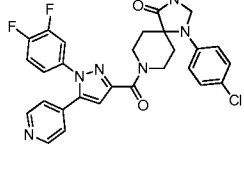
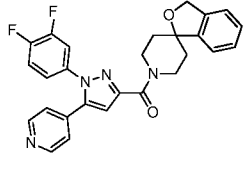
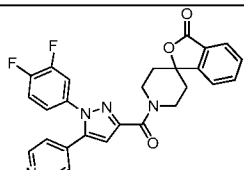
[0250] Where needed, 1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one is made according to Synthetic Scheme D. Scheme D can be modified to provide substitutions at positions other than the 4-position on the phenyl ring as well as provide substitutions other than fluorine. Other amines used in the preparation of the final compounds illustrated in

5 Table 5 according to Scheme E are commercially available or can be synthesized by one of ordinary skill.

Table 5. Example compounds of the disclosure.

Cpd ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
54		48%	532.18 (M+H) ⁺ , 91.71%	δ 8.60-8.61 (m, 2H), 7.87 (d, J= 8.40 Hz, 2H), 7.61 (d, J= 8.40 Hz, 2H), 7.31 (m, 2H), 7.22-7.26 (m, 3H), 7.15-1.17 (m, 1H), 6.97-7.0 (m, 1H), 4.68-4.76 (m, 2H), 4.42 (m, 1H), 3.53 (s, 2H), 2.94 (m, 1H), 2.68 (m, 1H), 2.28-2.39 (m, 2H) and 1.59-1.79 (m, 2H)
55		35%	565.19 (M+H) ⁺ , 94.13%	δ 8.80 (br s, 1H), 8.59-8.61 (m, 2H), 7.85 (d, J= 8.0 Hz, 2H), 7.58 (d, J= 8.0 Hz, 2H), 7.30 (m, 2H), 7.21 (s, 1H), 7.09 (t, J= 8.40 Hz, 1H), 6.86 (m, 2H), 4.59 (s, 2H), 4.46 (m, 2H), 3.88 (m, 1H), 3.54 (m, 1H), 2.19-2.30 (m, 2H) and 1.74-1.78 (m, 2H)
56		31%	581.39 (M+H) ⁺ , 95.05%	δ 8.88 (br s, 1H), 8.61 (d, J= 5.20 Hz, 2H), 7.85 (d, J= 8.0 Hz, 2H), 7.59 (d, J= 8.0 Hz, 2H), 7.32 (d, J= 5.60 Hz, 2H), 7.24-7.26 (m, 3H), 6.77 (d, J= 8.80 Hz, 2H), 4.61 (s, 2H), 4.50 (m, 2H), 3.85-3.90 (m, 1H), 3.51-3.57 (m, 1H), 2.36-2.40 (m, 2H) and 1.71-1.81 (m, 2H)
57		53%	505.13 (M+H) ⁺ , 95.89%	δ 8.61 (d, J= 5.60 Hz, 2H), 7.87 (d, J= 8.40 Hz, 2H), 7.61 (d, J= 8.40 Hz, 2H), 7.29-7.31 (m, 6H), 7.21 (s, 1H), 5.04 (s, 2H), 4.59-4.61 (m, 2H), 3.47-3.54 (m, 1H), 3.11-3.16 (m, 1H), 1.90-2.0 (m, 2H) and 1.68-1.77 (m, 2H)
58		56%	519.18 (M+H) ⁺ , 97.08%	δ 8.61 (m, 2H), 7.76-7.88 (m, 5H), 7.60-7.63 (m, 3H), 7.31 (m, 2H), 7.24 (s, 1H), 4.76-4.79 (m, 1H), 4.67-4.70 (m, 1H), 3.51-3.57 (m, 1H), 3.14-3.21 (m, 1H), 2.26-2.37 (m, 2H) and 1.71-1.80 (m, 2H)
177		37%	569.42 (M+H) ⁺ , 98.48%	δ 11.25 (br s, 1H), 8.61 (d, J= 6.0 Hz, 2H), 7.87 (d, J= 8.40 Hz, 2H), 7.61 (d, J= 8.40 Hz, 2H), 7.32 (d, J= 6.0 Hz, 2H), 7.22 (s, 1H), 7.0-7.06 (m, 1H), 6.77-6.80 (m, 1H), 4.79-4.82 (m, 1H), 4.62-4.70 (m, 2H), 3.32 (m, 1H), 2.93-2.99 (m, 1H), 2.11-2.21 (m, 2H) and 1.84-1.92 (m, 2H)
178		25%	601.43 (M+H) ⁺ , 99.83%	δ 11.27 (br s, 1H), 8.61 (d, J= 6.0 Hz, 2H), 7.87 (d, J= 8.40 Hz, 2H), 7.61 (d, J= 8.40 Hz, 2H), 7.45-7.48 (m, 1H), 7.35-7.37 (m, 1H), 7.32 (d, J= 6.0 Hz, 2H), 7.23 (d, J= 5.60 Hz, 2H), 4.71-4.80 (m, 2H), 4.54-4.60 (m, 1H), 3.32 (m, 1H), 2.93-2.99 (m, 1H), 2.29-2.37 (m, 2H) and 1.79-1.90 (m, 2H)
60		52%	518.35 (M+H) ⁺ , 96.48%	(DMSO-d ₆ @ 373°K) δ 8.61 (d, J= 6.0 Hz, 2H), 7.86 (d, J= 8.40 Hz, 2H), 7.66 (d, J= 8.40 Hz, 2H), 7.31 (d, J= 5.60 Hz, 2H), 7.22 (m, 5H), 5.22 (m, 1H), 5.05 (m, 1H), 4.85 (m, 1H), 4.60 (m, 1H), 4.25 (m, 1H), 3.46 (m, 1H) and 2.82 (m, 2H)

Cpd ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
61		41%	547.18 (M+H) ⁺ , 93.76%	δ 8.61 (m, 2H), 7.87 (d, J= 8.80 Hz, 2H), 7.61 (d, J= 8.40 Hz, 2H), 7.31 (m, 3H), 7.23 (s, 1H), 7.15 (m, 1H), 7.02-7.06 (m, 2H), 4.70-4.78 (m, 2H), 4.54 (m, 1H), 3.37 (m, 1H), 3.30 (m, 2H), 2.97 (m, 2H), 2.30-2.39 (m, 2H) and 1.77-1.86 (m, 2H)
62		47%	562.18 (M+H) ⁺ , 97.04%	δ 8.59 (m, 2H), 7.86 (m, 2H), 7.59 (d, J= 8.0 Hz, 1H), 7.53 (d, J= 8.0 Hz, 1H), 7.40 (m, 5H), 7.26-7.29 (m, 2H), 7.06-7.13 (m, 1H), 5.01 (m, 1H), 4.52-4.66 (m, 2H), 4.45 (m, 1H), 3.98 (m, 1H), 3.60 (m, 1H), 3.05 (m, 1H), 2.66 (m, 1H), 1.90 (m, 1H), 1.56-1.76 (m, 2H) and 1.26 (m, 1H)
63		50%	491.18 (M+H) ⁺ , 98.64%	δ 8.60 (d, J= 5.60 Hz, 2H), 7.87 (d, J= 8.40 Hz, 2H), 7.60 (d, J= 8.40 Hz, 2H), 7.30 (m, 2H), 7.18 (s, 1H), 3.95 (m, 2H), 3.74 (m, 2H), 3.34 (m, 4H) and 2.09 (m, 4H)
65		81%	518.35 (M+H) ⁺ , 98.95%	δ 8.61 (d, J= 6.0 Hz, 2H), 7.88 (d, J= 8.40 Hz, 2H), 7.67-7.71 (m, 2H), 7.61 (d, J= 8.40 Hz, 2H), 7.30-7.38 (m, 4H), 7.20 (s, 1H), 4.48-4.56 (m, 2H), 3.40-3.52 (m, 2H), 3.15 (m, 1H), 2.21 (m, 2H) and 1.80-1.88 (m, 2H)
66		41%	489.13 (M+H) ⁺ , 99.36%	δ 10.54 (br s, 1H), 8.61 (m, 2H), 7.90-7.93 (m, 3H), 7.70 (m, 2H), 7.63 (m, 1H), 7.42 (m, 2H) and 7.33 (m, 2H)
67		54%	494.21 (M+H) ⁺ , 95.76%	δ 10.33 (br s, 1H), 8.61 (m, 2H), 7.90-7.92 (m, 2H), 7.70 (m, 2H), 7.53-7.59 (m, 2H), 7.40 (s, 1H), 7.32 (m, 2H), 7.15 (m, 1H), 4.65 (s, 2H) and 3.27 (s, 3H)
68		87%	488.18 (M+H) ⁺ , 98.83%	δ 8.92 (br s, 1H), 8.60 (d, J= 4.80 Hz, 2H), 7.88 (d, J= 8.0 Hz, 2H), 7.60 (d, J= 8.0 Hz, 2H), 7.30 (d, J= 5.60 Hz, 2H), 7.18 (s, 1H), 4.40 (m, 1H), 4.24 (m, 1H), 3.55 (m, 4H) and 1.94 (m, 4H)
69		51%	521.13 (M+H) ⁺ , 99.69%	δ 10.49 (s, 1H), 8.62 (d, J= 5.60 Hz, 2H), 7.97 (d, J= 1.60 Hz, 1H), 7.93 (d, J= 8.40 Hz, 2H), 7.87 (d, J= 8.80 Hz, 1H), 7.71 (d, J= 8.0 Hz, 2H), 7.42-7.44 (m, 2H), 7.34 (d, J= 6.00 Hz, 2H), 3.54 (s, 3H) and 3.52 (s, 3H)
70		27%	465.30 (M+H) ⁺ , 98.41%	δ 10.80 (br s, 1H), 8.63 (d, J= 5.60 Hz, 2H), 8.27 (br s, 1H), 7.91-7.97 (m, 3H), 7.85 (m, 1H), 7.72 (d, J= 8.40 Hz, 2H), 7.47 (s, 1H), 7.34 (d, J= 6.0 Hz, 2H) and 5.41 (s, 2H)
71		74%	473.24 (M+H) ⁺ , 98.86%	δ 8.60 (d, J= 4.40 Hz, 2H), 7.87 (d, J= 7.60 Hz, 2H), 7.60 (d, J= 7.60 Hz, 2H), 7.30 (d, J= 4.40 Hz, 2H), 7.18 (s, 1H), 4.22 (m, 1H), 4.07 (m, 1H), 3.86-3.94 (m, 2H), 3.67-3.75 (m, 2H), 1.70 (m, 4H) and 1.20 (m, 4H)

Cpd ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
72		56%	458.26 (M+H) ⁺ , 97.18%	δ 8.61 (d, J= 6.0 Hz, 2H), 7.88 (d, J= 8.40 Hz, 2H), 7.62 (d, J= 8.40 Hz, 2H), 7.29 (m, 2H), 7.22 (s, 1H), 4.33-4.79 (m, 3H), 3.89-4.05 (m, 2H), 3.63-3.73 (m, 1H), 3.18-3.21 (m, 1H), 3.01-3.10 (m, 1H) and 2.78-2.84 (m, 1H)
73		38%	547.44 (M+H) ⁺ , 97.83%	δ 8.61 (d, J= 6.0 Hz, 2H), 7.87 (d, J= 8.40 Hz, 2H), 7.66 (d, J= 8.0 Hz, 2H), 7.61 (d, J= 8.40 Hz, 2H), 7.39 (m, 2H), 7.31 (d, J= 6.0 Hz, 2H), 7.20 (s, 1H), 7.13-7.16 (m, 1H), 4.73-4.76 (m, 2H), 4.42-4.50 (m, 2H), 3.61 (m, 1H), 3.49 (m, 1H), 3.16 (m, 1H) and 1.64-1.80 (m, 4H)
74		50%	501.21 (M+H) ⁺ , 96.25%	δ 8.60 (d, J= 6.0 Hz, 2H), 7.87 (d, J= 8.40 Hz, 2H), 7.60 (d, J= 8.0 Hz, 2H), 7.30 (d, J= 6.0 Hz, 2H), 7.18 (s, 1H), 4.05-4.12 (m, 2H), 3.95 (m, 1H), 3.77-3.86 (m, 2H), 3.62-3.67 (m, 1H), 3.51 (m, 1H), 1.69 (m, 4H), 1.28-1.54 (m, 4H) and 0.89 (t, J= 6.80 Hz, 3H)
75		71%	499.21 (M+H) ⁺ , 98.50%	δ 8.91 (br s, 1H), 8.61 (d, J= 5.60 Hz, 2H), 7.87 (d, J= 8.40 Hz, 2H), 7.61 (d, J= 8.40 Hz, 2H), 7.30 (d, J= 6.0 Hz, 2H), 7.21 (s, 1H), 4.44 (m, 1H), 4.34 (m, 1H), 3.62 (m, 1H), 3.39 (m, 1H), 2.84 (s, 3H), 1.82-1.88 (m, 2H) and 1.62-1.70 (m, 2H)
76		55%	500.18 (M+H) ⁺ , 99.18%	δ 8.59 (d, J= 6.0 Hz, 2H), 7.68-7.72 (m, 1H), 7.52-7.59 (m, 1H), 7.21-7.29 (m, 6H), 7.15-7.17 (m, 1H), 6.99 (m, 1H), 4.67-4.77 (m, 2H), 4.42 (m, 1H), 3.53 (s, 2H), 3.39 (m, 1H), 2.93 (m, 1H), 2.26-2.38 (m, 2H) and 1.69-1.79 (m, 2H)
77		34%	533.37 (M+H) ⁺ , 98.79%	δ 8.80 (br s, 1H), 8.59 (d, J= 6.0 Hz, 2H), 7.64-7.69 (m, 1H), 7.51-7.58 (m, 1H), 7.28 (d, J= 6.0 Hz, 2H), 7.20 (m, 2H), 7.08-7.12 (m, 2H), 6.83-6.87 (m, 2H), 4.58 (s, 2H), 4.41-4.50 (m, 2H), 3.86 (m, 1H), 3.53 (m, 1H), 2.18-2.31 (m, 2H) and 1.73-1.82 (m, 2H)
78		33%	549.43 (M+H) ⁺ , 97.25%	δ 8.87 (br s, 1H), 8.59 (br s, 2H), 7.68-7.70 (m, 1H), 7.51-7.57 (m, 1H), 7.23-7.29 (m, 6H), 6.74-6.77 (m, 2H), 4.60 (s, 2H), 4.47-4.53 (m, 2H), 3.82-3.88 (m, 1H), 3.50-3.56 (m, 1H), 2.35-2.41 (m, 2H) and 1.70-1.80 (m, 2H)
79		81%	473.13 (M+H) ⁺ , 93.47%	δ 8.59 (d, J= 5.60 Hz, 2H), 7.66-7.71 (m, 1H), 7.52-7.59 (m, 1H), 7.27-7.32 (m, 6H), 7.23 (m, 1H), 7.19 (s, 1H), 5.04 (s, 2H), 4.55-4.61 (m, 2H), 3.43-3.52 (m, 1H), 3.09-3.15 (m, 1H), 1.88-1.98 (m, 2H) and 1.68-1.76 (m, 2H)
80		82%	487.17 (M+H) ⁺ , 95.38%	δ 8.60 (d, J= 4.80 Hz, 2H), 7.76-7.86 (m, 3H), 7.68-7.72 (m, 1H), 7.53-7.63 (m, 2H), 7.30 (d, J= 5.60 Hz, 2H), 7.22 (m, 2H), 4.77-4.80 (m, 1H), 4.66-4.69 (m, 1H), 3.50-3.56 (m, 1H), 3.13-3.20 (m, 1H), 2.24-2.28 (m, 2H) and 1.72-1.80 (m, 2H)

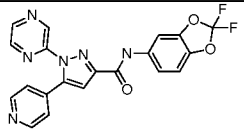
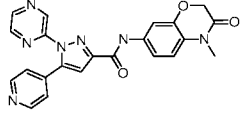
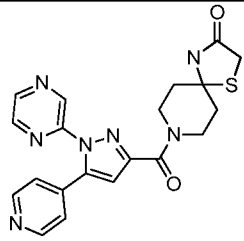
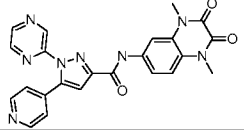
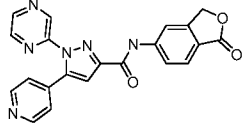
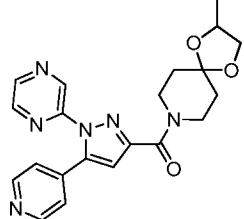
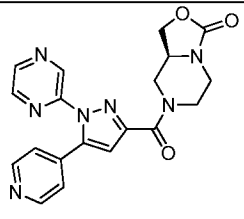
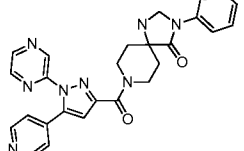
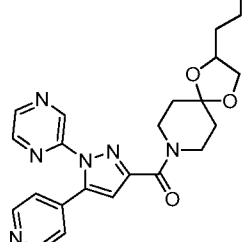
Cpd ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
82		71%	486.58 (M+H) ⁺ , 97.21%	δ 8.61 (m, 2H), 7.56-7.86 (m, 2H), 7.22-7.39 (m, 8H), 4.50-5.54 (m, 4H), 3.95-4.42 (m, 1H), 3.45 (m, 1H) and 2.79-2.91 (m, 3H)
83		58%	515.19 (M+H) ⁺ , 96.42%	δ 8.59 (d, J= 5.20 Hz, 2H), 7.68-7.72 (m, 1H), 7.52-7.59 (m, 1H), 7.28-7.29 (m, 3H), 7.22-7.24 (m, 2H), 7.15 (m, 1H), 7.02-7.08 (m, 2H), 4.69-4.79 (m, 2H), 4.55 (m, 1H), 3.30 (s, 3H), 2.92-2.98 (m, 2H), 2.28-2.37 (m, 2H) and 1.76-1.85 (m, 2H)
84		34%	530.17 (M+H) ⁺ , 92.49%	δ 8.58 (m, 2H), 7.54-7.71 (m, 2H), 7.40 (m, 5H), 7.23-7.26 (m, 3H), 7.05-7.11 (m, 1H), 5.01 (m, 1H), 4.52-4.66 (m, 2H), 4.43 (m, 1H), 3.98 (m, 1H), 3.60 (m, 1H), 3.03 (m, 1H), 2.66 (m, 1H), 1.90 (m, 1H), 1.56-1.76 (m, 2H) and 1.17 (m, 1H)
85		78%	459.10 (M+H) ⁺ , 99.41%	δ 8.59 (d, J= 4.80 Hz, 2H), 7.70 (m, 1H), 7.52-7.59 (m, 1H), 7.27 (d, J= 4.80 Hz, 2H), 7.22 (m, 1H), 7.17 (s, 1H), 3.94 (m, 2H), 3.73 (m, 2H), 3.34 (m, 4H) and 2.08 (m, 4H)
87		58%	485.99 (M+H) ⁺ , 97.66%	δ 8.59 (d, J= 6.0 Hz, 2H), 7.67-7.73 (m, 3H), 7.53-7.60 (m, 1H), 7.32-7.38 (m, 2H), 7.28 (m, 2H), 7.24 (m, 1H), 7.18 (s, 1H), 4.47-4.57 (m, 2H), 3.45 (m, 2H), 3.14 (m, 1H), 2.20 (m, 2H) and 1.79-1.90 (m, 2H)
88		57%	457.27 (M+H) ⁺ , 99.14%	δ 10.55 (br s, 1H), 8.60 (d, J= 6.0 Hz, 2H), 7.94 (m, 1H), 7.78-7.83 (m, 1H), 7.57-7.64 (m, 2H), 7.39-7.41 (m, 2H) and 7.32 (m, 3H)
89		88%	462.31 (M+H) ⁺ , 98.43%	δ 10.34 (br s, 1H), 8.60 (d, J= 6.0 Hz, 2H), 7.78-7.83 (m, 1H), 7.54-7.63 (m, 3H), 7.39 (s, 1H), 7.30-7.31 (m, 3H), 7.15 (d, J= 8.80 Hz, 1H), 4.65 (s, 2H) and 3.27 (s, 3H)
90		58%	456.30 (M+H) ⁺ , 99.11%	δ 8.92 (br s, 1H), 8.59 (d, J= 6.0 Hz, 2H), 7.67-7.72 (m, 1H), 7.53-7.60 (m, 1H), 7.28 (d, J= 6.0 Hz, 2H), 7.23 (m, 1H), 7.17 (s, 1H), 4.40 (m, 1H), 4.23 (m, 1H), 3.51-3.55 (m, 3H), 3.24 (m, 1H) and 1.93 (m, 4H)
91		49%	489.11 (M+H) ⁺ , 96.81%	δ 10.49 (s, 1H), 8.61 (d, J= 5.60 Hz, 2H), 7.95-7.98 (m, 1H), 7.81-7.89 (m, 2H), 7.59-7.65 (m, 1H), 7.41-7.44 (m, 2H), 7.32 (d, J= 6.0 Hz, 3H), 3.54 (s, 3H) and 3.52 (s, 3H)

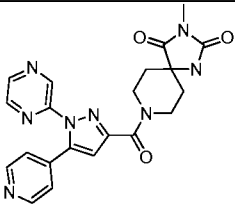
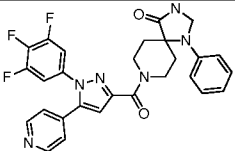
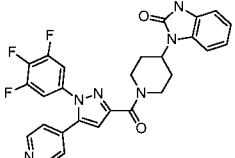
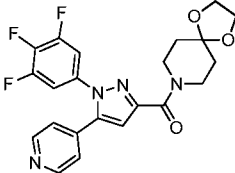
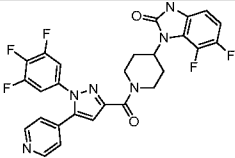
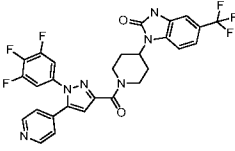
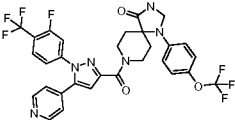
Cpd ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
92		33%	433.31 (M+H) ⁺ , 99.88%	δ 10.80 (s, 1H), 8.61 (d, J= 6.0 Hz, 2H), 8.27 (s, 1H), 7.98 (d, J= 8.80 Hz, 1H), 7.80-7.84 (m, 2H), 7.57-7.64 (m, 1H), 7.44 (s, 1H), 7.31-7.33 (m, 3H) and 5.41 (s, 2H)
93		82%	441.36 (M+H) ⁺ , 98.16%	δ 8.59 (d, J= 5.60 Hz, 2H), 7.66-7.70 (m, 1H), 7.52-7.59 (m, 1H), 7.27 (d, J= 6.0 Hz, 2H), 7.22 (m, 1H), 7.16 (s, 1H), 4.22 (m, 1H), 4.06 (m, 1H), 3.86-3.94 (m, 2H), 3.65-3.74 (m, 2H), 1.70 (m, 4H) and 1.20 (m, 4H)
94		57%	426.59 (M+H) ⁺ , 98.12%	δ 8.59 (d, J= 6.0 Hz, 2H), 7.70-7.75 (m, 1H), 7.53-7.60 (m, 1H), 7.28 (d, J= 4.80 Hz, 2H), 7.20 (m, 2H), 4.50-4.81 (m, 2H), 4.34-4.44 (m, 1H), 3.96-4.06 (m, 1H), 3.87 (m, 1H), 3.63-3.72 (m, 1H), 3.18-3.21 (m, 1H), 3.0-3.09 (m, 1H) and 2.77-2.86 (m, 1H)
95		43%	515.03 (M+H) ⁺ , 98.41%	δ 8.59 (m, 2H), 7.64-7.72 (m, 3H), 7.52-7.59 (m, 1H), 7.37-7.41 (m, 2H), 7.28 (m, 2H), 7.21 (m, 1H), 7.19 (s, 1H), 7.12-7.16 (m, 1H), 4.73-4.76 (m, 2H), 4.41-4.51 (m, 2H), 3.60 (m, 1H), 3.48 (m, 1H), 3.15 (m, 1H) and 1.66-1.80 (m, 4H)
96		67%	469.37 (M+H) ⁺ , 98.48%	δ 8.59 (d, J= 6.0 Hz, 2H), 7.66-7.70 (m, 1H), 7.52-7.59 (m, 1H), 7.27 (d, J= 6.0 Hz, 2H), 7.21 (m, 1H), 7.16 (s, 1H), 4.05-4.08 (m, 2H), 3.94-3.98 (m, 1H), 3.76-3.88 (m, 2H), 3.63-3.66 (m, 1H), 3.50 (m, 1H), 1.69 (m, 4H), 1.23-1.52 (m, 4H) and 0.88 (t, J= 6.80 Hz, 3H)
97		34%	465.29 (M+H) ⁺ , 99.18%	δ 8.93 (br s, 1H), 8.60 (d, J= 5.60 Hz, 2H), 7.69-7.73 (m, 1H), 7.54-7.61 (m, 1H), 7.29 (d, J= 5.60 Hz, 2H), 7.24 (m, 1H), 7.21 (s, 1H), 4.46 (m, 1H), 4.34 (m, 1H), 3.62 (m, 1H), 3.29 (m, 1H), 2.85 (s, 3H), 1.82-1.88 (m, 2H) and 1.61-1.67 (m, 2H)
98		65%	550.40 (M+H) ⁺ , 95.71%	δ 8.63 (m, 2H), 7.87-7.91 (m, 1H), 7.69-7.72 (m, 1H), 7.34-7.36 (m, 3H), 7.23-7.26 (m, 3H), 7.15-7.17 (m, 1H), 6.97-7.01 (m, 1H), 4.70 (m, 2H), 4.42 (m, 1H), 3.54 (s, 2H), 3.37 (m, 1H), 2.94 (m, 1H), 2.30-2.38 (m, 2H) and 1.71-1.79 (m, 2H)
99		43%	581.34 (M+H) ⁺ , 98.78%	δ 8.82 (br s, 1H), 8.63 (d, J= 5.60 Hz, 2H), 7.85-7.89 (m, 1H), 7.67-7.69 (m, 1H), 7.30-7.35 (m, 3H), 7.22 (s, 1H), 7.08-7.12 (m, 2H), 6.84-6.87 (m, 2H), 4.59 (s, 2H), 4.42-4.45 (m, 2H), 3.87 (m, 1H), 3.54 (m, 1H), 2.20-2.36 (m, 2H) and 1.73-1.80 (m, 2H)
100		50%	599.40 (M+H) ⁺ , 96.20%	δ 8.88 (br s, 1H), 8.64 (d, J= 4.40 Hz, 2H), 7.84-7.88 (m, 1H), 7.67-7.70 (m, 1H), 7.25-7.36 (m, 6H), 6.78 (d, J= 8.80 Hz, 2H), 4.61 (br s, 2H), 4.44-4.49 (m, 2H), 3.84-3.90 (m, 1H), 3.50-3.57 (m, 1H), 2.35-2.42 (m, 2H) and 1.71-1.81 (m, 2H)

Cpd ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
101		68%	523.33 (M+H) ⁺ , 95.04%	δ 8.63 (d, J= 6.0 Hz, 2H), 7.86-7.91 (m, 1H), 7.71 (m, 1H), 7.29-7.36 (m, 7H), 7.22 (s, 1H), 5.04 (s, 2H), 4.55-4.58 (m, 2H), 3.47-3.54 (m, 1H), 3.10-3.17 (m, 1H), 1.90-2.01 (m, 2H) and 1.68-1.77 (m, 2H)
102		53%	537.35 (M+H) ⁺ , 95.01%	δ 8.64 (d, J= 5.60 Hz, 2H), 7.78-7.91 (m, 4H), 7.70-7.73 (m, 1H), 7.60-7.64 (m, 1H), 7.33-7.36 (m, 3H), 7.25 (s, 1H), 4.66-4.76 (m, 2H), 3.54-3.57 (m, 1H), 3.14-3.21 (m, 1H), 2.29-2.36 (m, 2H) and 1.72-1.80 (m, 2H)
103		31%	571.31 (M+H) ⁺ , 99.71%	δ 8.64 (d, J= 5.20 Hz, 2H), 7.85-7.91 (m, 4H), 7.70-7.73 (m, 1H), 7.33-7.36 (m, 3H), 7.24 (s, 1H), 4.66-4.76 (m, 2H), 3.49-3.55 (m, 1H), 3.12-3.19 (m, 1H), 2.30-2.37 (m, 2H) and 1.74-1.83 (m, 2H)
104		67%	536.36 (M+H) ⁺ , 96.92%	δ 8.64-8.65 (m, 2H), 7.70-7.97 (m, 2H), 7.18-7.42 (m, 8H), 5.13-5.52 (m, 1H), 3.48-5.0 (m, 4H), 3.30 (m, 1H) and 2.79-2.91 (m, 3H)
105		70%	565.37 (M+H) ⁺ , 94.01%	δ 8.63 (d, J= 6.0 Hz, 2H), 7.87-7.91 (m, 1H), 7.69-7.72 (m, 1H), 7.34-7.36 (m, 4H), 7.24 (s, 1H), 7.13-7.16 (m, 1H), 7.04-7.08 (m, 2H), 4.70-4.74 (m, 2H), 4.53-4.59 (m, 1H), 3.37 (m, 1H), 3.30 (s, 3H), 2.94-3.0 (m, 1H), 2.30-2.38 (m, 2H) and 1.77-1.86 (m, 2H)
106		86%	580.35 (M+H) ⁺ , 95.40%	δ 8.62 (m, 2H), 7.85-7.91 (m, 1H), 7.59-7.71 (m, 1H), 7.24-7.40 (m, 8H), 7.07-7.14 (m, 1H), 5.01 (m, 1H), 4.57-4.62 (m, 2H), 4.43 (m, 1H), 3.98 (m, 1H), 3.59 (m, 1H), 3.03 (m, 1H), 2.72 (m, 1H), 1.85-1.94 (m, 1H), 1.56-1.77 (m, 2H) and 1.23 (m, 1H)
107		76%	509.31 (M+H) ⁺ , 95.64%	δ 8.63 (d, J= 6.0 Hz, 2H), 7.88 (m, 1H), 7.70-7.72 (m, 1H), 7.32-7.34 (m, 3H), 7.19 (s, 1H), 3.94 (m, 2H), 3.74 (m, 2H), 3.35 (m, 4H) and 2.09 (m, 4H)
108		31%	536.36 (M+H) ⁺ , 95.15%	δ 8.63 (d, J= 5.60 Hz, 2H), 7.89 (t, J= 8.40 Hz, 1H), 7.67-7.73 (m, 3H), 7.35 (m, 5H), 7.21 (s, 1H), 4.47-4.54 (m, 2H), 3.39-3.52 (m, 2H), 3.13-3.19 (m, 1H), 2.18-2.25 (m, 2H) and 1.18-1.23 (m, 2H)
109		57%	507.27 (M+H) ⁺ , 97.62%	δ 10.56 (s, 1H), 8.64-8.65 (m, 2H), 7.94-7.90 (m, 2H), 7.85 (m, 1H), 7.62 (dd, J= 8.80 & 2.00 Hz, 1H) and 7.39-7.43 (m, 5H)
110		77%	510.23 (M+H) ⁺ , 97.05%	δ 10.35 (s, 1H), 8.65 (d, J= 6.00 Hz, 2H), 7.93 (d, J= 8.00 Hz, 1H), 7.86 (m, 1H), 7.59 (d, J= 2.40 Hz, 1H), 7.54 (dd, J= 8.80 & 2.40 Hz, 1H), 7.38-7.41 (m, 4H), 7.16 (d, J= 8.8Hz, 1H), 4.66 (s, 2H) and 3.28 (s, 3H)

Cpd ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
111		58%	504.25 (M-H) ⁺ , 98.75%	δ 8.62-8.63 (m, 2H), 8.40 (s, 1H), 7.89 (t, J= 8.00 Hz, 1H), 7.72 (m, 1H), 7.33-7.35 (m, 3H), 7.20 (s, 1H), 4.35-4.39 (m, 1H), 4.21-4.24 (m, 1H), 3.69 (m, 4H), 3.30 (m, 1H) and 2.08-2.11 (m, 3H)
112		54%	539.14 (M+H) ⁺ , 98.59%	δ 10.43 (s, 1H), 8.65 (d, J= 6.0 Hz, 2H), 7.91-7.96 (m, 2H), 7.85 (d, J= 8.0 Hz, 2H), 7.38-7.45 (m, 5H), 3.55 (s, 3H) and 3.54 (s, 3H)
113		38%	481.20 (M-H) ⁺ , 99.50%	δ 10.80 (s, 1H), 8.65 (d, J= 6.0 Hz, 2H), 8.27 (s, 1H), 7.92-7.98 (m, 2H), 7.84-7.89 (m, 2H), 7.48 (s, 1H), 7.39-7.43 (m, 3H) and 5.42 (s, 2H)
114		67%	491.36 (M+H) ⁺ , 99.52%	δ 8.62 (d, J= 6.00 Hz, 2H), 7.89 (d, J= 8.40 Hz, 1H), 7.71 (m, 1H), 7.32-7.35 (m, 3H), 7.19 (s, 1H), 4.19-4.22 (m, 1H), 4.05-4.10 (m, 1H), 3.76-3.95 (m, 4H), 3.40-3.46 (m, 1H), 1.69-1.70 (m, 4H) and 1.19-1.22 (m, 3H)
115		81%	476.11 (M+H) ⁺ , 99.38%	δ 8.63 (d, J= 5.60 Hz, 2H), 7.89 (t, J= 8.00 Hz, 1H), 7.76 (d, J= 10.40 Hz, 1H), 7.35 (br s, 3H), 7.24 (s, 1H), 4.51-4.76 (m, 2H), 4.34-4.54 (m, 1H), 3.88-4.07 (m, 2H), 3.64-3.73 (m, 1H), 3.08-3.11 (m, 1H), 3.19-3.22 (m, 1H) and 2.82-2.87 (m, 1H)
116		57%	303.75 (M+H) ⁺ , 99.72%	δ 8.62 (d, J= 6.40 Hz, 2H), 7.89 (t, J= 8.40 Hz, 1H), 7.65-7.72 (m, 3H), 7.35-7.41 (m, 5H), 7.22 (s, 1H), 7.15 (t, J= 7.20 Hz, 1H), 4.71-4.76 (m, 2H), 4.42-4.47 (m, 2H), 3.61-3.63 (m, 1H), 3.47-3.53 (m, 1H), 3.16-3.17 (m, 1H) and 1.68-1.79 (m, 4H)
117		39%	519.17 (M+H) ⁺ , 99.31%	δ 8.62 (d, J= 5.20 Hz, 2H), 7.89 (t, J= 8.4 Hz, 1H), 7.70 (d, J= 10.8 Hz, 1H), 7.32-7.35 (m, 3H), 7.19 (s, 1H), 4.07-4.09 (m, 2H), 3.76-3.96 (m, 3H), 3.62-3.65 (m, 1H), 3.50-3.51 (m, 1H), 1.74 (br s, 4H), 1.23-1.69 (m, 4H) and 0.88-0.92 (m, 3H)
118		67%	517.13 (M+H) ⁺ , 99.26%	δ 8.94 (s, 1H), 8.63 (d, J= 4.80 Hz, 2H), 7.89 (t, J= 7.6 Hz, 1H), 7.72 (d, J= 12.0 Hz, 1H), 7.34-7.35 (m, 3H), 7.23 (s, 1H), 4.31-4.43 (m, 2H), 3.58-3.64 (m, 1H), 3.29 (m, 1H), 2.84 (s, 3H), 1.85-1.89 (m, 2H) and 1.64-1.70 (m, 2H)
119		29%	533.35 (M+H) ⁺ , 96.97%	δ 8.84 (s, 1H), 8.63 (m, 2H), 8.04-8.10 (m, 2H), 7.38 (d, J= 6.0 Hz, 2H), 7.23-7.28 (m, 3H), 7.17 (d, J= 8.40 Hz, 1H), 6.99 (t, J= 7.2 Hz, 1H), 4.72 (m, 2H), 4.40-4.46 (m, 1H), 3.54 (s, 2H), 3.35-3.41 (m, 1H), 2.92-2.98 (m, 1H), 2.33-2.40 (m, 1H), 1.71-1.80 (m, 2H) and 1.07-1.11 (m, 1H)

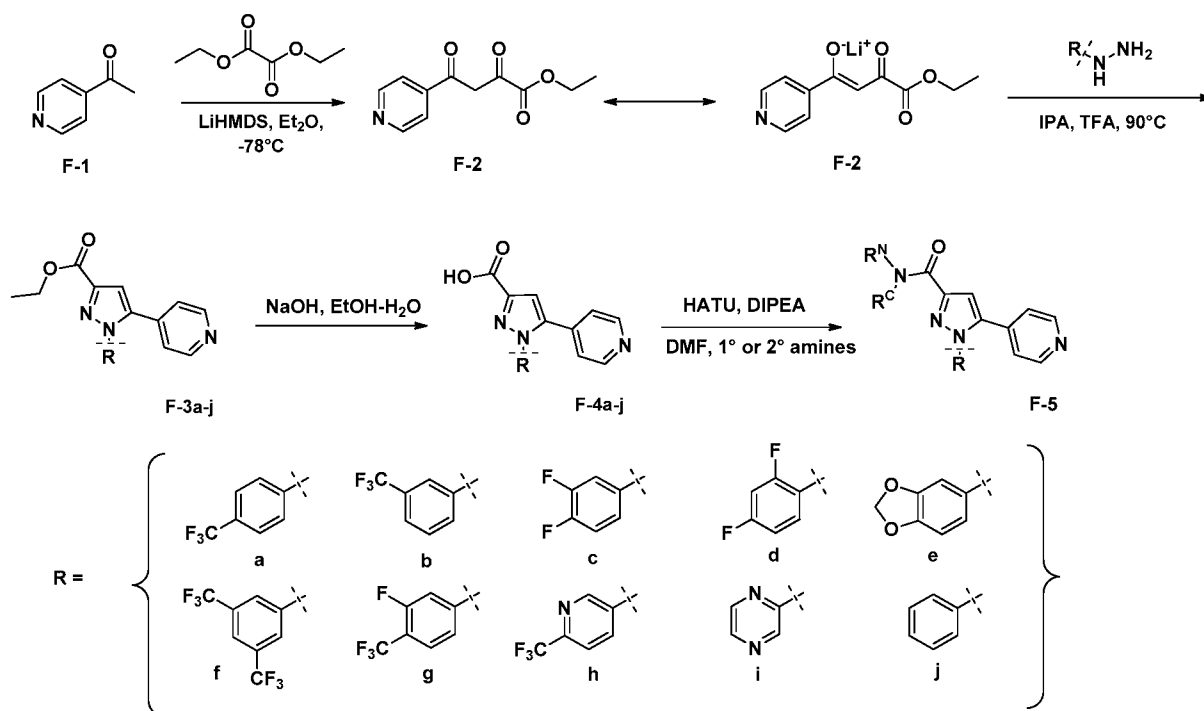
Cpd ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
120		38%	564.37 (M-H) ⁺ , 98.73%	δ 8.82 (br s, 2H), 8.63 (d, J= 6.0 Hz, 2H), 8.03 (s, 2H), 7.37 (d, J= 6.0 Hz, 2H), 7.26 (s, 1H), 7.10 (t, J= 8.80 Hz, 2H), 6.84 (m, 2H), 4.65 (s, 2H), 4.59-4.60 (m, 2H), 3.86-3.92 (m, 1H), 3.51-3.58 (m, 1H), 3.35-3.39 (m, 1H), 2.19-2.29 (m, 2H) and 1.07-1.11 (m, 1H)
121		46%	582.41 (M+H) ⁺ , 96.72%	δ 8.88 (br s, 2H), 8.83 (s, 1H), 8.64 (d, J= 5.60 Hz, 2H), 8.03 (br s, 2H), 7.38 (d, J= 5.60 Hz, 2H), 7.24-7.29 (m, 3H), 6.78 (d, J= 8.80 Hz, 2H), 4.61 (br s, 2H), 4.51 (m, 2H), 3.86-3.91 (m, 1H), 3.51-3.57 (m, 1H), 2.41 (m, 2H) and 1.72-1.81 (m, 2H)
122		30%	506.36 (M+H) ⁺ , 98.17%	δ 8.84 (br s, 1H), 8.64 (d, J= 6.0 Hz, 2H), 8.03-8.09 (m, 2H), 7.37-7.39 (m, 2H), 7.29-7.33 (m, 5H), 5.05 (s, 2H), 4.58 (m, 2H), 3.48-3.55 (m, 1H), 3.12-3.15 (m, 1H), 1.90-1.99 (m, 2H) and 1.69-1.78 (m, 2H)
123		41%	520.34 (M+H) ⁺ , 95.11%	δ 8.86 (br s, 1H), 8.64 (d, J= 6.0 Hz, 2H), 8.04-8.10 (m, 2H), 7.77-7.87 (m, 3H), 7.62 (t, J= 7.20 Hz, 1H), 7.38 (d, J= 6.0 Hz, 2H), 7.29 (s, 1H), 4.67-4.76 (m, 2H), 3.56 (m, 1H), 3.19 (m, 1H) and 2.25-2.37 (m, 4H)
124		70%	554.30 (M+H) ⁺ , 97.55%	δ 8.85 (br s, 1H), 8.64 (d, J= 6.0 Hz, 2H), 8.04-8.10 (m, 2H), 7.84-7.92 (m, 3H), 7.38 (dd, J= 4.40 & 2.0 Hz, 2H), 7.28 (s, 1H), 4.67-4.77 (m, 2H), 3.53 (m, 1H), 3.16 (m, 1H), 2.69 (m, 1H) and 2.49-2.50 (m, 3H)
125		46%	519.37 (M+H) ⁺ , 98.55%	δ 8.83-8.95 (distorted s, 1H), 8.64 (m, 2H), 8.05-8.16 (m, 2H), 7.23-7.41 (m, 7H), 5.00-5.17 (m, 1H), 4.54-4.92 (m, 3H), 3.97-4.44 (m, 1H), 3.49-3.56 (m, 1H) and 2.67-2.89 (m, 3H)
126		59%	548.35 (M+H) ⁺ , 95.06%	δ 8.84 (s, 1H), 8.63 (d, J= 5.6 Hz, 2H), 8.04-8.09 (m, 2H), 7.38 (d, J= 5.6 Hz, 2H), 7.28-7.32 (m, 2H), 7.14-7.16 (m, 1H), 7.06-7.08 (m, 2H), 4.73 (m, 2H), 4.54-4.60 (m, 1H), 3.43 (m, 1H), 3.31 (s, 3H), 2.95-3.04 (m, 1H), 2.33-2.39 (m, 2H) and 1.78-1.86 (m, 2H)
127		46%	563.38 (M+H) ⁺ , 98.89%	δ 8.76-8.83 (two signals due to rotational isomer, 1H), 8.62 (br s, 2H), 7.98-8.05 (m, 2H), 7.32-7.40 (m, 7H), 7.11-7.17 (two signals due to rotational isomer, 1H), 4.99-5.03 (m, 1H), 4.53-4.62 (m, 2H), 4.40-4.43 (m, 1H), 3.97-4.01 (m, 1H), 3.60-3.62 (m, 1H), 3.06-3.09 (m, 1H), 2.67-2.73 (m, 1H), 1.83-1.95 (m, 1H), 1.55-1.78 (m, 2H) and 1.24-1.30 (m, 1H)
128		88%	492.30 (M+H) ⁺ , 97.31%	δ 8.83 (s, 1H), 8.63 (d, J= 6.0 Hz, 2H), 8.06-8.07 (m, 2H), 7.36 (d, J= 6.4 Hz, 2H), 7.23 (s, 1H), 3.94 (m, 2H), 3.74 (m, 2H), 3.33-3.35 (m, 4H) and 2.10 (m, 4H)
129		71%	452.36 (M+H) ⁺ , 98.30%	δ 9.18 (s, 1H), 8.73 (d, J= 2.8 Hz, 1H), 8.58 (d, J= 5.6 Hz, 2H), 8.42 (s, 1H), 7.68-7.72 (m, 2H), 7.33-7.38 (m, 4H), 7.21 (s, 1H), 4.50 (m, 2H), 3.37-3.54 (m, 2H), 3.15-3.21 (m, 1H), 2.20-2.23 (m, 2H) and 1.82-1.91 (m, 2H)

Cpd ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
130		46%	421.24 (M-H) ⁺ , 99.49%	δ 10.60 (s, 1H), 9.33 (s, 1H), 8.78 (d, J= 2.4 Hz, 1H), 8.60 (d, J= 6.0 Hz, 2H), 8.46-8.47 (m, 1H), 7.95 (d, J= 2.0 Hz, 1H), 7.61-7.64 (m, 1H) and 7.39-7.44 (m, 4H)
131		93%	426.26 (M-H) ⁺ , 95.02%	δ 10.39 (s, 1H), 9.35 (s, 1H), 8.77 (d, J= 2.4 Hz, 1H), 8.60 (d, J= 6.0 Hz, 2H), 8.45 (s, 1H), 7.55-7.60 (m, 2H), 7.40-7.41 (m, 3H), 7.17 (d, J= 8.8 Hz, 1H), 4.67 (s, 2H) and 3.33 (s, 3H)
132		29%	422.30 (M+H) ⁺ , 98.86%	δ 9.17 (s, 1H), 8.94 (br s, 1H), 8.73 (d, J= 2.4 Hz, 1H), 8.57-8.59 (m, 2H), 8.41-8.42 (m, 1H), 7.35-7.37 (m, 2H), 7.19 (s, 1H), 4.22-4.38 (m, 2H), 3.55-3.60 (m, 3H), 3.28 (m, 1H) and 1.90-1.97 (m, 4H)
133		31%	455.11 (M+H) ⁺ , 98.49%	δ 10.55 (s, 1H), 9.36 (s, 1H), 8.79 (d, J= 2.40 Hz, 1H), 8.61 (d, J= 5.60 Hz, 2H), 8.47 (br s, 1H), 8.00 (br s, 1H), 7.85-7.89 (m, 1H), 7.40-7.47 (m, 4H), 3.55 (s, 3H) and 3.54 (s, 3H)
134		31%	399.10 (M+H) ⁺ , 92.75%	δ 10.85 (s, 1H), 9.36 (s, 1H), 8.79 (d, J= 2.40 Hz, 1H), 8.60 (d, J= 5.60 Hz, 2H), 8.47 (br s, 1H), 8.28 (s, 1H), 7.98 (d, J= 8.0 Hz, 1H), 7.86 (d, J= 8.40 Hz, 1H), 7.47 (s, 1H), 7.41 (d, J= 6.0 Hz, 2H) and 5.42 (s, 2H)
135		44%	407.37 (M+H) ⁺ , 99.68%	δ 9.16 (s, 1H), 8.73 (d, J= 2.8 Hz, 1H), 8.57-8.58 (m, 2H), 8.40-8.41 (m, 1H), 7.35-7.36 (m, 2H), 7.19 (s, 1H), 4.21-4.25 (m, 1H), 4.05-4.10 (m, 1H), 3.63-3.98 (m, 4H), 3.40-3.46 (m, 1H), 1.72 (m, 4H) and 1.20 (m, 3H)
136		37%	392.29 (M+H) ⁺ , 97.02%	δ 9.23 (d, J= 9.2 Hz, 1H), 8.74 (d, J= 2.4 Hz, 1H), 8.58 (d, J= 6.0 Hz, 2H), 8.41 (s, 1H), 7.36 (br s, 2H), 7.23 (d, J= 2.4 Hz, 1H), 4.52-4.78 (m, 2H), 4.37-4.43 (m, 1H), 3.90-4.08 (m, 2H), 3.66-3.74 (m, 1H), 3.12-3.33 (m, 2H) and 2.83-2.89 (m, 1H)
137		79%	481.39 (M+H) ⁺ , 97.37%	δ 9.17 (s, 1H), 8.73 (d, J= 2.4 Hz, 1H), 8.57-8.59 (m, 2H), 8.41-8.42 (m, 1H), 7.66 (d, J= 8.0 Hz, 2H), 7.36-7.41 (m, 4H), 7.21 (s, 1H), 7.15 (t, J= 7.2 Hz, 1H), 4.17-4.79 (m, 2H), 4.44-4.46 (m, 2H), 3.63 (t, J= 9.2 Hz, 1H), 3.49-3.55 (m, 1H), 3.18-3.22 (m, 1H) and 1.70-1.75 (m, 4H)
138		33%	435.38 (M+H) ⁺ , 99.02%	δ 9.16 (s, 1H), 8.72 (d, J= 2.4 Hz, 1H), 8.58 (d, J= 2.4 Hz, 2H), 8.41 (s, 1H), 7.36 (d, J= 5.6 Hz, 2H), 7.19 (s, 1H), 4.05-4.09 (m, 2H), 3.66-3.96 (m, 4H), 3.49-3.51 (m, 1H), 1.71 (m, 4H), 1.23-1.57 (m, 4H) and 0.90 (t, J= 6.8 Hz, 3H)

Cpd ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
139		37%	431.28 (M-H) ⁺ , 99.81%	δ 9.16 (s, 1H), 8.93 (s, 1H), 8.73 (d, J= 2.4 Hz, 1H), 8.58 (d, J= 6.0 Hz, 2H), 8.42 (s, 1H), 7.36 (d, J= 5.6 Hz, 2H), 7.22 (s, 1H), 4.31-4.43 (m, 2H), 3.61-3.72 (m, 1H), 2.85 (s, 3H), 1.83-1.94 (m, 2H), 1.69 (m, 2H) and 1.23-1.27 (m, 1H)
140		36%	531.32 (M-H) ⁺ , 99.38%	δ 8.84 (br s, 1H), 8.60 (d, J= 6.4 Hz, 2H), 7.51-7.55 (m, 2H), 7.31-7.32 (m, 2H), 7.20-7.24 (m, 3H), 6.74-6.78 (m, 3H), 4.62 (s, 2H), 4.47-4.53 (m, 2H), 3.83-3.89 (m, 1H), 3.49-3.56 (m, 1H) and 1.69-1.88 (m, 4H)
141		28%	517.31 (M-H) ⁺ , 98.75%	δ 8.60 (d, J= 6.0 Hz, 2H), 7.55-7.58 (m, 2H), 7.32 (d, J= 6.0 Hz, 2H), 7.23-7.24 (m, 2H), 6.97 (m, 3H), 4.69-4.76 (m, 2H), 4.47-4.53 (m, 1H), 3.29-3.60 (m, 2H), 2.92-2.98 (m, 1H), 2.29-2.36 (m, 2H) and 1.75-1.81 (m, 2H)
142		47%	445.30 (M+H) ⁺ , 99.52%	δ 8.59-8.60 (m, 2H), 7.53-7.57 (m, 2H), 7.29-7.31 (m, 2H), 7.19 (s, 1H), 3.92 (m, 6H), 3.71 (m, 2H) and 1.75-1.88 (m, 4H)
175		29%	555.43 (M+H) ⁺ , 99.51%	δ 11.25 (br s, 1H), 8.60 (d, J= 6.0 Hz, 2H), 7.54-7.58 (m, 2H), 7.32 (d, J= 6.0 Hz, 2H), 7.23 (s, 1H), 7.0-7.07 (m, 1H), 6.77-6.80 (m, 1H), 4.78-4.81 (m, 1H), 4.66-4.69 (m, 2H), 3.30 (m, 1H), 2.92-2.98 (m, 1H), 2.13-2.19 (m, 2H) and 1.84-1.90 (m, 2H)
176		22%	587.40 (M+H) ⁺ , 99.83%	δ 11.26 (br s, 1H), 8.61 (d, J= 6.0 Hz, 2H), 7.54-7.58 (m, 2H), 7.45-7.47 (m, 1H), 7.35-7.37 (m, 1H), 7.32 (d, J= 6.0 Hz, 2H), 7.21-7.24 (m, 2H), 4.70-4.78 (m, 2H), 4.53-4.59 (m, 1H), 3.30 (m, 1H), 2.92-2.98 (m, 1H), 2.25-2.35 (m, 2H) and 1.79-1.90 (m, 2H)
179		10%	649.53 (M+H) ⁺ , 96.93%	δ 8.90 (s, 1H), 8.60-8.64 (m, 2H), 7.85 (t, J= 7.2 Hz, 1H), 7.69 (d, J= 10.8 Hz, 1H), 7.30-7.36 (m, 3H), 7.20-7.25 (m, 3H), 6.82 (d, J= 8.0 Hz, 2H), 6.54 (s, 1H), 4.63 (s, 2H), 4.44-4.51 (m, 2H), 3.84-3.86 (m, 1H), 3.51-3.57 (m, 1H), 2.59 (m, 1H) and 1.71-1.87 (m, 2H)

[0251] In another embodiment, compounds of the disclosure are made according to Scheme F.

Scheme F



[0252] Preparation of ethyl 2,4-dioxo-4-(pyridin-4-yl)butanoate (F-2): A solution of 4-acetyl pyridine (10.0 g, 82.55 mmol) in diethyl ether (160 mL) was cooled to -78°C followed by addition of LiHMDS (15.16 g, 90.80 mmol). The resulting reaction mixture was stirred at -78°C for 45 min followed by drop wise addition of diethyl oxalate (13.5 mL, 98.92 mmol) in about 30 min. The reaction mixture was then left to stir at room temperature for 16 h. After completion of the reaction (TLC and MS monitoring), the solution was then cooled 0°C and the resulting precipitate was filtered to get the desired product as an off-white solid (18.0 g, 98%), which was carried forward to the next step without purification.

[0253] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 8.66 (d, $J=4.80$ Hz, 2H), 7.70 (d, $J=5.20$ Hz, 2H), 6.43 (s, 1H), 4.15 (q, $J=7.20$ Hz, 2H) and 1.25 (t, $J=7.20$ Hz, 3H).

[0254] **General procedure for the preparation of compounds F-3a-j:** To an ice-cold solution of ethyl 2,4-dioxo-4-(pyridin-4-yl)butanoate **F-2** (1.0 eq) in IPA was added a respective hydrazine (1.10 eq) and TFA (2.0 eq). The resulting reaction mixture was warmed up to room temperature and then stirred at 90°C for 4-5 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics were washed with brine, dried

over anhydrous sodium sulfate, filtered and concentrated. The crude was purified over silica gel (100-200 Mesh, 10-15% EtOAc-hexane) to get the desired product.

[0255] Ethyl 5-(pyridin-4-yl)-1-(4-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxylate (F-3a): ¹H-NMR (400 MHz, CDCl₃): δ 8.61 (d, *J*= 6.0 Hz, 2H), 7.66 (d, *J*= 8.4 Hz, 2H), 7.47 (d, *J*= 8.4 Hz, 2H), 7.17 (s, 1H), 7.11 (m, 2H), 4.44 (q, *J*= 7.20 Hz, 2H) and 1.41 (t, *J*= 7.20 Hz, 3H). LCMS: 362.21 (M+H)⁺, 99.95%. Yield: 50%.

[0256] Ethyl 5-(pyridin-4-yl)-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxylate (F-3b): ¹H-NMR (400 MHz, CDCl₃): δ 8.60 (d, *J*= 6.0 Hz, 2H), 7.73 (s, 1H), 7.67 (d, *J*= 8.0 Hz, 1H), 7.49 (m, 1H), 7.35 (m, 1H), 7.23 (s, 1H), 7.14 (m, 2H), 4.29 (q, *J*= 7.20 Hz, 2H) and 1.42 (t, *J*= 7.20 Hz, 3H). LCMS: 362.22 (M+H)⁺, 91.70%. Yield: 62%.

[0257] Ethyl 1-(3, 4-difluorophenyl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylate (F-3c): ¹H-NMR (400 MHz, CDCl₃): δ 8.61 (d, *J*= 6.0 Hz, 2H), 7.31 (m, 1H), 7.30 (s, 1H), 7.19 (m, 1H), 7.04 (m, 2H), 7.01 (m, 1H), 4.43 (q, *J*= 7.20 Hz, 2H) and 1.39 (t, *J*= 7.20 Hz, 3H). LCMS: 330.14 (M+H)⁺, 93.07%. Yield: 55%.

[0258] Ethyl 1-(2, 4-difluorophenyl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylate (F-3d): ¹H-NMR (400 MHz, CDCl₃): δ 8.62 (d, *J*= 6.4 Hz, 2H), 7.82 (m, 1H), 7.55 (m, 1H), 7.53 (s, 1H), 7.34 (m, 3H), 4.32 (q, *J*= 7.20 Hz, 2H) and 1.30 (t, *J*= 7.20 Hz, 3H). LCMS: 330.21 (M+H)⁺, 91.46%. Yield: 65%.

[0259] Ethyl 1-(benzo[d][1,3]dioxol-5-yl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylate (F-3e): ¹H-NMR (400 MHz, CDCl₃): δ 8.57 (d, *J*= 6.0 Hz, 2H), 7.10 (m, 3H), 6.81 (s, 1H), 6.72 (m, 2H), 6.04 (s, 2H), 4.42 (q, *J*= 7.20 Hz, 2H) and 1.40 (t, *J*= 7.20 Hz, 3H). LCMS: 338.20 (M+H)⁺, 77.49%. Yield: 20%.

[0260] Ethyl 1-(3, 5-bis (trifluoromethyl) phenyl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylate (F-3f): ¹H-NMR (400 MHz, CDCl₃): δ 8.56 (dd, *J*= 1.6 & 4.40 Hz, 2H), 7.90 (s, 1H), 7.82 (s, 2H), 7.20 (s, 1H), 7.12 (dd, *J*= 1.6 & 4.40 Hz, 2H), 4.45 (q, *J*= 7.20 Hz, 2H) and 1.42 (t, *J*= 7.20 Hz, 3H). LCMS: 430.26 (M+H)⁺, 93.03%. Yield: 32%.

[0261] Ethyl 1-(3-fluoro-4-(trifluoromethyl) phenyl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylate (F-3g): ¹H-NMR (400 MHz, CDCl₃): δ 8.68 (dd, *J*= 1.6 & 4.40 Hz, 2H), 7.60 (m, 1H), 7.36 (m, 1H), 7.14 (m, 4H), 4.44 (q, *J*= 7.20 Hz, 2H) and 1.39 (t, *J*= 6.80 Hz, 3H). MS: 380.0 (M+H)⁺. Yield: 45%.

[0262] **Ethyl 5-(pyridin-4-yl)-1-(6-(trifluoromethyl) pyridin-3-yl)-1H-pyrazole-3-carboxylate (F-3h):** $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.67 (m, 3H), 7.92 (dd, $J = 2.0$ & 8.40 Hz, 1H), 7.76 (s, 1H), 7.18 (m, 3H), 4.45 (q, $J = 7.20$ Hz, 2H) and 1.42 (t, $J = 6.80$ Hz, 3H). LCMS: 362.89 ($\text{M}+\text{H}$) $^+$, 98.45%. Yield: 50%.

5 [0263] **Ethyl 1-(pyrazin-2-yl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylate (F-3i):** $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 9.21 (d, $J = 1.20$ Hz, 1H), 8.62 (m, 2H), 8.60 (m, 1H), 8.23 (dd, $J = 1.2$ & 2.40 Hz, 1H), 7.17 (d, $J = 6.0$ Hz, 2H), 7.14 (s, 1H), 4.45 (q, $J = 7.20$ Hz, 2H) and 1.42 (t, $J = 6.80$ Hz, 3H). LCMS: 296.18 ($\text{M}+\text{H}$) $^+$, 96.22%. Yield: 30%.

10 [0264] **Ethyl 1-phenyl-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylate (F-3j):** $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 8.55 (d, $J = 6.0$ Hz, 2H), 7.51 (m, 3H), 7.38 (m, 3H), 7.24 (m, 2H), 4.35 (q, $J = 7.20$ Hz, 2H) and 1.32 (t, $J = 7.20$ Hz, 3H). Yield: 33%.

[0265] **General procedure for the preparation of compounds F-4a-j:** To an ice-cold solution of compound (F-3a-j) (1.0 eq) in EtOH was added dropwise an aqueous solution of sodium hydroxide (3.0 eq). The resulting solution was stirred at room temperature for 4 h.
15 After completion of the reaction (TLC monitoring), the solvent was evaporated, added H_2O to the residue followed by extraction with EtOAc (2 x 100 mL). The organic layer was discarded and the pH of the aqueous layer was adjusted to ~6 by adding 1N HCl. The resulting precipitate was filtered and dried under vacuum to get the desired product (60-80%) as a white solid.

20 [0266] **5-(Pyridin-4-yl)-1-(4-(trifluoromethyl) phenyl)-1H-pyrazole-3-carboxylic acid (F-4a):** $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 12.84 (br s, 1H), 8.58 (d, $J = 5.60$ Hz, 2H), 7.87 (d, $J = 8.4$ Hz, 2H), 7.59 (d, $J = 8.4$ Hz, 2H), 7.28 (m, 3H). LCMS: 334.13 ($\text{M}+\text{H}$) $^+$, 97.98%. Yield: 95%.

25 [0267] **5-(Pyridin-4-yl)-1-(3-(trifluoromethyl) phenyl)-1H-pyrazole-3-carboxylic acid (F-4b):** $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 8.58 (d, $J = 6.00$ Hz, 2H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.79 (s, 1H), 7.69 (m, 1H), 7.62 (d, $J = 8.0$ Hz, 1H), 7.31 (s, 1H), 7.26 (m, 2H). LCMS: 334.13 ($\text{M}+\text{H}$) $^+$, 98.62%. Yield: 94%.

30 [0268] **1-(3, 4-Difluorophenyl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylic acid (F-4c):** $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 13.17 (br s, 1H), 8.57 (d, $J = 5.60$ Hz, 2H), 7.69 (m, 1H), 7.54 (m, 1H), 7.22 (m, 4H). MS: 302.18 ($\text{M}+\text{H}$) $^+$. Yield: 78%.

[0269] **1-(2, 4-Difluorophenyl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylic acid (F-4d):** ¹H-NMR (400 MHz, DMSO-d₆): δ 13.20 (br s, 1H), 8.56 (d, *J*= 5.60 Hz, 2H), 7.80 (m, 1H), 7.51 (m, 1H), 7.32 (m, 2H), 7.25 (m, 2H). LCMS: 301.80 (M+H)⁺, 98.31%. Yield: 85%.

[0270] **1-(Benzo[d][1,3]dioxol-5-yl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylic acid (F-4e):** ¹H-NMR (400 MHz, DMSO-d₆): δ 13.12 (br s, 1H), 8.56 (m, 2H), 7.25-7.27 (m, 3H), 7.04 (m, 1H), 6.97 (d, *J*= 8.0 Hz, 1H), 6.79-6.81 (m, 1H) and 6.14 (s, 2H). LCMS: 310.10 (M+H)⁺, 99.56%. Yield: 82%.

[0271] **1-(3,5-Bis(trifluoromethyl)phenyl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylic acid (F-4f):** ¹H-NMR (400 MHz, DMSO-d₆): δ 13.17 (br s, 1H), 8.59 (d, *J*= 6.0 Hz, 2H), 8.26 (s, 1H), 8.07 (s, 2H), 7.32 (m, 3H). LCMS: 402.15 (M+H)⁺, 91.73%. Yield: 94%.

[0272] **1-(3-Fluoro-4-(trifluoromethyl) phenyl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylic acid (F-4g):** ¹H-NMR (400 MHz, DMSO-d₆): δ 8.60 (d, *J*= 5.6 Hz, 2H), 7.88 (m, 1H), 7.67 (s, 1H), 7.32 (m, 4H). LCMS: 352.17 (M+H)⁺, 98.60%. Yield: 92%.

[0273] **5-(Pyridin-4-yl)-1-(6-(trifluoromethyl) pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (F-4h):** ¹H-NMR (400 MHz, DMSO-d₆): δ 13.07 (br s, 1H), 8.81 (s, 1H), 8.60 (d, *J*= 6.0 Hz, 2H), 8.05 (m, 2H), 7.34 (m, 3H). LCMS: 335.13 (M+H)⁺, 97.97%. Yield: 75%.

[0274] **1-(Pyrazin-2-yl)-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylic acid (F-4i):** ¹H-NMR (400 MHz, DMSO-d₆): δ 13.40 (br s, 1H), 9.15 (s, 1H), 8.75 (d, *J*= 6.4 Hz, 1H), 8.56 (m, 2H), 8.43 (s, 1H), 7.33 (s, 3H). LCMS: 268.17 (M+H)⁺, 99.0%. Yield: 74%.

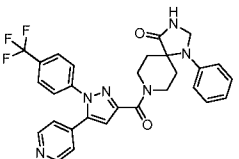
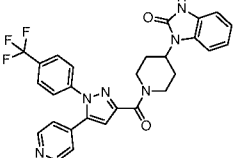
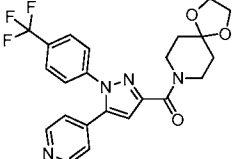
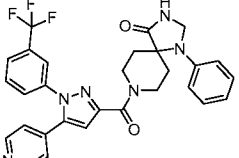
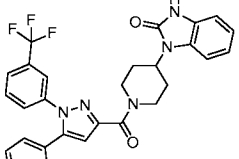
[0275] **1-Phenyl-5-(pyridin-4-yl)-1H-pyrazole-3-carboxylic acid (F-4j):** ¹H-NMR (400 MHz, DMSO-d₆): δ 13.11 (br s, 1H), 8.55 (d, *J*= 5.60 Hz, 2H), 7.50 (m, 3H), 7.38 (m, 2H), 7.31 (s, 1H) and 7.23 (d, *J*= 6.0 Hz, 2H). Yield: 61%.

[0276] **General procedure for the preparation of final compounds (F-5):** To an ice-cold solution of carboxylic acids **F-4(a-j)** (1.0 eq), in DMF (2.0 mL) was added DIPEA (3.0 eq) and HATU (1.50 eq). The resulting mixture was stirred under nitrogen atmosphere at 0°C for 15 min followed by addition of the respective amine (1.20 eq). The reaction mixture was then stirred at room temperature for 16 h. After the completion of the reaction (TLC monitoring), the solution was diluted with ice cold water (30 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified via prep-

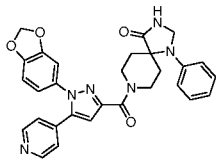
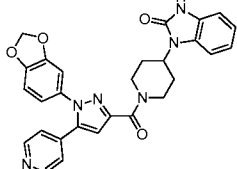
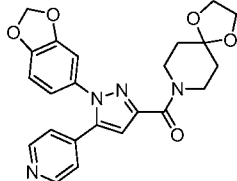
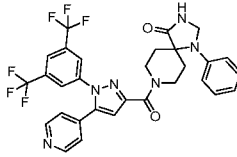
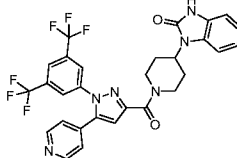
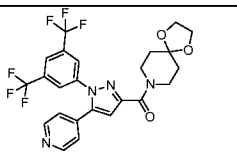
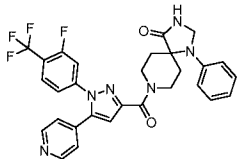
TLC using the solvent systems 3-5%MeOH-DCM. The final step was performed on 75-100 mg scale.

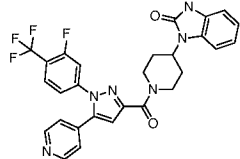
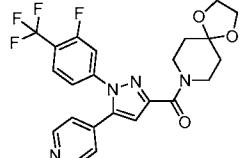
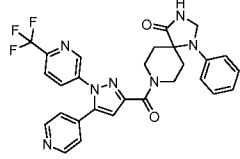
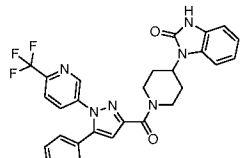
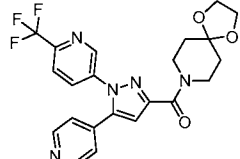
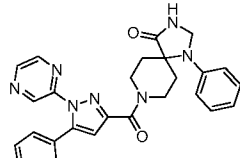
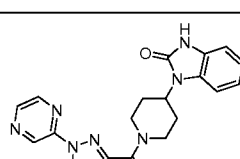
[0277] Amines used in the preparation of the final compounds illustrated in Table 6 according to Scheme F are commercially available or can be synthesized by one of ordinary skill.

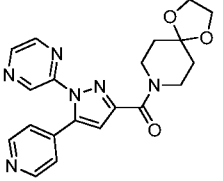
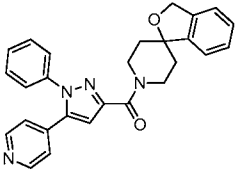
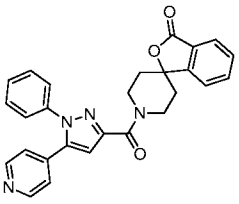
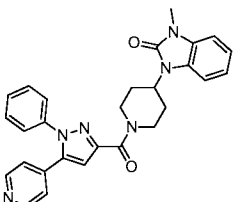
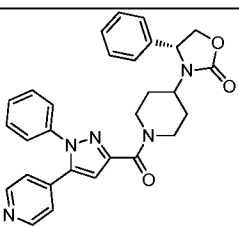
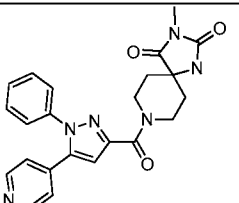
Table 6. Additional compounds of the disclosure prepared according the general method disclosed in Scheme F.

Cpd. ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
143		43%	547.16 (M+H) ⁺ , 96.32%	δ 8.84 (br s, 1H), 8.61 (d, J= 6.0 Hz, 2H), 7.85 (d, J= 8.40 Hz, 2H), 7.59 (d, J= 8.0 Hz, 2H), 7.31 (d, J= 6.0 Hz, 2H), 7.19-7.23 (m, 3H), 6.73-6.78 (m, 3H), 4.61 (s, 2H), 4.51 (t, J= 13.20 Hz, 2H), 3.88 (t, J= 13.20 Hz, 1H), 3.54 (t, J= 12.40 Hz, 1H), 2.60 (m, 2H) and 1.71-1.80 (m, 2H)
144		58%	533.16 (M+H) ⁺ , 95.43%	δ 10.86 (br s, 1H), 8.61 (d, J= 6.0 Hz, 2H), 7.87 (d, J= 8.80 Hz, 2H), 7.61 (d, J= 8.40 Hz, 2H), 7.32 (d, J= 5.60 Hz, 2H), 7.23 (m, 2H), 6.97 (m, 3H), 4.74 (t, J= 15.20 Hz, 2H), 4.51 (m, 1H), 3.30 (m, 1H), 2.95 (m, 1H), 2.26-2.37 (m, 2H) and 1.76-1.85 (m, 2H)
145		60%	459.09 (M+H) ⁺ , 95.06%	δ 8.60 (d, J= 6.0 Hz, 2H), 7.87 (d, J= 8.40 Hz, 2H), 7.60 (d, J= 8.40 Hz, 2H), 7.30 (d, J= 6.0 Hz, 2H), 7.18 (s, 1H), 3.92 (br s, 6H), 3.71 (m, 2H), and 1.68 (t, J= 5.20 Hz, 4H)
146		49%	547.23 (M+H) ⁺ , 92.28%	δ 8.83 (br s, 1H), 8.59 (d, J= 5.60 Hz, 2H), 7.82 (d, J= 7.20 Hz, 1H), 7.75 (s, 1H), 7.63-7.70 (m, 2H), 7.29 (d, J= 6.0 Hz, 2H), 7.19-7.22 (m, 3H), 6.73-6.78 (m, 3H), 4.61 (s, 2H), 4.51 (m, 2H), 3.86 (t, J= 6.0 Hz, 1H), 3.53 (t, J= 13.20 Hz, 1H), 2.59 (m, 2H) and 1.70-1.80 (m, 2H)
147		57%	533.16 (M+H) ⁺ , 99.17%	δ 10.86 (br s, 1H), 8.59 (d, J= 6.0 Hz, 2H), 7.84 (d, J= 7.20 Hz, 1H), 7.76 (s, 1H), 7.66-7.71 (m, 2H), 7.30 (d, J= 6.0 Hz, 2H), 7.23-7.24 (m, 2H), 6.97-6.99 (m, 3H), 4.72 (m, 2H), 4.50 (m, 1H), 3.36 (m, 1H), 2.95 (m, 1H), 2.29-2.36 (m, 2H) and 1.76-1.85 (m, 2H)

Cpd. ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
148		58%	459.11 (M+H) ⁺ , 97.12%	δ 8.59 (d, <i>J</i> = 6.0 Hz, 2H), 7.85 (d, <i>J</i> = 7.60 Hz, 1H), 7.75 (s, 1H), 7.64-7.73 (m, 2H), 7.28 (d, <i>J</i> = 6.0 Hz, 2H), 7.18 (s, 1H), 3.92 (br s, 6H), 3.71 (m, 2H), and 1.68 (t, <i>J</i> = 5.20 Hz, 4H)
149		35%	515.34 (M+H) ⁺ , 95.94%	CDCl ₃ : δ 8.59 (d, <i>J</i> = 5.60 Hz, 2H), 7.12-7.28 (m, 6H), 7.06 (s, 1H), 6.97 (m, 1H), 6.90 (m, 1H), 6.82 (d, <i>J</i> = 8.0 Hz, 2H), 6.13 (br s, 1H), 4.76-4.78 (m, 4H), 4.03 (m, 1H), 3.68 (m, 1H), 2.63-2.72 (m, 2H) and 1.80-2.0 (m, 2H)
150		36%	501.30 (M+H) ⁺ , 99.02%	δ 10.86 (br s, 1H), 8.59 (d, <i>J</i> = 6.0 Hz, 2H), 7.70-7.72 (m, 1H), 7.52-7.59 (m, 1H), 7.29 (d, <i>J</i> = 6.0 Hz, 2H), 7.22-7.24 (m, 3H), 6.97-7.0 (m, 3H), 4.69-4.79 (m, 2H), 4.50 (t, <i>J</i> = 12.0 Hz, 1H), 3.27 (m, 1H), 2.94 (t, <i>J</i> = 12.0 Hz, 1H), 2.28-2.36 (m, 2H) and 1.76-1.84 (m, 2H)
151		78%	427.32 (M+H) ⁺ , 98.52%	CDCl ₃ : δ 8.62 (d, <i>J</i> = 6.0 Hz, 2H), 7.18-7.21 (m, 2H), 7.28 (d, <i>J</i> = 6.0 Hz, 2H), 7.13 (m, 2H), 7.02 (s, 1H), 6.96-6.98 (m, 1H), 4.09 (t, <i>J</i> = 6.0 Hz, 2H), 4.0 (m, 4H), 3.89 (t, <i>J</i> = 6.80 Hz, 2H) and 1.81 (m, 4H)
152		56%	515.16 (M+H) ⁺ , 94.94%	δ 8.83 (br s, 1H), 8.58 (d, <i>J</i> = 5.60 Hz, 2H), 7.77-7.83 (m, 1H), 7.46-7.53 (m, 1H), 7.18-7.33 (m, 6H), 6.73-6.76 (m, 3H), 4.61 (s, 2H), 4.49 (m, 2H), 3.85 (m, 1H), 3.52 (m, 1H), 2.59 (m, 2H) and 1.69-1.79 (m, 2H)
153		59%	501.12 (M+H) ⁺ , 98.92%	δ 10.86 (br s, 1H), 8.58 (d, <i>J</i> = 5.60 Hz, 2H), 7.80-8.6 (m, 1H), 7.52 (t, <i>J</i> = 8.40 Hz, 1H), 7.23-7.34 (m, 5H), 6.96 (m, 3H), 4.73 (m, 2H), 4.49 (m, 1H), 3.36 (m, 1H), 2.94 (m, 1H), 2.28-2.37 (m, 2H) and 1.75-1.84 (m, 2H)
154		46%	427.07 (M+H) ⁺ , 97.93%	δ 8.57 (d, <i>J</i> = 6.0 Hz, 2H), 7.86-7.84 (m, 1H), 7.52 (d, <i>J</i> = 8.0 Hz, 1H), 7.33 (d, <i>J</i> = 8.40 Hz, 1H), 7.23-7.26 (m, 3H), 3.88-3.91 (m, 6H), 3.71 (m, 2H) and 1.67 (m, 4H)

Cpd. ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
155		47%	523.29 (M+H) ⁺ , 94.27%	δ 8.83 (br s, 1H), 8.57 (d, J= 5.60 Hz, 2H), 7.27 (d, J= 5.60 Hz, 2H), 7.18-7.23 (m, 3H), 7.05 (d, J= 2.0 Hz, 1H), 6.95 (d, J= 8.0 Hz, 1H), 6.73-6.77 (m, 4H), 6.11 (s, 2H), 4.58-4.61 (m, 3H), 4.49 (m, 1H), 3.84 (m, 1H), 3.52 (m, 1H), 2.50 (m, 2H) and 1.70-1.78 (m, 2H)
156		39%	507.02 (M-H) ⁺ , 99.10%	δ 10.86 (br s, 1H), 8.58 (d, J= 6.0 Hz, 2H), 7.28 (d, J= 6.0 Hz, 2H), 7.22 (m, 1H), 7.18 (s, 1H), 7.08 (d, J= 1.60 Hz, 1H), 6.95-7.0 (m, 4H), 6.80 (dd, J= 2.0 and 8.40 Hz respectively, 1H), 6.12 (s, 2H), 4.85 (d, J= 13.20 Hz, 1H), 4.72 (d, J= 11.20 Hz, 1H), 4.49 (t, J= 12.80 Hz, 1H), 3.26 (m, 1H), 2.93 (m, 1H), 2.27-2.36 (m, 2H) and 1.76-1.83 (m, 2H)
157		38%	435.06 (M+H) ⁺ , 98.73%	δ 8.57 (d, J= 6.0 Hz, 2H), 7.26 (d, J= 6.40 Hz, 2H), 7.13 (s, 1H), 7.06 (d, J= 2.0 Hz, 1H), 6.98 (d, J= 8.40 Hz, 1H), 6.79 (dd, J= 2.0 and 8.0 Hz respectively, 1H), 6.13 (s, 2H), 3.92-3.96 (m, 6H), 3.70 (m, 2H) and 1.67 (m, 4H)
158		43%	615.16 (M+H) ⁺ , 96.93%	δ 8.84 (br s, 1H), 8.61 (d, J= 6.0 Hz, 2H), 8.20 (s, 1H), 8.04 (m, 2H), 7.34 (d, J= 5.60 Hz, 2H), 7.20-7.25 (m, 3H), 6.73-6.79 (m, 3H), 4.62 (s, 2H), 4.40-4.50 (m, 2H), 3.86 (m, 1H), 3.54 (m, 1H), 2.56 (m, 2H) and 1.70-1.80 (m, 2H)
159		70%	601.12 (M+H) ⁺ , 99.75%	δ 10.86 (br s, 1H), 8.61 (d, J= 6.0 Hz, 2H), 8.23 (s, 1H), 8.07 (m, 2H), 7.35 (d, J= 6.0 Hz, 2H), 7.24 (m, 2H), 6.97-6.99 (m, 3H), 4.64-4.73 (m, 2H), 4.51 (t, J= 12.40 Hz, 1H), 3.36 (m, 1H), 2.97 (t, J= 12.0 Hz, 1H), 2.33 (t, J= 13.60 Hz, 2H) and 1.76-1.85 (m, 2H)
160		61%	527.07 (M+H) ⁺ , 95.45%	δ 8.61 (d, J= 6.0 Hz, 2H), 8.23 (s, 1H), 8.06 (s, 2H), 7.33 (d, J= 6.0 Hz, 2H), 7.20 (s, 1H), 3.88-3.92 (m, 6H), 3.72 (m, 2H) and 1.68 (m, 4H)
161		37%	565.17 (M+H) ⁺ , 96.70%	δ 8.84 (br s, 1H), 8.63 (d, J= 6.0 Hz, 2H), 7.86 (t, J= 8.0 Hz, 1H), 7.69 (d, J= 11.60 Hz, 1H), 7.30-7.36 (m, 3H), 7.20-7.24 (m, 3H), 6.73-6.78 (m, 3H), 4.62 (s, 2H), 4.48-4.50 (m, 2H), 3.87 (t, J= 11.20 Hz, 1H), 3.54 (t, J= 11.60 Hz, 1H), 2.56 (m, 2H) and 1.71-1.86 (m, 2H)

Cpd. ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
162		51%	551.12 (M+H) ⁺ , 98.94%	δ 10.86 (br s, 1H), 8.63 (d, <i>J</i> = 5.60 Hz, 2H), 7.89 (t, <i>J</i> = 8.0 Hz, 1H), 7.72 (d, <i>J</i> = 11.20 Hz, 1H), 7.35 (m, 3H), 7.24 (m, 2H), 6.97-6.99 (m, 3H), 4.72 (m, 2H), 4.51 (t, <i>J</i> = 12.40 Hz, 1H), 3.35 (m, 1H), 2.96 (t, <i>J</i> = 13.20 Hz, 1H), 2.29-2.40 (m, 2H) and 1.76-1.85 (m, 2H)
163		56%	477.11 (M+H) ⁺ , 96.46%	δ 8.62 (d, <i>J</i> = 4.80 Hz, 2H), 7.88 (t, <i>J</i> = 8.0 Hz, 1H), 7.71 (d, <i>J</i> = 11.20 Hz, 1H), 7.33 (m, 3H), 7.19 (s, 1H), 3.92 (m, 6H), 3.71 (m, 2H) and 1.69 (m, 4H)
164		40%	548.20 (M+H) ⁺ , 96.66%	δ 8.84 (m, 2H), 8.64 (d, <i>J</i> = 6.0 Hz, 2H), 8.03 (s, 2H), 7.38 (d, <i>J</i> = 6.0 Hz, 2H), 7.28 (s, 1H), 7.21 (t, <i>J</i> = 8.0 Hz, 2H), 6.73-6.78 (m, 3H), 4.62 (s, 2H), 4.49-4.51 (m, 2H), 3.88 (t, <i>J</i> = 11.60 Hz, 1H), 3.54 (t, <i>J</i> = 11.60 Hz, 1H), 2.56 (m, 2H) and 1.72-1.80 (m, 2H)
165		44%	534.13 (M+H) ⁺ , 99.22%	δ 10.86 (br s, 1H), 8.40 (s, 1H), 8.64 (d, <i>J</i> = 6.0 Hz, 2H), 8.03-8.09 (m, 2H), 7.38 (d, <i>J</i> = 6.0 Hz, 2H), 7.28 (s, 1H), 7.24 (m, 1H), 6.97 (m, 3H), 4.72 (m, 2H), 4.51 (t, <i>J</i> = 12.0 Hz, 1H), 3.35 (m, 1H), 2.97 (t, <i>J</i> = 12.0 Hz, 1H), 2.29-2.38 (m, 2H) and 1.77-1.86 (m, 2H)
166		41%	460.15 (M+H) ⁺ , 98.30%	δ 8.82 (br s, 1H), 8.63 (d, <i>J</i> = 5.20 Hz, 2H), 8.05 (s, 2H), 7.36 (d, <i>J</i> = 6.0 Hz, 2H), 7.22 (s, 1H), 3.92 (m, 6H), 3.72 (m, 2H) and 1.69 (m, 4H)
167		28%	481.28 (M+H) ⁺ , 97.91%	δ 9.12 (s, 1H), 8.85 (s, 1H), 8.69 (d, <i>J</i> = 2.40 Hz, 1H), 8.59 (d, <i>J</i> = 5.60 Hz, 2H), 8.39 (s, 1H), 7.38 (d, <i>J</i> = 6.0 Hz, 2H), 7.20-7.24 (m, 3H), 6.73-6.80 (m, 3H), 4.63 (s, 2H), 4.45-4.51 (m, 2H), 3.89 (t, <i>J</i> = 12.40 Hz, 1H), 3.54 (t, <i>J</i> = 12.0 Hz, 1H), 2.62 (m, 1H), 2.44 (m, 1H) and 1.74-1.81 (m, 2H)
168		43%	467.24 (M+H) ⁺ , 99.30%	δ 10.87 (br s, 1H), 9.17 (s, 1H), 8.72 (s, 1H), 8.59 (d, <i>J</i> = 5.20 Hz, 2H), 8.41 (s, 1H), 7.38 (d, <i>J</i> = 5.20 Hz, 2H), 7.24-7.26 (m, 2H), 6.97 (m, 3H), 4.73 (d, <i>J</i> = 13.20 Hz, 2H), 4.55 (m, 1H), 3.39 (m, 1H), 2.97 (m, 1H), 2.37 (m, 2H) and 1.78-1.85 (m, 2H)

Cpd. ID	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
169		37%	393.34 (M+H) ⁺ , 99.28%	δ 9.15 (s, 1H), 8.72 (m, 1H), 8.58 (d, <i>J</i> = 6.0 Hz, 2H), 8.41 (s, 1H), 7.36 (d, <i>J</i> = 6.0 Hz, 2H), 7.18 (s, 1H), 3.93 (m, 6H), 3.73 (m, 2H) and 1.71 (m, 4H)
170		48%	437.24 (M+H) ⁺ , 96.34%	δ 8.56 (m, 2H), 7.47 (m, 3H), 7.38 (m, 2H), 7.19-7.28 (m, 7H), 5.03 (s, 2H), 4.56-4.67 (m, 2H), 3.49 (t, <i>J</i> = 12.0 Hz, 1H), 3.12 (t, <i>J</i> = 12.0 Hz, 1H), 1.89-1.96 (m, 2H) and 1.67-1.76 (m, 2H)
171		51%	451.15 (M+H) ⁺ , 95.28%	δ 8.57 (d, <i>J</i> = 6.0 Hz, 2H), 7.76-7.86 (m, 3H), 7.61 (t, <i>J</i> = 8.40 Hz, 1H), 7.48-7.50 (m, 3H), 7.37-7.39 (m, 2H), 7.22-7.25 (m, 3H), 4.85 (d, <i>J</i> = 10.40 Hz, 1H), 4.70 (m, 1H), 3.53 (m, 1H), 3.16 (t, <i>J</i> = 10.80 Hz, 1H), 2.25-2.32 (m, 2H) and 1.71-1.79 (m, 2H)
172		52%	479.12 (M+H) ⁺ , 98.91%	δ 8.56 (d, <i>J</i> = 6.0 Hz, 2H), 7.47-7.50 (m, 3H), 7.37-7.39 (m, 2H), 7.28-7.31 (m, 1H), 7.21-7.25 (m, 3H), 7.13-7.15 (m, 1H), 7.02-7.07 (m, 2H), 4.84 (d, <i>J</i> = 13.20 Hz, 1H), 4.73 (d, <i>J</i> = 12.40 Hz, 1H), 4.53 (m, 1H), 3.70 (s, 3H), 3.36 (m, 1H), 2.95 (m, 1H), 2.26-2.40 (m, 2H) and 1.77-1.85 (m, 2H)
173		68%	494.39 (M+H) ⁺ , 97.19%	δ 8.54 (d, <i>J</i> = 4.80 Hz, 2H), 7.48 (m, 3H), 7.31-7.39 (m, 7H), 7.21 (m, 2H), 7.04-7.11 (m, 1H), 5.01 (t, <i>J</i> = 8.0 Hz, 1H), 4.41-4.71 (m, 3H), 3.98 (m, 1H), 3.59 (m, 1H), 3.03 (m, 1H), 2.68 (m, 1H), 1.90 (m, 1H), 1.56-1.76 (m, 2H) and 1.23-1.27 (m, 1H)
174		59%	431.10 (M+H) ⁺ , 99.54%	δ 8.91 (br s, 1H), 8.56 (d, <i>J</i> = 5.60 Hz, 2H), 7.48-7.49 (m, 3H), 7.36-7.38 (m, 2H), 7.19-7.24 (m, 3H), 4.47 (d, <i>J</i> = 13.60 Hz, 1H), 4.33 (d, <i>J</i> = 12.80 Hz, 1H), 3.63 (t, <i>J</i> = 12.0 Hz, 1H), 3.25 (m, 1H), 2.84 (s, 3H), 1.81-1.98 (m, 2H) and 1.66 (m, 2H)

Experimental procedures:

[0278] Yields reported herein refer to purified products (unless specified) and are not optimised. Analytical TLC was performed on Merck silica gel 60 F₂₅₄ aluminium-backed plates. Compounds were visualised by UV light and/or stained with either I₂ or potassium permanganate solution followed by heating. Flash column chromatography was performed on silica gel. ¹H-NMR spectra were recorded on a Bruker Avance-400 MHz spectrometer with a

BBO (Broad Band Observe) and BBFO (Broad Band Fluorine Observe) probe. Chemical shifts (δ) are expressed in parts per million (ppm) downfield by reference to tetramethylsilane as the internal standard. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet) and br s (broad singlet). Coupling constants (J) are given in hertz (Hz). LCMS analyses were performed either on an Acquity BEH C-18 column (2.10 $\times$ 100 mm, 1.70 μ m) or Acquity HSS-T3 (2.1 $\times$ 100 mm, 1.8 μ m) using the Electrospray Ionisation (ESI) technique. The following solvents, reagents or scientific terminology may be referred to by their abbreviations:

	TLC	Thin Layer Chromatography
10	CDCl_3	Deuterated chloroform
	DMF	N,N-Dimethylformamide
	TEA/ Et_3N	Triethylamine
	DIPEA	Diisopropylethylamine (Hunig's base)
	NBS	N-Bromosuccinimide
15	LiHMDS	Lithium bis(trimethylsilyl)amide
	HATU	N,N,N,N-Tetramethyl-O-(7-azabenzotriazol-1-yl)uroniumhexafluorophosphate
	AcOH	Acetic acid
	TFA	Trifluoroacetic acid
20	mL	milliliters
	mmol	millimoles
	h	hour or hours
	min	minute or minutes
	g	grams
25	mg	milligrams
	μl	Microlitres
	eq	Equivalents
	rt or RT	Room temperature, ambient, about 27°C
30	MS	Mass spectrometry

[0279] The final compounds were purified via RP prep-HPLC employing either of the 2 methods mentioned below.

1. Column : SUNFIRE C 18 (19x250)mm, 5 μ particle size, Mobile phase: **A** 0.1% TFA in Water, **B** ACN

Flow mode :

Time	% A	% B
1.00	50	50
15.00	36	74
15.10	10	90
17.00	10	90
17.10	50	50
20.00	50	50

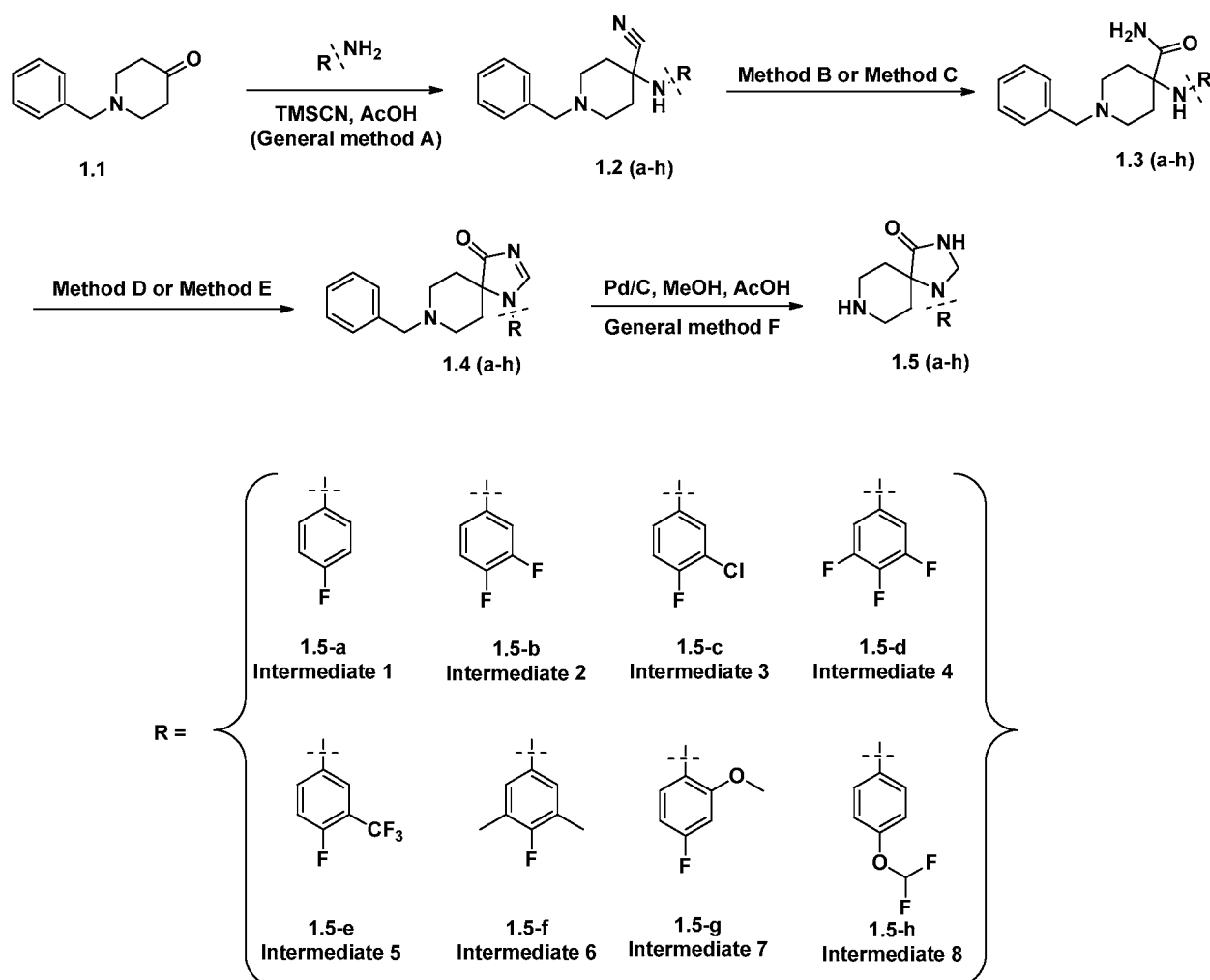
Or

- 5 2. Column : X TERRA C 18 (19x250)mm, 5 μ particle size, Mobile phase: **A** 5mM Ammonium Acetate n water, **B** ACN

Flow mode :

Time	% A	%B
1.00	60	40
10.00	35	65
11.00	35	65
11.10	60	40
14.00	60	40

Scheme 1



Reference: WO 2005/040166 and Tett. Lett; 2007, 55, 501-502

5 General procedure for the preparation of 2 (a-h):

[0280] **General method A:** To an ice-cold solution of 1-benzylpiperidin-4-one **1.1** (5.0 - 7.0 g, 1.0 eq) in acetic acid was added respective amines (1.1 eq) and trimethylsilyl cyanide (1.5 eq). The resulting reaction mass was stirred at RT for 18 h. After completion of the reaction (TLC monitoring), the reaction mass was cooled to 0°C and the pH adjusted to ~10 using 5.0 N sodium hydroxide solution. The aqueous part was extracted with DCM (3 x 250 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was triturated with diethyl ether to get the desired product **1.2 (a-h)** as off white solid.

[0281] **1-Benzyl-4-((4-fluorophenyl)amino)piperidine-4-carbonitrile (1.2-a):** ^1H -NMR (400 MHz, CDCl_3): δ 7.35-7.38 (m, 5H), 6.90-6.95 (m, 4H), 3.54 (s, 2H), 3.48 (br s, 1H), 2.80-2.84 (m, 2H), 2.38-2.41 (m, 2H), 2.22-2.24 (m, 2H) and 1.89-1.94 (m, 2H). LC-MS: 310.23 ($\text{M}+\text{H}$) $^+$, 95.66%. Yield: 58%.

5 [0282] **1-Benzyl-4-((3,4-difluorophenyl)amino)piperidine-4-carbonitrile (1.2-b):** ^1H -NMR (400 MHz, CDCl_3): δ 7.27-7.31 (m, 5H), 7.03-7.08 (m, 1H), 6.75-6.79 (m, 1H), 6.60-6.63 (m, 1H), 3.59 (br s, 1H), 3.55 (s, 2H), 2.80-2.84 (m, 2H), 2.41-2.47 (m, 2H), 2.26-2.39 (m, 2H) and 1.87-1.89 (m, 2H). LC-MS: 328.42 ($\text{M}+\text{H}$) $^+$, 94.27%. Yield: 40%.

[0283] **1-Benzyl-4-((3-chloro-4-fluorophenyl)amino)piperidine-4-carbonitrile (1.2-c):**
10 ^1H -NMR (400 MHz, CDCl_3): δ 7.28-7.34 (m, 5H), 7.01-7.05 (m, 1H), 6.95-6.97 (m, 1H), 6.79-6.82 (m, 1H), 3.57 (s, 3H), 2.80-2.83 (m, 2H), 2.41-2.46 (m, 2H), 2.24-2.27 (m, 2H) and 1.87-1.92 (m, 2H). LC-MS: 344.28 ($\text{M}+\text{H}$) $^+$, 99.52%. Yield: 32%.

[0284] **1-Benzyl-4-((3,4,5-trifluorophenyl)amino)piperidine-4-carbonitrile (1.2-d):** ^1H -NMR (400 MHz, CDCl_3): δ 7.31-7.34 (m, 5H), 6.48-6.51 (m, 2H), 3.73 (s, 1H), 3.56 (s, 2H),
15 2.75-2.80 (m, 2H), 2.45-2.48 (m, 2H), 2.29-2.32 (m, 2H) and 1.86-1.88 (m, 2H). MS: 346.00 ($\text{M}+\text{H}$) $^+$, 99.52%. Yield: 25%.

[0285] **1-Benzyl-4-((4-fluoro-3-(trifluoromethyl)phenyl)amino)piperidine-4-carbonitrile (1.2-e):** ^1H -NMR (400 MHz, CDCl_3): δ 7.29-7.31 (m, 5H), 7.10-7.11 (m, 3H), 3.69 (s, 1H), 3.56 (s, 2H), 2.82-2.85 (m, 2H), 2.45-2.48 (m, 2H), 2.19-2.22 (m, 2H) and 1.92-
20 1.92 (m, 2H). LC-MS: 378.33 ($\text{M}+\text{H}$) $^+$, 94.03%. Yield: 45%.

[0286] **1-Benzyl-4-((4-fluoro-3,5-dimethylphenyl)amino)piperidine-4-carbonitrile (1.2-f):** ^1H -NMR (400 MHz, CDCl_3): δ 7.26-7.31 (m, 5H), 6.55-6.57 (m, 1H), 6.37-6.38 (m, 1H), 3.60 (s, 1H), 3.53 (s, 2H), 2.76-2.81 (m, 2H), 2.45-2.50 (m, 2H), 2.28-2.32 (m, 2H), 2.09 (m, 6H), and 1.88-1.93 (m, 2H). MS: 338.33 ($\text{M}+\text{H}$) $^+$, Yield: 60%.

25 [0287] **1-Benzyl-4-((4-fluoro-2-methoxyphenyl)amino)piperidine-4-carbonitrile (1.2-g):** ^1H -NMR (400 MHz, CDCl_3): δ 7.31-7.35 (m, 5H), 6.99-7.03 (m, 1H), 6.58-6.62 (m, 2H), 4.09 (s, 1H), 3.82 (s, 3H), 3.55 (s, 2H), 2.73-2.76 (m, 2H), 2.44-2.47 (m, 2H), 2.27-2.31 (m, 2H) and 1.90-1.93 (m, 2H). MS: 340.25 ($\text{M}+\text{H}$) $^+$. Yield: 60%.

[0288] **1-Benzyl-4-((4-(difluoromethoxy)phenyl)amino)piperidine-4-carbonitrile (1.2-h):** ^1H -NMR (400 MHz, CDCl_3): δ 7.25-7.34 (m, 5H), 7.02 (d, $J=8.8$ Hz, 2H), 6.89 (d, $J=8.8$

30

Hz, 2H), 3.61 (br s, 1H), 3.49 (s, 3H), 2.80-2.83 (m, 2H), 2.43-2.47 (m, 2H), 2.17-2.22 (m, 2H) and 1.88-1.94 (m, 2H). LC-MS: 358.0 (M+H)⁺, 96.98%. Yield: 52.23%.

[0289] General procedure for the preparation of 1.3 (a-h): General Method B: An ice cold solution of **1.2 (a-g)** (3.0 - 4.0 g, 1.0 eq) in 90% aqueous sulphuric acid was stirred at 0°C for 30.0 min, then warm up to RT and stirred for 16 h. After completion of the reaction (TLC monitoring), the reaction mass was cooled to 0°C and the pH adjusted to ~10 using 5.0 N sodium hydroxide solution. The aqueous part was extracted with DCM. The combined organics were dried over anhydrous sodium sulphate, filtered and concentrated. The crude was triturated with diethyl ether to get the desired products **1.3 (a-g)** as off-white solids.

[0290] General Method C: To an ice-cold solution of 1-benzyl-4-((4-(difluoromethoxy)phenyl)amino)piperidine-4-carbonitrile **1.2-h** (2.5 g, 7.0 mmol, 1.0 eq) in DMSO was added H₂O₂ (30% aqueous solution, 1.5 eq) and K₂CO₃ (0.2 eq). The resulting reaction mixture was stirred at RT for 30.0 min. After completion of reaction (TLC monitoring), H₂O was added and extracted with DCM (3 times). The combined organics was dried over anhydrous sodium sulphate, filtered and concentrated. The crude was triturated with diethyl ether to get the desired product **1.3-h** as an off-white solid.

[0291] 1-Benzyl-4-(4-fluorophenylamino)piperidine-4-carboxamide (1.3-a): ¹H-NMR (400 MHz, CDCl₃): δ 7.23-7.25 (m, 5H), 6.85-6.87 (m, 3H), 6.54-6.55 (m, 2H), 5.47 (br s, 1H), 3.93 (s, 1H), 3.48 (s, 2H), 2.72-2.74 (m, 2H), 2.28-2.29 (m, 2H), 2.04-2.07 (m, 2H) and 1.86-1.89 (m, 2H). LCMS: 328.22 (M+H)⁺, 98.42%. Yield: 84%.

[0292] 1-Benzyl-4-((3,4-difluorophenyl)amino)piperidine-4-carboxamide (1.3-b): ¹H-NMR (400 MHz, CDCl₃): δ 7.31-7.33 (m, 5H), 6.89-6.92 (m, 1H), 6.79 (br s, 1H), 6.45-6.48 (m, 1H), 6.29-6.31 (m, 1H), 5.51 (br s, 1H), 3.98 (s, 1H), 3.49 (s, 2H), 2.74-2.75 (m, 2H), 2.28-2.31 (m, 2H), 2.04-2.07 (m, 2H) and 1.85-1.87 (m, 2H). LCMS: 346.14 (M+H)⁺, 94.52%. Yield: 85%.

[0293] 1-Benzyl-4-((3-chloro-4-fluorophenyl)amino)piperidine-4-carboxamide (1.3-c): ¹H-NMR (400 MHz, CDCl₃): δ 7.28-7.32 (m, 6H), 7.07-7.00 (m, 2H), 6.68 (br s, 1H), 6.50 (br s, 1H), 5.75 (br s, 1H), 3.42 (s, 2H), 2.50-2.52 (m, 2H), 2.22-2.24 (m, 2H), 1.98-2.00 (m, 2H) and 1.76-1.79 (m, 2H). LCMS: 362.05 (M+H)⁺, 90.00%. Yield: 79%.

[0294] 1-Benzyl-4-((3,4,5-trifluorophenyl)amino)piperidine-4-carboxamide (1.3-d): ¹H-NMR (400 MHz, CDCl₃): δ 7.28-7.34 (m, 6H), 7.11 (br s, 1H), 6.31-6.35 (m, 2H), 6.11

(br s, 1H), 3.48 (s, 2H), 2.50-2.53 (m, 2H), 2.22-2.25 (m, 2H), 1.95-1.97 (m, 2H) and 1.77-1.80 (m, 2H). LCMS: 364.00 (M+H)⁺, 91.64%. Yield: 40%.

[0295] 1-Benzyl-4-((4-fluoro-3-(trifluoromethyl)phenyl)amino)piperidine-4-carboxamide (1.3-e): ¹H-NMR (400 MHz, CDCl₃): δ 7.28-7.35 (m, 5H), 7.17-7.22 (m, 2H), 7.08 (br s, 1H), 6.94-6.95 (m, 1H), 6.73-6.75 (m, 1H), 6.00 (br s, 1H), 3.42 (s, 2H), 2.49-2.53 (m, 2H), 2.23-2.28 (m, 2H), 1.97-2.02 (m, 2H) and 1.76-1.80 (m, 2H). LCMS: 396.20 (M+H)⁺, 95.56%. Yield: 45%.

[0296] 1-Benzyl-4-((4-fluoro-3,5-dimethylphenyl)amino)piperidine-4-carboxamide (1.3-f): ¹H-NMR (400 MHz, CDCl₃): δ 7.28-7.34 (m, 6H), 7.15 (br s, 1H), 7.01 (s, 1H), 6.21-6.27 (m, 2H), 3.48 (s, 2H), 2.50-2.51 (m, 2H), 2.22-2.24 (m, 2H), 2.06 (d, J=6.0 Hz, 6H), 1.96-1.99 (m, 2H) and 1.77-1.81 (m, 2H). MS: 356.37 (M+H)⁺. Yield: 56.6%.

[0297] 1-Benzyl-4-((4-fluoro-2-methoxyphenyl)amino)piperidine-4-carboxamide (1.3-g): ¹H-NMR (400 MHz, CDCl₃): δ 7.22-7.30 (m, 6H), 7.05 (br s, 1H), 6.80-6.83 (m, 1H), 6.54-6.58 (m, 1H), 6.25-6.28 (m, 1H), 4.55 (s, 1H), 3.82 (s, 3H), 3.33-3.38 (m, 2H), 2.54-2.56 (m, 2H), 1.94-2.08 (m, 4H) and 1.80-1.83 (m, 2H). LCMS: 358.40 (M+H)⁺, 99.78%. Yield: 61.38%.

[0298] 1-Benzyl-4-((4-(difluoromethoxy)phenyl)amino)piperidine-4-carboxamide (1.3-h): ¹H-NMR (400 MHz, CDCl₃): δ 7.21-7.29 (m, 6H), 7.02 (br s, 1H), 6.90-6.95 (m, 3H), 6.56 (d, J=8.8 Hz, 2H), 3.42 (s, 3H), 2.53-2.59 (m, 2H), 2.32-2.36 (m, 2H), 1.99-2.11 (m, 2H) and 1.82-1.90 (m, 2H). MS: 376.30 (M+H)⁺. Yield: 30%.

General procedure for the preparation of 1.4 (a-h):

[0299] General Method D: A solution of compounds **1.3 (a-c)** (2.0-4.0 g, 1.0 eq), in triethylorthoformate and AcOH (3:1) was irradiated by microwave in a sealed tube to 190°C for 2h. The reaction mixture was diluted with water and extracted with EtOAc. The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified over silica gel (100-200 M, 2-4% MeOH-DCM) to get the desired products **1.4 (a-c)** as off-white solids.

[0300] General Method E: To a solution of compounds **1.3 (a-h)** (1.0-2.5 g, 1.0 eq) in methanol was added DMF-DMA (3.0 eq). The resulting reaction mass was heated at 65°C for h. After completion of reaction (TLC monitoring), the solvent was evaporated to dryness. The

resulting crude residue was triturated with diethyl ether to get the desired product as an off-white solid product **1.4 (a-h)**.

[0301] **8-Benzyl-1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (1.4-a):** H-NMR (400 MHz, DMSO- d_6): δ 8.65 (s, 1H), 7.44-7.46 (m, 2H), 7.31-7.34 (m, 2H), 7.13-7.16 (m, 5H), 3.41 (s, 2H), 2.66-2.69 (m, 2H), 2.41-2.44 (m, 2H) and 1.75-1.78 (m, 4H). MS: 338.22 (M+H)⁺. Yield: 48% with **method D** and 89% with **method E**.

[0302] **8-Benzyl-1-(3,4-difluorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (4-b):** ¹H-NMR (400 MHz, DMSO- d_6): δ 8.69 (s, 1H), 7.66-7.71 (m, 1H), 7.56-7.61 (m, 1H), 7.19-7.30 (m, 6H), 3.47 (s, 2H), 2.72-2.78 (m, 2H), 2.43-2.46 (m, 2H) and 1.72-1.80 (m, 4H). LCMS: 356.40 (M+H)⁺, 87.67%. Yield: 22% with **method D** and 85% with **method E**.

[0303] **8-Benzyl-1-(3-chloro-4-fluorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (1.4-c):** LCMS: 372.40 (M+H)⁺, 75.07%. Yield: 20% with **method D**.

[0304] **8-Benzyl-1-(3,4,5-trifluorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (1.4-d):** ¹H-NMR (400 MHz, DMSO- d_6): δ 8.71 (s, 1H), 7.57-7.60 (m, 2H), 7.24-7.28 (m, 5H), 3.49 (s, 2H), 2.73-2.75 (m, 2H), 2.48-2.49 (m, 2H), 1.83-1.85 (m, 2H) and 1.71-1.77 (m, 2H). MS: 373.96 (M+H)⁺. Yield: 65% with **method E**.

[0305] **8-benzyl-1-(4-fluoro-3-(trifluoromethyl)phenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (1.4-e):** ¹H-NMR (400 MHz, DMSO- d_6): δ 8.22 (s, 1H), 7.33-7.42 (m, 8H), 3.50 (s, 2H), 2.92-2.95 (m, 2H), 2.68-2.70 (m, 2H), 1.90-1.91 (m, 2H) and 1.72-1.73 (m, 2H). MS: 406.56 (M+H)⁺. Yield: 63% with **method E**.

[0306] **8-Benzyl-1-(4-fluoro-3,5-dimethylphenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (1.4-f):** ¹H-NMR (400 MHz, DMSO- d_6): δ 8.15 (s, 1H), 7.48-7.49 (m, 4H), 7.26-7.28 (m, 1H), 7.80-7.81 (m, 2H), 3.60 (s, 2H), 2.87-2.91 (m, 2H), 2.59-2.61 (m, 2H), 2.28 (s, 6H), 1.88-1.89 (m, 2H) and 1.56-1.58 (m, 2H). MS: 366.35 (M+H)⁺. Yield: 79% with **method E**.

[0307] **8-Benzyl-1-(4-fluoro-2-methoxyphenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (1.4-g):** ¹H-NMR (400 MHz, DMSO- d_6): δ 8.01 (s, 1H), 7.22-7.26 (m, 5H), 7.08-7.12 (m, 1H), 6.70-6.74 (m, 2H), 3.77 (s, 3H), 3.55 (s, 2H), 2.87-2.95 (m, 2H), 2.59-2.62 (m, 2H) and 1.83-1.98 (m, 4H). LCMS: 368.00 (M+H)⁺, 90.91%. Yield: 78% with **method E**.

[0308] **8-Benzyl-1-(4-(difluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (1.4-h):** ¹H-NMR (400 MHz, DMSO- d_6): δ 8.67 (s, 1H), 7.45 (d, $J=8.8$ Hz, 2H), 7.30 (d,

$J=8.8$ Hz, 2H), 7.21-7.26 (m, 5H), 3.46 (s, 2H), 3.28-3.32 (m, 1H), 2.67-2.72 (m, 2H), 2.45-2.49 (m, 2H) and 1.74-1.75 (m, 4H). MS: 386.0 (M+H)⁺. Yield: 53% with **method E**.

General procedure for the preparation of 1.5 (a-h):

5 **[0309] General Method F:** To a solution of compounds **1.4 (a-h)** (0.50-1.5 g, 1.0 eq) in MeOH and AcOH (40:1, 20 mL) were added Pd-C (10 mol% w/w) and the resulting solution was stirred under hydrogen atmosphere (1 atm) at ambient temperature for 16 h. The reaction mixture was filtered through celite bed and the filtrate was concentrated under reduced pressure. The residue was purified over silica gel (basic alumina, 2-4% MeOH-DCM) to get the desired products **1.5 (a-h)** as off white solids.

10 **[0310] 1-(4-Fluorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (1.5-a): Intermediate 1:** ¹H-NMR (400 MHz, DMSO-d₆): δ 8.81 (br s, 1H), 7.05-7.08 (m, 2H), 6.95-6.96 (m, 2H), 4.58 (s, 2H), 3.34-3.37 (m, 3H), 2.97-2.99 (m, 2H), 2.35-2.36 (m, 2H) and 1.61-1.63 (m, 2H). LCMS: 250.23 (M+H)⁺, 88.25%. Yield: 90%

[0311] 1-(3,4-Difluorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (1.5-b):
15 **Intermediate 2:** ¹H-NMR (400 MHz, DMSO-d₆): δ 8.77 (br s, 1H), 7.17-7.28 (m, 2H), 6.90-6.94 (m, 1H), 6.68-6.71 (m, 1H), 4.55 (s, 2H), 3.22-3.25 (m, 2H), 2.94-2.97 (m, 2H), 2.37-2.40 (m, 2H) and 1.54-1.57 (m, 2H). MS: 268.25 (M+H)⁺. Yield: 86%

[0312] 1-(3-Chloro-4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (1.5-c):
Intermediate 3: MS: 284.12 (M+H)⁺. Yield: 50%.

20 **[0313] 1-(3,4,5-Trifluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (1.5-d):**
Intermediate 4: ¹H-NMR (400 MHz, DMSO-d₆): δ 9.27 (s, 1H), 9.07 (s, 1H), 6.90-6.92 (m, 1H), 4.59 (s, 2H), 3.28-3.33 (m, 2H), 2.74-2.76 (m, 2H), 2.50-2.52 (m, 2H) and 1.82-1.85 (m, 2H). MS: 286.24 (M+H)⁺. Yield: 60%.

**[0314] 1-(4-Fluoro-3-(trifluoromethyl)phenyl)-1,3,8-triazaspiro[4.5]decan-4-one (1.5-
25 e): Intermediate 5:** ¹H-NMR (400 MHz, DMSO-d₆): δ 8.77 (br s, 1H), 7.33-7.35 (m, 2H), 6.92-6.93 (m, 1H), 6.70-6.71 (m, 1H), 4.62 (s, 2H), 3.17-3.20 (m, 2H), 2.88-2.90 (m, 2H), 2.33-2.39 (m, 2H) and 1.53-1.56 (m, 2H). LCMS: 318.29 (M+H)⁺, 90.82%. Yield: 64%.

[0315] 1-(4-Fluoro-3,5-dimethylphenyl)-1,3,8-triazaspiro[4.5]decan-4-one (1.5-f):
Intermediate 6: ¹H-NMR (400 MHz, DMSO-d₆): δ 8.83 (s, 1H), 7.66-7.68 (m, 1H), 6.60-

6.66 (m, 2H), 4.54 (s, 2H), 3.38-3.41 (m, 2H), 3.12-3.16 (m, 2H), 2.50-2.53 (m, 2H), 2.19 (s, 6H) and 1.67-1.70 (m, 2H). MS: 278.32 (M+H)⁺. Yield: 80%.

[0316] 1-(4-Fluoro-2-methoxyphenyl)-1,3,8-triazaspiro[4.5]decan-4-one (1.5-g):

Intermediate 7: ¹H-NMR (400 MHz, DMSO-d₆): δ 8.51 (s, 1H), 7.62-7.69 (m, 1H), 7.22-

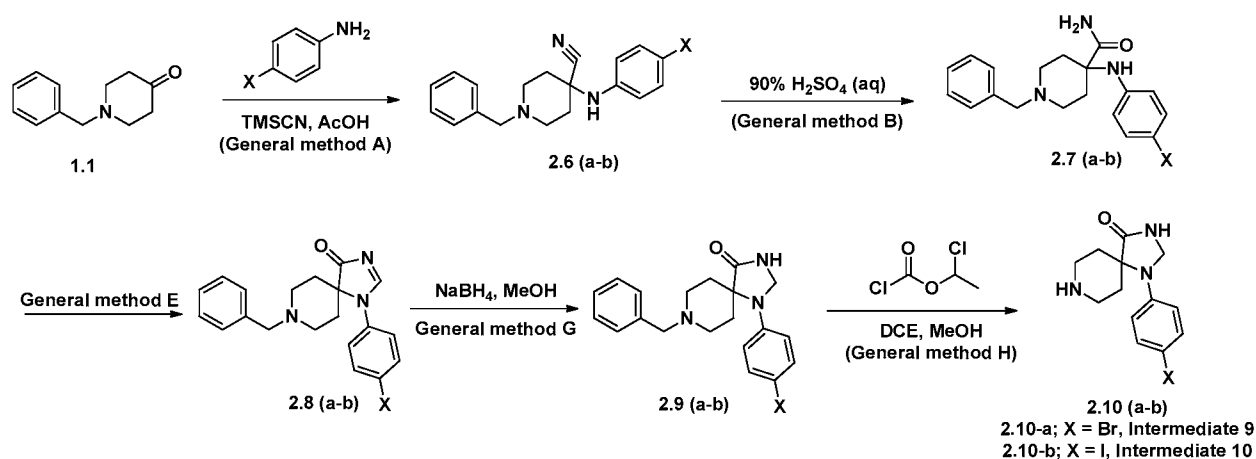
5 7.26 (m, 1H), 6.92-6.98 (m, 1H), 6.72-6.76 (m, 1H), 4.66 (s, 2H), 3.76 (s, 3H), 3.19-3.26 (m, 2H), 2.90-3.01 (m, 2H), 2.50-2.54 (m, 2H) and 1.50-1.52 (m, 2H). MS: 280.26 (M+H)⁺. Yield: 71%.

[0317] 1-(4-(Difluoromethoxy)phenyl)-1,3,8-triazaspiro[4.5]decan-4-one (1.5-h):

Intermediate 8: ¹H-NMR (400 MHz, DMSO-d₆): δ 9.05 (br s, 1H), 7.10-7.13 (m, 3H), 6.93-

10 6.96 (m, 2H), 4.57 (s, 2H), 3.25-3.28 (m, 3H), 2.97-2.99 (m, 2H), 2.40-2.42 (m, 2H) and 1.59-1.64 (m, 2H). MS: 298.34 (M+H)⁺. Yield: 78%.

Scheme 2



15 **General procedure for the preparation of 2.6 (a-b):** Prepared following general method A.

1-Benzyl-4-((4-bromophenyl)amino)piperidine-4-carbonitrile (2.6-a): ¹H-NMR (400 MHz, CDCl₃): δ 7.35-7.38 (m, 7H), 6.79 (d, *J*=8.4 Hz, 2H), 6.30 (br s, 1H), 3.51 (s, 2H), 2.74-2.76 (m, 2H), 2.28-2.31 (m, 4H) and 1.81-1.83 (m, 2H). MS: 369.98 (M+H)⁺. Yield: 52%.

20 **1-Benzyl-4-((4-iodophenyl)amino)piperidine-4-carbonitrile (2.6-b):** ¹H-NMR (400 MHz, CDCl₃): δ 7.45 (d, *J*=7.6 Hz, 2H), 7.26-7.30 (m, 5H), 6.68 (d, *J*=2.0 Hz, 2H), 6.32 (br s, 1H), 3.51 (s, 2H), 2.73-2.75 (m, 2H), 2.28-2.34 (m, 4H) and 1.81-1.83 (m, 2H). MS: 418.35 (M+H)⁺. Yield: 40%.

General procedure for the preparation of 2.7 (a-b): Prepared following general **method B**.

1-Benzyl-4-(4-bromophenylamino)piperidine-4-carboxamide (2.7-a): ¹H-NMR (400 MHz, CDCl₃): δ 7.34-7.56 (m, 10H), 6.51-6.53 (m, 2H), 3.41 (s, 2H), 2.66-2.72 (m, 2H), 2.23-2.26 (m, 2H), 1.96-1.98 (m, 2H) and 1.78-1.82 (m, 2H). MS: 388.26 (M+H)⁺. Yield: 60%.

1-Benzyl-4-(iodophenylamino)piperidine-4-carboxamide (2.7-b): ¹H-NMR (400 MHz, CDCl₃): δ 7.26-7.37 (m, 8H), 7.01 (s, 1H), 6.41 (d, *J*=8.4 Hz, 2H), 5.72 (br s, 1H), 3.41 (s, 2H), 2.49-2.52 (m, 2H), 2.20-2.25 (m, 2H), 1.95-2.00 (m, 2H) and 1.78-1.81 (m, 2H). LCMS: 436.32 (M+H)⁺, 93.67%. Yield: 41%.

General procedure for the preparation of 2.8 (a-b): Prepared following general **method E**.

[0318] 8-Benzyl-1-(4-bromophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (2.8-a): ¹H-NMR (400 MHz, DMSO-d₆): δ 8.25 (s, 1H), 7.60 (d, *J*=8.4 Hz, 2H), 7.26-7.31 (m, 5H), 7.08 (d, *J*=7.2 Hz, 2H), 3.59 (s, 2H), 2.86-2.88 (m, 2H), 2.30-2.35 (m, 2H), 2.02-2.06 (m, 2H) and 1.65-1.68 (m, 2H). LCMS: 398.31 (M+H)⁺, 83.8%. Yield: 89%.

[0319] 8-Benzyl-1-(4-iodophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (2.8-b): ¹H-NMR (400 MHz, DMSO-d₆): δ 8.70 (s, 1H), 7.86 (d, *J*=8.4 Hz, 2H), 7.19-7.30 (m, 7H), 3.47 (s, 2H), 2.72-2.78 (m, 2H), 2.46-2.49 (m, 2H) and 1.70-1.79 (m, 4H). MS: 446.18 (M+H)⁺. Yield: 59%.

General procedure for the preparation of 2.9 (a-b):

[0319] General method G: To an ice-cold solution of compound **2.8 (a-b)** (1.0-1.5 g, 1.0 eq) in methanol was added NaBH₄ (2.5 eq) portion-wise. The resulting reaction mixture was stirred at RT for 2h. After completion of reaction (TLC monitoring), cooled to 0°C added water and extracted with EtOAc (3 times). The combined organics was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was triturated with diethyl ether to get desired products **2.9 (a-b)** as off white solids.

[0320] 8-Benzyl-1-(4-bromophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (2.9-a): ¹H-NMR (400 MHz, DMSO-d₆): δ 8.66 (s, 1H), 7.39 (d, *J*=8.8 Hz, 2H), 7.31-7.34 (m, 4H), 7.24-7.26 (m, 1H), 6.79 (d, *J*=8.8 Hz, 2H), 4.55 (s, 2H), 3.52-3.54 (m, 2H), 2.66-2.71 (m, 4H) and 1.54-1.58 (m, 4H). LCMS: 400.32 (M+H)⁺, 98.11%. Yield: 83%.

8-Benzyl-1-(4-iodophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (2.9-b): $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 8.66 (s, 1H), 7.53 (d, $J=8.8$ Hz, 2H), 7.31-7.34 (m, 4H), 7.24 (br s, 1H), 6.67 (d, $J=8.4$ Hz, 2H), 4.50 (s, 2H), 3.52-3.53 (m, 2H), 2.66-2.69 (m, 4H) and 1.53-1.57 (m, 4H). LCMS: 448.20 ($\text{M}+\text{H}$) $^+$, 96.28%. Yield: 91%.

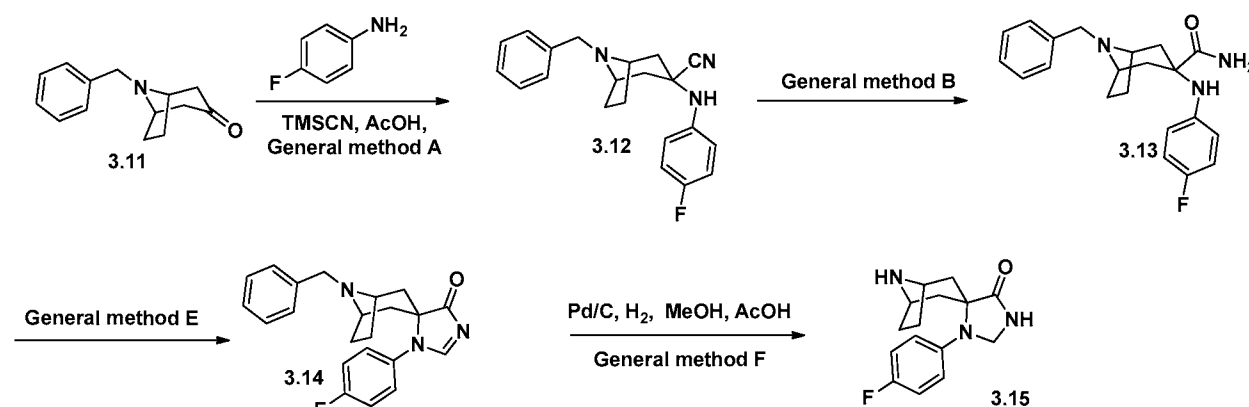
5 General procedure for the preparation of 2.10 (a-b):

[0321] **General method H:** To an ice-cold solution of **2.9 (a-b)** (0.50-1.0 g, 1.0 eq) in DCE was added 1-chloroethyl chloroformate (2.0 eq). The resulting reaction mixture was refluxed for 5h. After completion of reaction (TLC monitoring), solvent was evaporated to dryness. The crude residue was dissolved in MeOH and heated at 65°C for 16h. After completion of reaction (TLC monitoring), solvent was evaporated. The crude was purified over silica gel (100-200M), and eluted with 3-5% MeOH/DCM to get the desired products **2.10 (a-b)** as off-white solids.

[0322] **1-(4-Bromophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (2.10-a): Intermediate 9:** LCMS: 310.16 ($\text{M}+\text{H}$) $^+$, 87.90%. Yield: 43%.

15 [0323] **1-(4-Iodophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (2.10-b): Intermediate 10:** $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 9.34 (br s, 1H), 8.99 (s, 1H), 7.45 (d, $J=8.8$ Hz, 2H), 6.89 (d, $J=8.8$ Hz, 2H), 4.61 (s, 2H), 3.51-3.53 (m, 2H), 3.28-3.33 (m, 2H), 2.79-2.83 (m, 2H) and 1.75-1.79 (m, 2H). LCMS: 358.17 ($\text{M}+\text{H}$) $^+$, 89.37%. Yield: 68%.

Scheme 3



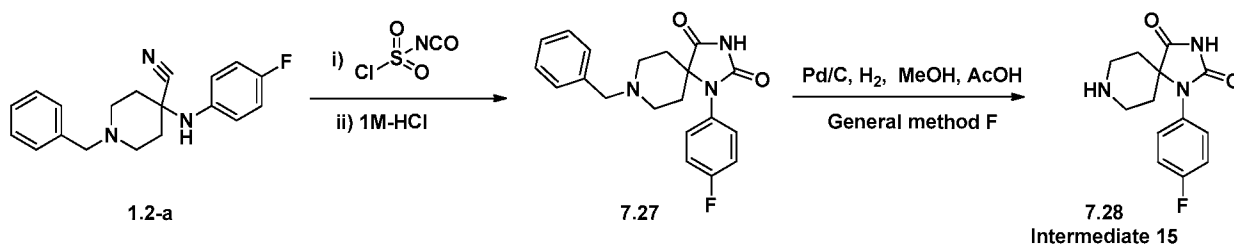
[0324] **Preparation of 8-benzyl-3-((4-fluorophenyl)amino)-8-azabicyclo[3.2.1]octane-3-carbonitrile (3.12):** Prepared following general method A. MS: 336.14 ($\text{M}+\text{H}$) $^+$. Yield: 32%.

[0325] Preparation of 8-benzyl-3-((4-fluorophenyl)amino)-8-azabicyclo[3.2.1]octane-3-carboxamide (3.13): Prepared following general **method B**. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 7.63 (br s, 1H), 7.46-7.52 (m, 2H), 7.41-7.46 (m, 2H), 7.26-7.30 (m, 3H), 6.87-6.91 (m, 2H), 6.59 (br s, 2H), 5.44 (m, 1H), 4.15 (m, 1H), 3.83-3.85 (s, 2H), 3.37-3.40 (m, 2H), 2.72-2.78 (m, 2H), 2.12-2.17 (m, 2H) and 1.80-1.90 (m, 2H). LCMS: 354.36 ($\text{M}+\text{H}$) $^+$, 93.06%. Yield: 45%.

[0326] Preparation of 8-benzyl-3'-(4-fluorophenyl)-8-azaspiro[bicyclo[3.2.1]octane-3,4'-imidazol]-5'(3'H)-one (3.14): Prepared following general **method E**. MS: 363.98 ($\text{M}+\text{H}$) $^+$. Yield: 50%.

[0327] Preparation of 3'-(4-fluorophenyl)-8-azaspiro[bicyclo[3.2.1]octane-3,4'-imidazolidin]-5'-one (3.15): **Intermediate 11:** Prepared following the general **method F**. MS: 276.18 ($\text{M}+\text{H}$) $^+$. Yield: 29%.

Scheme 7

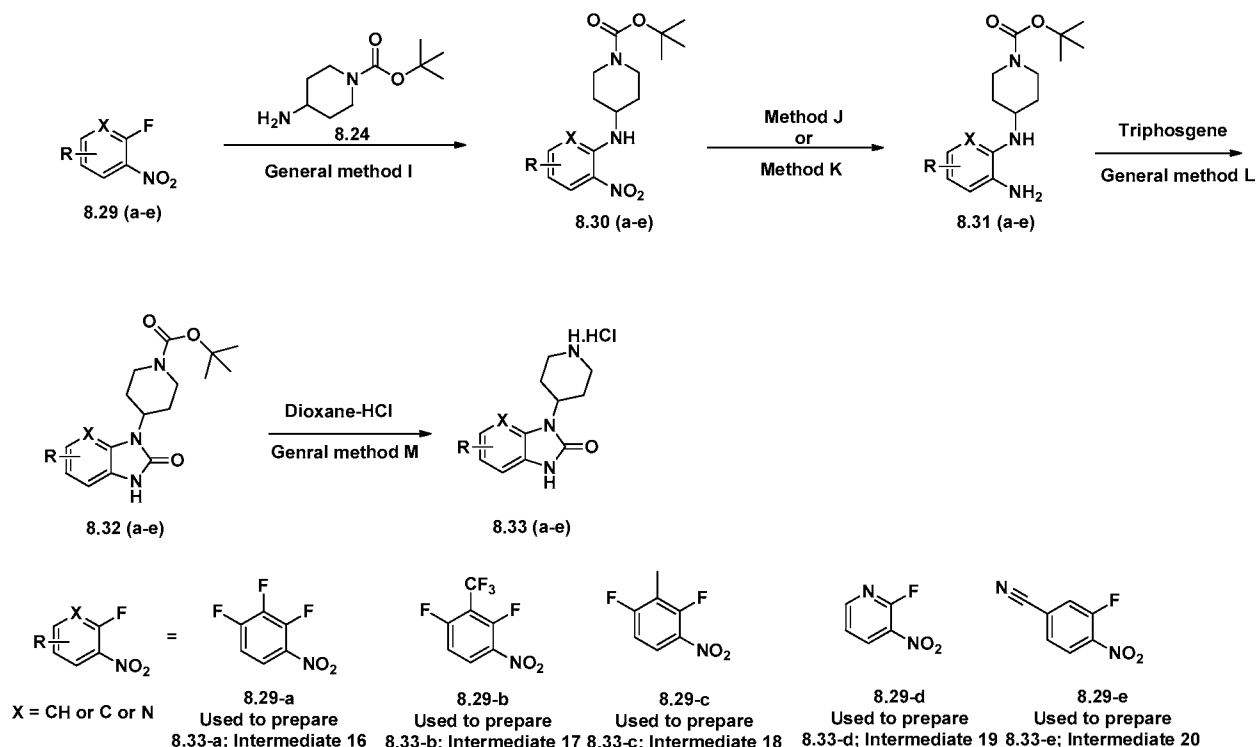


[0328] Preparation of 8-benzyl-1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decane-2,4-dione (7.27): To an ice-cold solution of 1-benzyl-4-((4-fluorophenyl)amino)piperidine-4-carbonitrile **1.2-a** (1.0 g, 3.23 mmol) in CHCl_3 (50 mL) was added chlorosulfonyl isocyanate (0.56 mL, 6.47 mmol). The reaction mass was stirred at RT for 1h. After completion of the reaction (TLC monitoring), the reaction mass was concentrated to get off white solid product, which was dissolved in 1M-HCl (100 mL) and heated at 100°C for 2h. After completion of the reaction (TLC monitoring), reaction mass was cooled to 0°C and adjusted the pH ~10 using 5N-NaOH solution. The resulting solid was filtered and washed with diethyl ether to get desired product **7.27** (1.0 g, 87%) as off white solid.

[0329] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 11.08 (br s, 1H), 7.19-7.32 (m, 9H), 3.31-3.37 (m, 2H), 2.55-2.65 (m, 4H), 1.94-1.97 (m, 2H) and 1.58-1.63 (m, 2H). LCMS: 354.36 ($\text{M}+\text{H}$) $^+$, 98.93%.

[0330] Preparation of 1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decane-2,4-dione (7.28):

Intermediate 15 Prepared following the general **method F**: $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 8.61 (br s, 1H), 7.30-7.32 (m, 4H), 5.75-5.77 (m, 1H), 2.55-2.58 (m, 4H) and 1.84-1.92 (m, 4H). MS: 264.27 ($\text{M}+\text{H}$) $^+$. Yield: 94%.

5 Scheme 8**General procedure for the preparation of 8.30 (a-e):**

[0331] General method I: To an ice-cold solution of tert-butyl 4-aminopiperidine-1-carboxylate **8.24** (1.0-2.5 g, 1.0 eq) in DMF was added DIPEA (1.5 eq) and respective nitro compounds **8.29 (a-e)** (1.0 eq). The resulting reaction mixture was stirred at RT for 2-3 h. After completion of the reaction (TLC monitoring), the reaction mass was diluted with ice-cold water and extracted with EtOAc (3 times). The combined organics was washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude was purified over silica gel (100-200 M, 10-15% EtOAc-hexane) to get the desired product **8.30 (a-e)**.

[0332] Tert-butyl 4-((2,3-difluoro-6-nitrophenyl)amino)piperidine-1-carboxylate (8.30-a): $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.00-8.04 (m, 1H), 7.94 (d, J = 8.0 Hz, 1H), 6.48-6.54 (m, 1H), 4.01-4.02 (m, 3H), 2.94-2.99 (m, 2H), 2.04-2.06 (m, 2H) and 1.46-1.49 (m, 11H). LCMS: 356.52 ($\text{M}-\text{H}$) $^+$, 99.10%. Yield: 56%.

[0333] **Tert-butyl 4-((3-fluoro-6-nitro-2-(trifluoromethyl)phenyl)amino)piperidine-1-carboxylate (8.30-b):** ¹H-NMR (400 MHz, CDCl₃): δ 8.25-8.28 (m, 1H), 7.03 (m, 1H), 6.67-6.71 (m, 1H), 4.01-4.04 (m, 2H), 3.39-3.42 (m, 1H), 2.78-2.84 (m, 2H), 1.91-1.93 (m, 2H), 1.45 (s, 9H) and 1.40-1.41 (m, 2H). LCMS: 406.19 (M-H)⁺, 88.60%. Yield: 78%.

5 [0334] **Tert-butyl 4-((3-fluoro-2-methyl-6-nitrophenyl)amino)piperidine-1-carboxylate (8.30-c):** ¹H-NMR (400 MHz, CDCl₃): δ 7.98-8.02 (m, 1H), 8.62-8.67 (m, 1H), 3.97-4.02 (m, 2H), 2.48 (s, 1H), 3.38-3.40 (m, 1H), 2.80-2.86 (m, 2H), 2.24 (s, 3H), 1.85-1.88 (m, 2H), 1.44 (s, 9H) and 1.34-1.37 (m, 2H). LCMS: 352.28 (M-H)⁺, 99.33%. Yield: 40%.

10 [0335] **Tert-butyl 4-((3-nitropyridin-2-yl)amino)piperidine-1-carboxylate (8.30-d):** ¹H-NMR (400 MHz, CDCl₃): δ 8.38-8.41 (m, 2H), 8.15-8.16 (m, 1H), 6.63-6.66 (m, 1H), 4.32-4.39 (m, 1H), 2.48 (s, 1H), 4.05-4.07 (m, 1H), 2.96-3.02 (m, 2H), 2.04-2.07 (m, 2H), 1.55-1.62 (m, 2H) and 1.48 (s, 9H). LCMS: 321.24 (M-H)⁺, 95.81%. Yield: 80%.

15 [0336] **Tert-butyl 4-((5-cyano-2-nitrophenyl)amino)piperidine-1-carboxylate (8.30-e):** ¹H-NMR (400 MHz, CDCl₃): δ 8.25 (d, *J* = 8.8 Hz, 1H), 8.25 (m, *J* = 7.2 Hz, 1H), 7.17 (s, 1H), 6.86 (d, *J* = 8.8 Hz, 1H), 4.04-4.10 (m, 2H), 3.60-3.67 (m, 1H), 3.03-3.08 (m, 2H), 2.03-2.07 (m, 2H), 1.57-1.63 (m, 2H) and 1.51 (s, 9H). LCMS: 345.22 (M-H)⁺, 99.0%. Yield: 75.3%.

General procedure for the preparation of 8.31 (a-d):

20 [0337] **General method J:** To a solution of compound **8.30 (a-d)** (1.0-2.5 g, 1.0 eq) in EtOAc were added Pd-C (w/w, 10 mol %) and the resulting solution was stirred under hydrogen atmosphere (1 atm) at ambient temperature for 16 h. The reaction mixture was filtered through celite bed and the filtrate was concentrated under reduced pressure to get the desired product **8.31 (a-d)**.

25 [0338] **Tert-butyl 4-((6-amino-2,3-difluorophenyl)amino)piperidine-1-carboxylate (8.31-a):** ¹H-NMR (400 MHz, DMSO-d₆): δ 6.58-6.65 (m, 1H), 6.33-6.36 (m, 1H), 4.80 (br s, 2H), 3.87-4.05 (m, 3H), 3.17-3.20 (m, 1H), 2.73-2.75 (m, 2H), 1.73-1.76 (m, 2H), 1.39 (s, 9H) and 1.23-1.25 (m, 2H). LCMS: 328.41 (M+H)⁺, 97.70%. Yield: 97%.

[0339] **Tert-butyl 4-((6-amino-3-fluoro-2-(trifluoromethyl)phenyl)amino)piperidine-1-carboxylate (8.31-b):** ¹H-NMR (400 MHz, DMSO-d₆): δ 6.85-6.89 (m, 1H), 6.70-6.79 (m,

1H), 4.90 (br s, 2H), 3.92-3.99 (m, 3H), 3.09-3.11 (m, 1H), 2.64-2.68 (m, 2H), 1.69-1.73 (m, 2H), 1.38 (s, 9H) and 1.26-1.27 (m, 2H). LCMS: 356.30 (M-H)⁺, 96.01%. Yield: 75%.

[0340] Tert-butyl 4-((6-amino-3-fluoro-2-methylphenyl)amino)piperidine-1-

carboxylate (8.31-c): ¹H-NMR (400 MHz, DMSO-d₆): δ 6.62-6.64 (m, 1H), 6.51-6.53 (m, 1H), 4.10-4.12 (m, 3H), 3.41-3.45 (m, 2H), 3.11-3.14 (m, 1H), 2.66-2.69 (m, 2H), 2.14 (s, 3H), 1.85-1.86 (m, 2H), 1.42 (s, 9H) and 1.27-1.29 (m, 2H). LCMS: 324.31 (M-H)⁺, 88.69%. Yield: 80%.

[0341] Tert-butyl 4-((3-aminopyridin-2-yl)amino)piperidine-1-carboxylate (8.31-d):

¹H-NMR (400 MHz, CDCl₃): δ 6.68-6.69 (m, 1H), 7.86-7.88 (m, 1H), 6.51-6.55 (m, 1H), 4.49-4.53 (br s, 1H), 3.98-4.12 (m, 3H), 3.45-3.48 (m, 2H), 2.97-2.99 (m, 2H), 2.04-2.09 (m, 2H), 1.48 (s, 9H) and 1.30-1.32 (m, 2H). LCMS: 293.23 (M+H)⁺, 98.28%. Yield: 85%.

[0342] General method K: To a solution of compound **8.30-e** (1.0-2.0 g, 1.0 eq) in MeOH was added ammonium formate (5.0 eq) and Pd-C (w/w, 10 mol %) and the resulting solution was stirred under at RT for 3-4h. The reaction mixture was filtered through celite bed and the filtrate was concentrated under reduced pressure to get the desired product **8.31-e**.

[0343] Tert-butyl 4-((2-amino-5-cyanophenyl)amino)piperidine-1-carboxylate (8.31-e):

¹H-NMR (400 MHz, CDCl₃): δ 7.01 (d, *J* = 8.8 Hz, 1H), 6.87 (s, 1H), 6.68 (d, *J* = 8.8 Hz, 1H), 4.05-4.10 (br s, 3H), 3.36-3.39 (m, 1H), 2.91-2.94 (m, 2H), 2.00-2.03 (m, 4H) and 1.40 (s, 11H). MS: 317.39 (M+H)⁺. Yield: 85%.

General procedure for the preparation of 8.32 (a-e):

[0344] General method L: To an ice-cold solution of compound **8.31 (a-e)** (0.50-1.50 g, 1.0 eq) in THF was added Et₃N (2.0 eq) and triphosgene (1.5 eq). The resulting reaction mixture was stirred at RT for 4 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was purified over silica gel (100-200 M, 30-40% EtOAc-hexane) to get the desired product **8.32 (a-e)**.

[0345] Tert-butyl 4-(6, 7-difluoro-2-oxo-2, 3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-1-carboxylate (8.32-a):

¹H-NMR (400 MHz, DMSO-d₆): δ 11.24 (br s, 1H), 7.02-7.06 (m, 1H), 6.76-6.79 (m, 1H), 4.47-4.52 (m, 1H), 3.99-4.05 (m, 2H), 2.87-2.89 (m,

2H), 1.90-1.98 (m, 2H), 1.71-1.74 (m, 2H) and 1.42 (s, 9H). LCMS: 354.55 (M+H)⁺, 86.20%. Yield: 92%.

[0346] Tert-butyl 4-(6-fluoro-2-oxo-7-(trifluoromethyl)-2,3-dihydro-1H-

benzo[d]imidazol-1-yl)piperidine-1-carboxylate (8.32-b): ¹H-NMR (400 MHz, CDCl₃): δ

5 10.27 (br s, 1H), 7.17-7.21 (m, 1H), 6.91-6.99 (m, 1H), 3.70-3.73 (m, 3H), 2.68-2.74 (m, 4H), 1.71-1.73 (m, 2H) and 1.46 (s, 9H). LCMS: 354.55 (M+H)⁺, 86.20%. Yield: 72%.

[0347] Tert-butyl 4-(6-fluoro-7-methyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-

yl)piperidine-1-carboxylate (8.32-c): ¹H-NMR (400 MHz, CDCl₃): δ 9.02 (br s, 1H), 6.75-

6.82 (m, 2H), 4.49 (s, 1H), 4.30-4.32 (m, 2H), 2.73 (s, 3H), 2.44-2.48 (m, 2H), 1.79-1.80 (m,
10 2H), 1.60-1.62 (m, 2H) and 1.48 (s, 9H). LCMS: 350.36 (M+H)⁺, 90.82%. Yield: 80%.

[0348] Tert-butyl 4-(2-oxo-1,2-dihydro-3H-imidazo[4,5-b]pyridin-3-yl)piperidine-1-
carboxylate (8.32-d): LCMS: 319.33 (M+H)⁺, 87.69%. Yield: 85%.

[0349] Tert-butyl 4-(6-cyano-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-

1-carboxylate (8.32-e): ¹H-NMR (400 MHz, CDCl₃): δ 10.01 (br s, 1H), 7.38-7.41 (m, 2H),

15 7.16 (d, J=8.0 Hz, 1H), 4.37-4.45 (m, 3H), 2.84-2.90 (m, 2H), 2.30-2.35 (m, 2H), 1.83-1.85 (m, 2H) and 1.52 (s, 9H). LCMS: 343.37 (M+H)⁺, 86.18%. Yield: 60%.

General procedure for the preparation of 8.33 (a-e):

[0350] General method M: An ice-cold solution of compound **8.32 (a-e)** (0.5 g-1.0 g, 1.0 eq) in dioxane-HCl (~4N) was stirred at RT for 2h. After completion of the reaction (TLC
20 monitoring), the reaction mass was dried under reduced pressure. The crude was triturated with diethyl ether to get desired product **8.33 (a-e)** as off-white solids.

[0351] 6,7-Difluoro-1-(piperidin-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one

hydrochloride (8.33-a): Intermediate 16: ¹H-NMR (400 MHz, DMSO-d₆): δ 11.38 (br s,

1H), 9.44 (br s, 1H), 8.65 (br s, 1H), 7.01-7.07 (m, 1H), 6.78-6.79 (m, 1H), 4.58-4.60 (m,
25 1H), 3.63-3.65 (m, 2H), 2.45-3.49 (m, 2H), 3.03-3.12 (m, 2H) and 2.35-2.38 (m, 2H). LCMS: 254.11 (M+H)⁺, 95.61%. Yield: quantitative.

[0352] 6-Difluoro-1-(piperidin-4-yl)-7-(trifluoromethyl)-1,3-dihydro-2H-

benzo[d]imidazol-2-one hydrochloride (8.33-b): Intermediate 17: ¹H-NMR (400 MHz,

DMSO-d₆): δ 11.66 (br s, 1H), 9.40 (br s, 1H), 8.57 (br s, 1H), 7.28-7.28 (m, 1H), 7.04-7.08

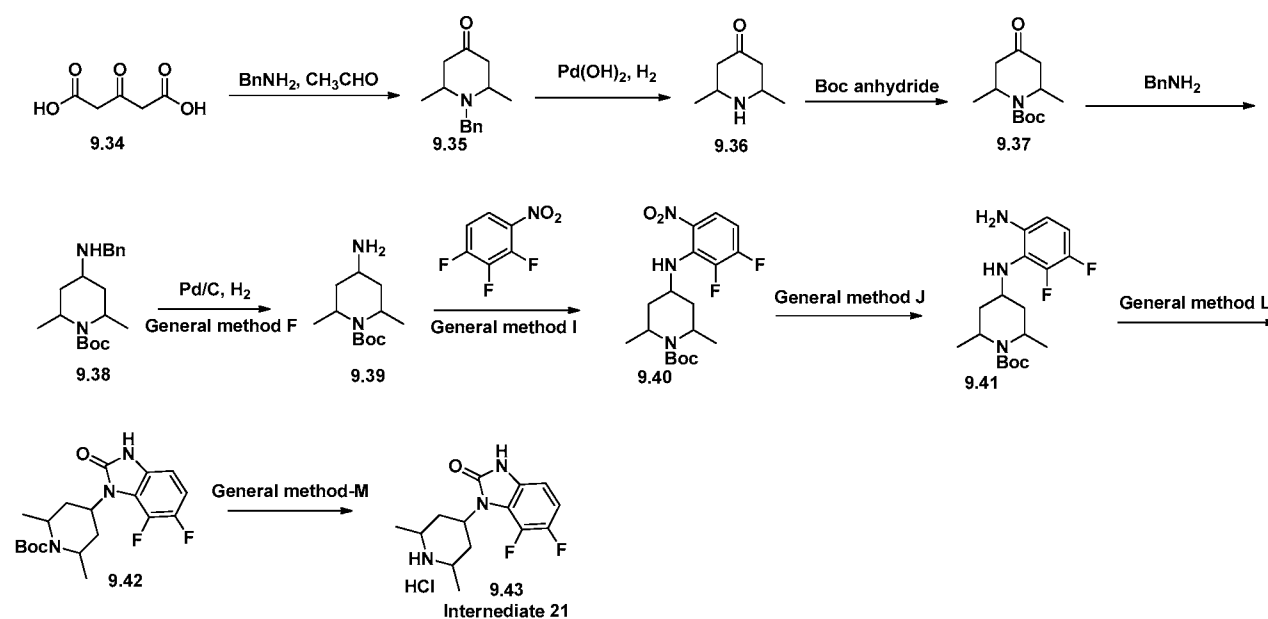
(m, 1H), 4.43-4.45 (m, 3H), 2.82-2.90 (m, 4H) and 1.88-1.98 (m, 2H). LCMS: 304.21 (M+H)⁺, 92.41%. Yield: 92%.

[0353] 6-Fluoro-7-methyl-1-(piperidin-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one hydrochloride (8.33-c): Intermediate 18: ¹H-NMR (400 MHz, DMSO-d₆): δ 10.94 (br s, 1H), 9.44 (br s, 1H), 8.48 (br s, 1H), 6.76-6.83 (m, 2H), 4.44-4.48 (m, 1H), 3.32-3.38 (m, 2H), 3.01-3.07 (m, 2H), 2.77-2.83 (m, 2H), 2.46 (s, 3H) and 1.93-1.96 (m, 2H). MS: 250.29 (M+H)⁺. Yield: 93%.

[0354] 3-(piperidin-4-yl)-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one hydrochloride (8.33-d): Intermediate 19: ¹H-NMR (400 MHz, DMSO-d₆): δ 10.25 (br s, 1H), 9.36 (br s, 1H), 8.57 (br s, 1H), 7.92 (d, *J*=7.6 Hz, 1H), 7.31 (d, *J*=7.6 Hz, 1H), 7.00 (t, *J*=7.6 Hz, 1H), 4.55-4.61 (m, 1H), 3.35-3.38 (m, 2H), 3.03-3.11 (m, 2H), 2.69-2.78 (m, 2H) and 1.86-1.89 (m, 2H). LCMS: 219.14 (M+H)⁺, 90.67%. Yield: 90%.

[0355] 2-oxo-3-(piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazole-5-carbonitrile hydrochloride (8.33-e): Intermediate 20: ¹H-NMR (400 MHz, DMSO-d₆): δ 11.55 (br s, 1H), 8.93 (br s, 1H), 8.75 (br s, 1H), 7.86 (s, 1H), 7.47 (d, *J*=7.2 Hz, 1H), 7.14 (d, *J*=8.8 Hz, 1H), 4.57-4.60 (m, 1H), 3.35-3.40 (m, 2H), 3.04-3.08 (m, 2H), 2.55-2.61 (m, 2H) and 1.85-1.88 (m, 2H). LCMS: 243.32 (M+H)⁺, 98.82%. Yield: 85%.

Scheme 9



Preparation of 1-benzyl-2,6-dimethylpiperidin-4-one (9.35):

[0356] To an ice cold solution of 3-oxopentanedioic acid **9.34** (10 g, 64.49 mmol) in water (30 mL) was added acetaldehyde (6 g, 137 mmol) and benzyl amine (7.50 mL, 64.49 mmol). The resulting yellow solution was stirred at RT for 78 h. After completion of reaction (TLC monitoring), cooled the reaction mass, adjust pH ~2 using 1N HCl and stirred for 1h at RT. The resulting mixture was neutralized with aq. NaHCO₃ solution and extracted with DCM (2 x 100 ml). Combined organics was washed with brine, dried with Na₂SO₄ and evaporated to get a brown liquid. The crude was purified by flash chromatography using 10% EtOAc / hexane to get product **9.35** (10 g, Yield: 68%) as a viscous liquid.

[0357] NMR (400 MHz, CDCl₃): δ 7.26-7.40 (m, 5H), 3.90-.94 (m, 1H), 3.51-3.53 (m, 1H), 3.24-3.30 (m, 2H), 2.42-2.51 (m, 2H), 2.12-2.21 (m, 2H) and 1.05 (m, 6H). MS: 218.10 (M+H)⁺.

[0358] **Preparation of 2,6-dimethylpiperidin-4-one (9.36):** To a solution of 1-benzyl-2,6-dimethylpiperidin-4-one **9.35** (8.0 g, 36.78 mmol) in IPA (100 mL) was added Pd(OH)₂ (10% w/w, 0.8 g, 3.67 mmol). The resulting mixture was stirred at RT for 16 h under H₂ atmosphere. After completion of reaction (TLC monitoring), reaction mass filtered through celite bed, washed with EtOAc (100 mL). The filtrate was concentrated under reduced pressure to get desired product **9.36** (3.6 g, Yield: 77%) as a viscous liquid. The crude was used for the next step without purification. MS: 128.14 (M+H)⁺.

[0359] **Preparation of tert-butyl 2,6-dimethyl-4-oxopiperidine-1-carboxylate (9.37):** To an ice-cold solution of 2,6-dimethylpiperidin-4-one **9.36** (3.6 g, 28.34 mmol) in DCM (50 mL) was added Et₃N (9.8 mL, 70.8 mmol) and boc anhydride (12.1 mL, 56.6 mmol). The resulting reaction mixture was stirred at RT for 16 h. After completion of the reaction (TLC monitoring), the reaction mass was diluted with water and extracted with DCM (3 times). The combined organics was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was purified over silica gel (100-200 M, 10-15% EtOAc-hexane) to get the desired product **9.37** (3.9 g, Yield: 60.9%).

[0360] ¹H-NMR (400 MHz, CDCl₃): δ 2.85 (d, *J*=6.4 Hz, 1H), 2.81 (d, *J*=6.4 Hz, 1H), 2.38-2.39 (m, 2H), 2.34-2.36 (m, 2H), 1.48 (s, 9H) and 1.25-1.27 (m, 6H). MS: 228.08 (M+H)⁺.

[0361] **Preparation of tert-butyl 4-(benzylamino)-2,6-dimethylpiperidine-1-carboxylate (9.38):** To an ice-cold solution of tert-butyl 2,6-dimethyl-4-oxopiperidine-1-carboxylate **9.37** (3.4 g, 14.9 mmol) in DCM (50 mL) was added benzyl amine (2.13 mL, 17.9 mmol) and AcOH (1.02 mL, 17.9 mmol). The resulting mixture was stirred at 0°C for 2h followed by addition of sodium tri-acetoxyborohydride (6.3 g, 29.8 mmol). The resulting reaction mixture was stirred at RT for 16 h. After completion of the reaction (TLC monitoring), the reaction mass was diluted with water and extracted with DCM (3 times). The combined organics was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was purified over silica gel (100-200 M, 20% EtOAc-hexane) to get the desired product **9.38** (1.8 g, Yield: 37.8%). MS: 319.34 (M+H)⁺.

[0362] **Preparation of tert-butyl 4-amino-2,6-dimethylpiperidine-1-carboxylate (9.39):** Prepared following the general **method F**. MS: 229.20 (M+H)⁺. Yield: Quantitative.

[0363] **Preparation of tert-butyl 4-((2,3-difluoro-6-nitrophenyl)amino)-2,6-dimethylpiperidine-1-carboxylate (9.40):** Prepared following the general **method I**. ¹H-NMR (400 MHz, CDCl₃): δ 7.95-8.04 (m, 2H), 6.47-6.54 (m, 1H), 4.30-4.35 (m, 2H), 3.88-3.89 (m, 1H), 2.31-2.34 (m, 1H), 2.18-2.20 (m, 1H), 1.88-1.90 (m, 2H), 1.62 (s, 9H) and 1.31-1.33 (m, 6H). MS: 386.31 (M+H)⁺. Yield: 35%.

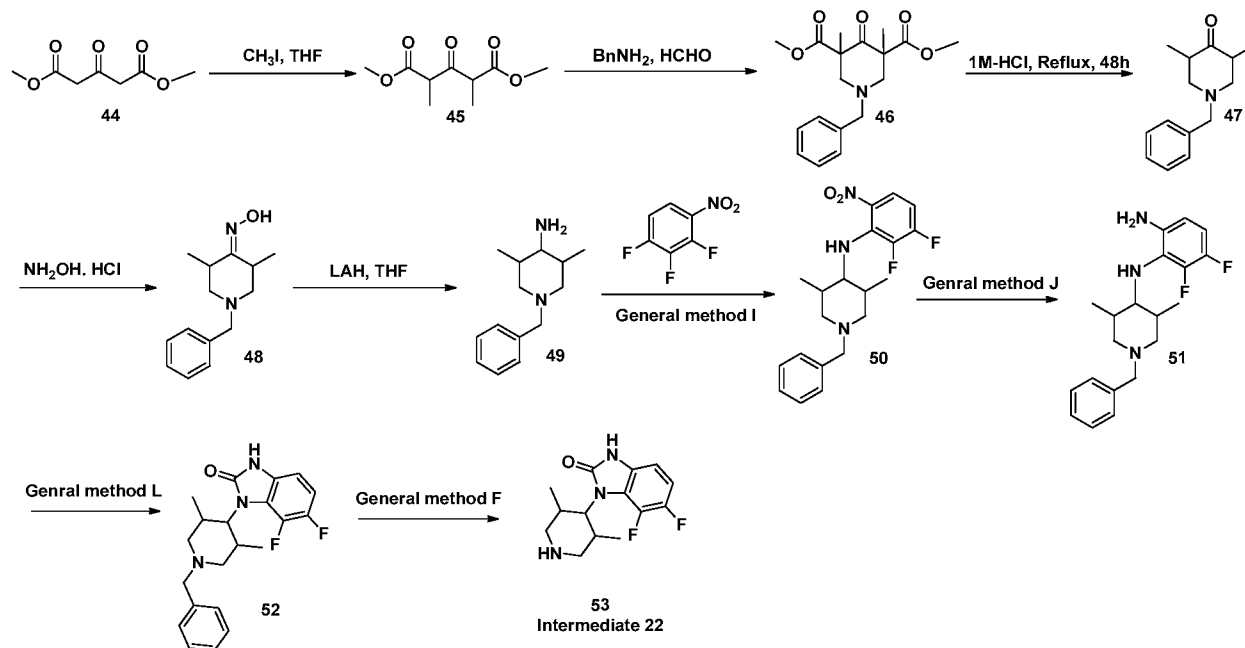
[0364] **Preparation of tert-butyl 4-((6-amino-2,3-difluorophenyl)amino)-2,6-dimethylpiperidine-1-carboxylate (9.41):** Prepared following the general **method J**. ¹H-NMR (400 MHz, DMSO-d₆): δ 6.57-6.64 (m, 1H), 6.34-6.36 (m, 1H), 4.78 (s, 2H), 4.16 (s, 1H), 4.01-4.03 (m, 1H), 3.89-3.91 (m, 1H), 3.62 (br s, 1H), 1.88-1.89 (m, 1H), 1.72-1.74 (m, 2H), 1.35-1.39 (m, 1H), 1.39 (s, 9H) and 1.31-1.33 (m, 6H). MS: 356.38 (M+H)⁺. Yield: 35%.

[0365] **Preparation of tert-butyl 4-(6,7-difluoro-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-2,6-dimethylpiperidine-1-carboxylate (9.42):** Prepared following the general **method L**. LCMS: 380.28 (M-H)⁺, 84.35%. Yield: 80%.

[0366] **Preparation of 1-(2,6-dimethylpiperidin-4-yl)-6,7-difluoro-1,3-dihydro-2H-benzo[d]imidazol-2-one hydrochloride (9.43): Intermediate 21:** Prepared following the general **method M**. ¹H-NMR (400 MHz, DMSO-d₆): δ 11.33 (br s, 1H), 9.20-9.25 (m, 1H), 8.89-8.99 (m, 1H), 7.01-7.04 (m, 1H), 6.75-6.78 (m, 1H), 4.73-4.79 (m, 1H), 3.61-3.64 (m,

2H), 3.35-3.38 (m, 1H), 2.19-2.25 (m, 1H), 2.00-2.03 (m, 1H), 1.81-1.84 (m, 1H) and 1.29-1.35 (m, 6H). LCMS: 280.13 (M-H)⁺, 84.65%. Yield: 90%.

Scheme 10



5

Preparation of dimethyl 2,4-dimethyl-3-oxopentanedioate (45):

[0367] To an ice-cold solution of dimethyl 3-oxopentanedioate **44** (10.0 g, 57.47 mmol) in THF (150 mL) was added K₂CO₃ (11.8 g, 86.2 mmol) and methyl iodide (9.0 mL, 143.67 mmol). The resulting reaction mixture was stirred at RT for 16 h. After completion of the reaction (TLC monitoring), the reaction mass was diluted with water and extracted with DCM (3 times). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to get desired product **45** (10.0 g, Yield: 86%) as viscous liquid.

[0368] ¹H-NMR (400 MHz, CDCl₃): δ 5.09-5.16 (m, 2H), 3.85-3.87 (m, 6H) and 3.51-3.54 (m, 6H). MS: 203.10 (M+H)⁺.

Preparation of dimethyl 1-benzyl-3,5-dimethyl-4-oxopiperidine-3,5-dicarboxylate (46):

[0369] To an ice-cold solution of dimethyl 2,4-dimethyl-3-oxopentanedioate **45** (10.0 g, 49.3 mmol) in CH₃OH (100 mL) was added 1M-HCl (15.0 mL), benzylamine (5.4 mL, 49.3 mmol) and formaldehyde (37% in H₂O, 9.0 mL, 108.46 mmol). The resulting reaction mixture was stirred at RT for 72 h. After completion of the reaction (TLC monitoring), the

20

reaction mass was diluted with water and extracted with EtOAc (3 times). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to get desired product **46** (12.0 g, Yield: 73%) as a viscous liquid. The crude was used for the next step without purification. MS: 334.18 (M+H)⁺.

5 Preparation of 1-benzyl-3,5-dimethylpiperidin-4-one (47):

[0370] A solution of dimethyl 1-benzyl-3,5-dimethyl-4-oxopiperidine-3,5-dicarboxylate **46** (12.0 g, 36.01 mmol) in 1N-HCl (100 mL) was heated at 100°C for 16h. After completion of the reaction (TLC monitoring), the reaction mass was cooled to 0°C, adjust pH ~10 using ammonium hydroxide solution and extracted with DCM (3 times). The combined organics was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to get desired product **47** (7.5 g, Yield: quantitative) as viscous liquid. The crude was used for next step without purification.

[0371] ¹H-NMR (400 MHz, CDCl₃): δ 7.32-7.35 (m, 5H), 3.64-3.66 (m, 2H), 3.10-3.13 (m, 2H), 2.66-2.69 (m, 2H), 2.02-2.07 (m, 2H) and 0.95 (d, *J*=6.4 Hz, 6H). MS: 203.10 (M+H)⁺.

[0372] **Preparation of 1-benzyl-3,5-dimethylpiperidin-4-one oxime (48):** To a solution of hydroxylamine hydrochloride (2.4 g, 34.56 mmol) in H₂O (30 mL) was added CH₃COONa (5.6 g, 69.12 mmol). The reaction mixture was heat at 60°C and followed by addition of 1-benzyl-3,5-dimethylpiperidin-4-one **47** (5.0 g, 23.04 mmol). The resulting reaction mixture was heated at 60°C for 2h. After completion of the reaction (TLC monitoring), the reaction mass was cooled to RT and extracted with DCM (3 times). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to get desired product **48** (5.0 g, Yield: quantitative).

[0373] ¹H-NMR (400 MHz, CDCl₃): δ 10.28 (s, 1H), 7.44-7.58 (m, 5H), 3.40-3.50 (m, 2H), 3.20-3.22 (m, 2H), 2.56-2.59 (m, 2H), 2.03-2.10 (m, 2H) and 1.17 (d, *J*=7.2 Hz, 6H). MS: 233.20 (M+H)⁺.

[0374] **Preparation of 1-benzyl-3,5-dimethylpiperidin-4-amine (49):** To an ice-cold solution of 1-benzyl-3,5-dimethylpiperidin-4-one oxime **48** (2.0 g, 8.62 mmol) was added LAH (2.0 M in THF, 13.0 mL). The resulting reaction mixture was heated at 65°C for 3h. After completion of the reaction (TLC monitoring), the reaction mass was cooled to 0°C, added drop wise 15% NaOH solution (10 mL). The reaction mass was filtered through a

celite bed, and washed with EtOAc (100 mL). The filtrate was dried over anhydrous Na_2SO_4 , filtered and concentrated to get desired product **49** (1.4 g, Yield: 70%). MS: 219.21 ($\text{M}+\text{H}$)⁺.

[0375] Preparation of 1-benzyl-N-(2,3-difluoro-6-nitrophenyl)-3,5-dimethylpiperidin-4-amine (50): Prepared following the general **Method I**. ¹H-NMR (400 MHz, CDCl_3): δ

5 8.02-8.05 (m, 1H), 7.38-7.50 (m, 5H), 6.44-6.51 (m, 1H), 4.29-4.30 (m, 1H), 3.70-3.73 (m, 2H), 2.81-2.84 (m, 2H), 2.11-2.17 (m, 2H), 1.55-1.57 (m, 2H), 1.31-1.32 (m, 1H) and 0.86 (d, $J=6.4$ Hz, 6H). LCMS: 376.06 ($\text{M}+\text{H}$)⁺, 96.22%. Yield: 25%.

[0376] Preparation of N1-(1-benzyl-3,5-dimethylpiperidin-4-yl)-5,6-difluorobenzene-1,2-diamine (51): Prepared following the general **Method J**. LCMS: 344.39 ($\text{M}-\text{H}$)⁺,

10 81.10%. Yield: 80%.

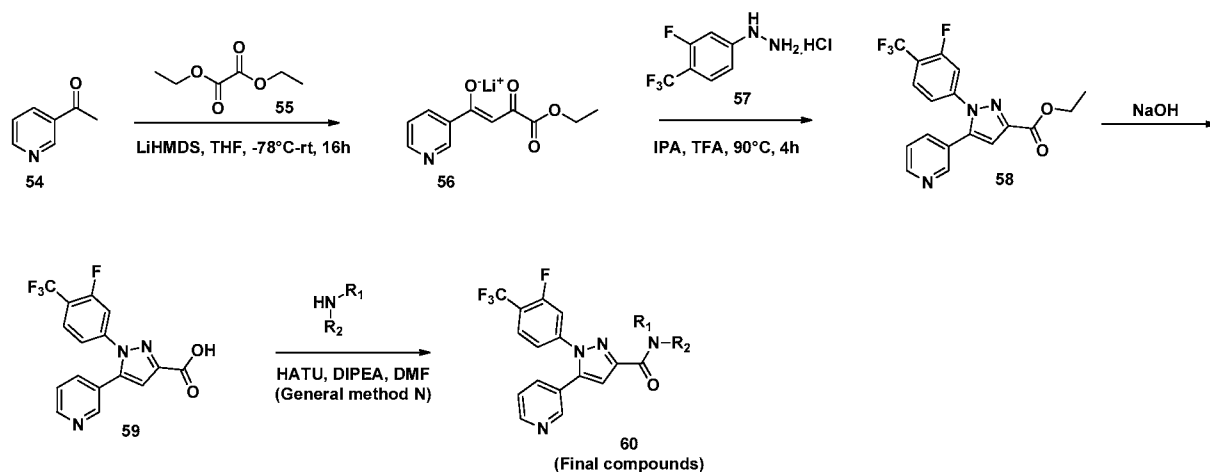
[0377] Preparation of 1-(1-benzyl-3,5-dimethylpiperidin-4-yl)-6,7-difluoro-1,3-dihydro-2H-benzo[d]imidazol-2-one (52): Prepared following the general **Method L**. MS: 370.36 ($\text{M}-\text{H}$)⁺. Yield: 60%.

Preparation of 1-(3,5-dimethylpiperidin-4-yl)-6,7-difluoro-1,3-dihydro-2H-

15 **benzo[d]imidazol-2-one (53): Intermediate 22:** Prepared following the general **Method F**. ¹H-NMR (400 MHz, CDCl_3): δ 10.25 (br s, 1H), 7.02-7.09 (m, 1H), 6.75-6.79 (m, 1H), 4.58 (br s, 1H), 3.48-3.51 (m, 2H), 3.38-3.40 (m, 2H), 3.00-3.02 (m, 2H), 1.22-1.25 (m, 1H) and 0.80 (d, $J=6.4$ Hz, 6H). LCMS: 282.25 ($\text{M}+\text{H}$)⁺, 88.77%. Yield: 90%.

Synthesis of final compounds

20 Scheme 11



[0378] Preparation of 4-ethoxy-3,4-dioxo-1-(pyridin-3-yl)but-1-en-1-olate lithium salt (55): A solution of 3-acetyl pyridine **54** (20 g, 165.09 mmol) in di-ethyl ether (250 mL) was cooled to -78°C followed by addition of LiHMDS (1.0 M in THF, 181.60 mL, 181.60 mmol). The resulting reaction mixture was stirred at -78°C for 45 min followed by drop wise addition of diethyl oxalate **55** (27.03 mL, 198.10 mmol) in about 20 min. The reaction mixture was then left to stir at room temperature for 16 h. After completion of the reaction (TLC and MS monitoring), the solution was then cooled to 0°C and the resulting precipitate was filtered to get the desired product **56** as an off-white solid (30 g), which was carried forward to the next step without purification.

[0379] ¹H-NMR (400 MHz, DMSO-d₆): δ 8.95 (s, 1H), 8.61 (d, *J* = 4.0 Hz, 1H), 8.14 (m, 1H), 7.44 (m, 1H), 6.40 (m, 1H), 4.12 (q, *J* = 7.20 Hz, 2H) and 1.21 (t, *J* = 7.2 Hz, 3H). MS: 221.95 (M+H)⁺. Yield: 82%.

[0380] Preparation of ethyl 1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (58): To an ice-cold solution of 4-ethoxy-3,4-dioxo-1-(pyridin-3-yl)but-1-en-1-olate lithium salt **56** (10 g, 45.23 mmol) in IPA (60 mL) was added (3-fluoro-4-(trifluoromethyl)phenyl)hydrazine hydrochloride **57** (10.5 g, 54.28 mmol) and TFA (7.25 mL, 90.46 mL). The resulting reaction mixture was warm up to room temperature and then stirred at 90°C for 4-5 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified over silica gel (100-200 M, 10-15% EtOAc-hexane) to get the desired product **58** (8.0 g, 47%).

[0381] ¹H-NMR (400 MHz, CDCl₃): δ 8.72 (m, 2H), 7.74 (m, 3H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7.15 (s, 1H), 4.48 (q, *J* = 6.8 Hz, 2H) and 1.40 (t, *J* = 7.2 Hz, 3H). MS: 379.90 (M+H)⁺.

[0382] Preparation of 1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (59): To an ice-cold solution of ethyl 1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate **58** (8.0 g, 21.09 mmol) in EtOH (60 mL) was added drop wise an aqueous solution of sodium hydroxide (1.68 g, 42.18 mmol) in 8 mL H₂O. The resulting solution was stirred at room temperature for 2 h. After completion of the reaction (TLC monitoring), the solvent was evaporated, added H₂O to the residue followed by extraction with EtOAc (2 x 100 mL). The organic layer was

discarded and the pH of the aqueous layer was adjusted to ~4 by adding 1N HCl. The resulting precipitate was filtered and dried under vacuum to get the desired product **59** (4.5 g, 61%) as a white solid.

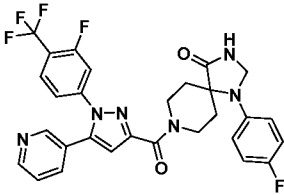
[0383] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 13.10 (br s, 1H), 8.59 (m, 2H), 7.88 (t, J = 8.0 Hz, 1H), 7.72 (d, J = 7.6 Hz, 1H), 7.65 (m, 1H), 7.45 (m, 1H), 7.35 (d, J = 8.4 Hz, 1H) and 7.26 (s, 1H). LCMS: 351.96 ($\text{M}+\text{H}$) $^+$, 93.37%.

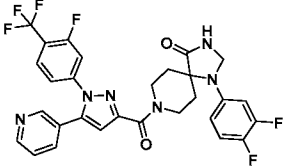
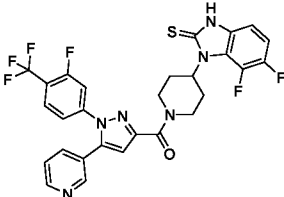
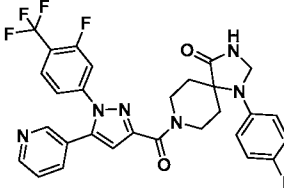
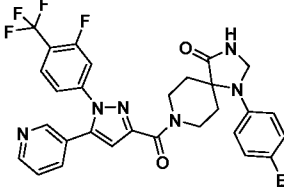
General procedure for the preparation of final compounds (General structure 60):

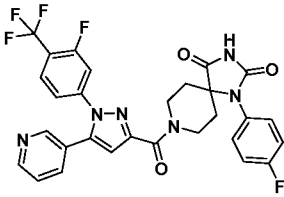
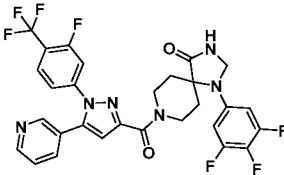
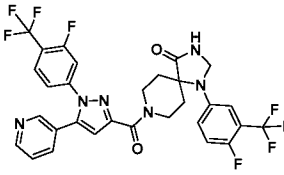
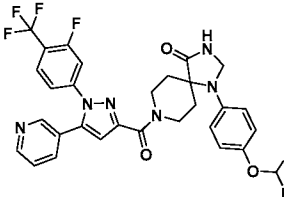
[0384] **General method N:** To an ice cold solution of 1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid **59** (0.150 g, 0.43 mmol), in DMF (2.0 mL) was added DIPEA (2.5 eq) and HATU (1.50 eq). The resulting mixture was stirred under nitrogen atmosphere at 0°C for 15 min followed by addition of respective amines (1.20 eq). The reaction mixture was then stirred at room temperature for 16 h. After the completion of the reaction (TLC monitoring), the solution was diluted with ice cold water (30 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified via prep-HPLC.

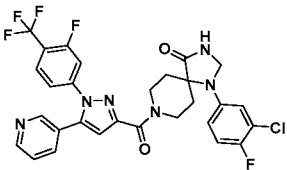
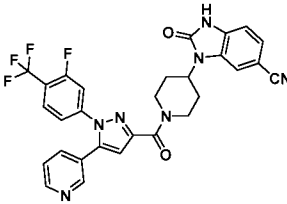
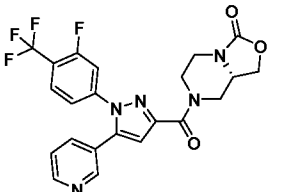
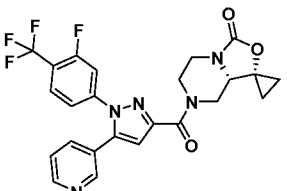
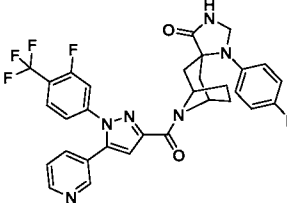
[0385] Please refer to **Table 6.1** for individual yields and the analytical data of the final compounds.

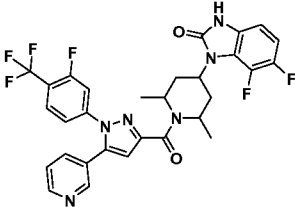
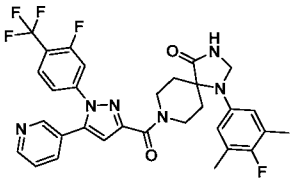
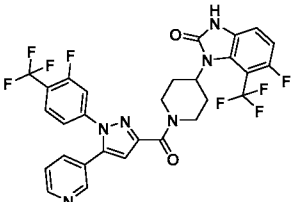
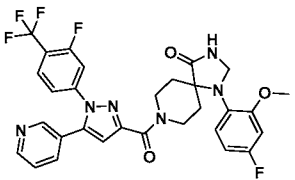
Table 6.1: Tabulated data of the final compounds including the individual yields obtained.

No.	Structure	Amine intermediate used	Yield (%)	LCMS	$^1\text{H-NMR}$ data (DMSO-d_6 , 400 MHz), unless otherwise specified
180		1	42	581.52 (M-H) $^+$, 99.91%	δ 8.81 (s, 1H), 8.59-8.62 (m, 2H), 7.83 (t, J = 8.0 Hz, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.61-7.64 (m, 1H), 7.44-7.47 (m, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.16 (s, 1H), 7.08-7.13 (m, 2H), 6.86-6.88 (m, 2H), 4.48-4.62 (m, 2H), 4.43-4.45 (m, 2H), 3.85-3.91 (m, 1H), 3.51-3.57 (m, 1H), 2.20-2.24 (m, 2H) and 1.74-1.78 (m, 2H)

181		2	10	599.35 (M-H) ⁺ , 99.71%	δ 8.89 (s, 1H), 8.60-8.62 (m, 2H), 7.82 (t, J = 8.0 Hz, 1H), 7.73 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 7.2 Hz, 1H), 7.44-7.47 (m, 1H), 7.28-7.34 (m, 2H), 7.16 (s, 1H), 6.75-6.79 (m, 1H), 6.57-6.60 (m, 1H), 4.60 (s, 2H), 4.47-4.49 (m, 2H), 3.83-3.89 (m, 1H), 3.50-3.55 (m, 1H), 2.32-2.40 (m, 2H) and 1.73-1.82 (m, 2H)
182		Commercial	9	603.44 (M+H) ⁺ , 95.32%	δ 8.61 (s, 2H), 7.82 (t, J = 8.64 Hz, 1H), 7.73 (d, J = 7.68 Hz, 1H), 7.64 (m, 1H), 7.44-7.47 (m, 1H), 7.33-7.35 (m, 1H), 7.24-7.31 (m, 2H), 7.19 (s, 1H), 6.99-7.01 (m, 1H), 5.64 (s, 1H), 4.85-4.89 (m, 1H), 4.71-4.74 (m, 1H), 3.40 (s, 1H), 2.05-2.09 (m, 2H) and 1.86 (s, 2H)
183		10	30	691.46 (M+H) ⁺ , 96.07%	δ 8.87 (s, 1H), 8.62-8.63 (m, 2H), 7.82 (t, J = 8.2 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.62-7.64 (m, 1H), 7.45-7.52 (m, 3H), 7.30 (d, J = 8.6 Hz, 1H), 7.08 (s, 1H), 6.59-6.61 (m, 2H), 4.59-4.60 (m, 2H), 4.48-4.50 (m, 2H), 3.84-3.90 (m, 1H), 3.47-3.56 (m, 1H), 2.38-2.42 (m, 2H) and 1.71-1.77 (m, 2H)
184		9	26	641.34 (M-H) ⁺ , 99.54%	δ 8.88 (s, 1H), 8.61-8.62 (m, 2H), 7.84 (t, J = 8.24 Hz, 1H), 7.73 (d, J = 7.88 Hz, 1H), 7.62-7.65 (m, 1H), 7.44-7.48 (m, 1H), 7.36 (d, J = 8.76 Hz, 2H), 7.29 (d, J = 8.6 Hz, 1H), 7.19 (s, 1H), 6.70-6.73 (m, 2H), 4.61 (s, 2H), 4.48-4.51 (m, 2H), 3.84-3.90 (m, 1H), 3.51-3.57 (m, 1H), 2.42-2.49 (m, 2H) and 1.71-1.81 (m, 2H)

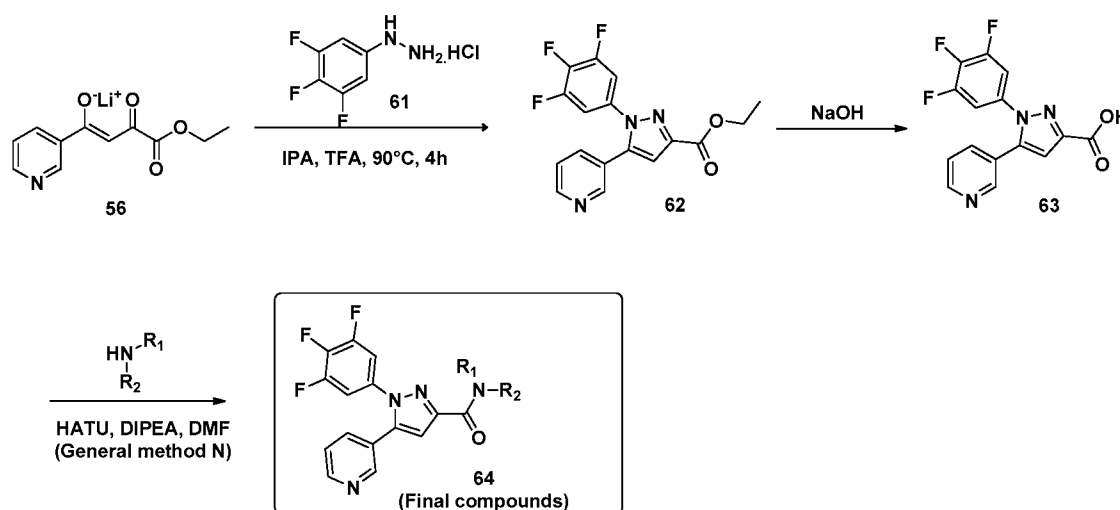
185		15	18	595.34 (M-H) ⁺ , 99.29%	δ 11.29 (br s, 1H), 8.60-8.62 (m, 1H), 8.56 (d, J= 1.52 Hz, 1H), 7.84 (t, J= 8.28 Hz, 1H), 7.70 (d, J= 8.12 Hz, 1H), 7.59 (d, J= 11.04 Hz, 1H), 7.44-7.48 (m, 1H), 7.27-7.37 (m, 5H), 7.07 (s, 1H), 4.48-4.51 (m, 1H), 4.32-4.36 (m, 1H), 3.78-3.84 (m, 1H), 3.42-3.48 (m, 1H), 2.13-2.22 (m, 2H) and 1.55-1.62 (m, 2H)
186		4	40	617.48 (M-H) ⁺ , 95.47%	δ 8.95 (s, 1H), 8.63-8.64 (m, 2H), 7.85 (t, J= 8.24 Hz, 1H), 7.78-7.80 (m, 1H), 7.60-7.63 (m, 1H), 7.48-7.51 (m, 1H), 7.27 (d, J= 8.76 Hz, 1H), 7.08 (s, 1H), 6.56-6.61 (m, 2H), 4.60 (s, 2H), 4.47-4.47 (m, 2H), 3.82-3.88 (m, 1H), 3.48-3.54 (m, 1H), 2.38-2.44 (m, 2H) and 1.73-1.81 (m, 2H)
187		5	18	651.54 (M-H) ⁺ , 95.32%	δ 8.93 (s, 1H), 8.62-8.64 (m, 2H), 7.82-7.86 (m, 1H), 7.75-7.77 (m, 1H), 7.60-7.63 (m, 1H), 7.47-7.50 (m, 1H), 7.38-7.42 (m, 1H), 7.27-7.29 (m, 1H), 7.15 (s, 1H), 7.06-7.08 (m, 1H), 6.94-6.97 (m, 1H), 4.68 (s, 2H), 4.47-4.51 (m, 2H), 3.75-3.80 (m, 1H), 3.49-3.55 (m, 1H), 2.32-2.41 (m, 2H) and 1.76-1.84 (m, 2H)
188		8	14	629.46 (M-H) ⁺ , 99.56%	δ 8.84 (s, 1H), 8.60-8.63 (m, 2H), 7.82 (t, J= 8.28 Hz, 1H), 7.72 (d, J= 8.28 Hz, 1H), 7.61-7.64 (m, 1H), 7.44-7.47 (m, 1H), 7.29-7.32 (m, 1H), 7.17 (s, 1H), 6.82-7.09 (m, 4H), 4.61 (s, 2H), 4.46-4.49 (m, 2H), 3.85-3.91 (m, 1H), 3.51-3.57 (m, 1H), 2.32-2.39 (m, 2H) and 1.74-1.82 (m, 2H)

189		3	8	617.26 (M+H) ⁺ , 93.55%	δ 8.88 (s, 1H), 8.60-8.62 (m, 2H), 7.82 (t, J = 8.4 Hz, 1H), 7.72 (d, J = 7.88 Hz, 1H), 7.62 (d, J = 7.6 Hz, 1H), 7.44-7.47 (m, 1H), 7.28-7.32 (m, 2H), 7.16 (s, 1H), 6.85-6.89 (m, 1H), 6.78-6.80 (m, 1H), 4.62 (s, 2H), 4.46-4.49 (m, 2H), 3.49-3.55 (m, 2H), 2.38-2.42 (m, 2H) and 1.74-1.79 (m, 2H)
190		20	13	574.46 (M-H) ⁺ , 99.75%	δ 11.46 (br s, 1H), 8.62-8.64 (m, 2H), 7.85-7.89 (m, 2H), 7.76 (d, J = 8.08 Hz, 1H), 7.64-7.67 (m, 1H), 7.43-7.50 (m, 2H), 7.33 (d, J = 8.12 Hz, 1H), 7.18 (s, 1H), 7.10-7.12 (m, 1H), 4.71-4.75 (m, 2H), 4.52-4.58 (m, 1H), 3.28-3.35 (m, 1H), 2.90-2.97 (m, 1H), 2.29-2.36 (m, 2H) and 1.78-1.86 (m, 2H)
191		Commer-cial	30	476.43 (M+H) ⁺ , 99.89%	δ 8.59-8.62 (m, 2H), 7.85 (t, J = 8.08 Hz, 1H), 7.69-7.73 (m, 2H), 7.44-7.47 (m, 1H), 7.31 (d, J = 7.88 Hz, 1H), 7.16 (s, 1H), 4.67-4.81 (m, 2H), 4.35-4.42 (m, 1H), 4.01-4.07 (m, 2H), 3.66-3.73 (m, 1H), 3.19-3.21 (m, 1H), 3.08-3.12 (m, 1H) and 2.78-2.84 (m, 1H)
192		Commer-cial	48	502.44 (M+H) ⁺ , 99.81%	δ 8.59-8.63 (m, 2H), 7.87 (s, 1H), 7.63-7.72 (m, 2H), 7.44-7.47 (m, 1H), 7.29-7.34 (m, 1H), 7.16 (s, 1H), 4.70-4.72 (m, 1H), 4.52-4.56 (m, 1H), 3.74-3.84 (m, 2H), 3.12-3.18 (m, 2H), 2.85-2.94 (m, 1H) and 0.94-1.08 (m, 4H)
193		11	5	609.52 (M+H) ⁺ , 99.73%	δ 8.79 (br s, 1H), 8.63 (s, 2H), 7.81 (t J = 8.4 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.57-7.60 (m, 1H), 7.45-7.48 (m, 1H), 7.33 (s, 1H), 7.27-7.29 (m, 1H), 6.90-6.94 (m, 2H), 6.72-6.75 (m, 2H), 5.24 (s, 1H),

					4.92 (s, 1H), 4.54 (s, 2H), 3.31-3.33 (m, 2H), 2.71-2.75 (m, 1H), 2.49-2.50 (m, 1H), 2.33-2.38 (m, 2H) and 1.82-1.92 (m, 2H)
194		21	15	613.23 (M-H) ⁺ , 96.59%	δ 11.25 (br s, 1H), 8.60-8.62 (m, 2H), 8.58 (t, J= 8.4 Hz, 1H), 7.73 (d, J= 8.0 Hz, 1H), 7.60-7.63 (m, 1H), 7.44-7.47 (m, 1H), 7.32 (d, J= 8.0 Hz, 1H), 7.12 (s, 1H), 7.00-7.06 (m, 1H), 6.76-6.79 (m, 1H), 4.82 (s, 1H), 4.67 (s, 1H), 3.91 (s, 1H), 2.22-2.27 (m, 2H), 1.88-1.91 (m, 1H), 1.78-1.81 (m, 1H), 1.52 (d, J= 6.4 Hz, 3H) and 1.44 (d, J= 6.8 Hz, 3H)
195		6	20	609.18 (M-H) ⁺ , 99.41%	δ 8.75 (s, 1H), 8.59-8.62 (m, 2H), 7.84 (t, J= 8.4 Hz, 1H), 7.72 (d, J= 8.0 Hz, 1H), 7.58-7.61 (m, 1H), 7.41-7.47 (m, 1H), 7.27 (d, J= 8.8 Hz, 1H), 7.12 (s, 1H), 6.58-6.59 (m, 2H), 4.55 (s, 2H), 4.39 (s, 2H), 3.81-3.87 (m, 2H), 2.28-2.32 (m, 1H), 2.18-2.21 (m, 1H), 2.08 (s, 6H) and 1.72-1.80 (m, 2H)
196		17	35	635.45 (M-H) ⁺ , 99.92%	δ 11.25 (br s, 1H), 8.60-8.62 (m, 2H), 7.85 (t, J= 8.0 Hz, 1H), 7.73 (d, J= 8.0 Hz, 1H), 7.65-7.68 (m, 1H), 7.44-7.47 (m, 1H), 7.33 (d, J= 8.0 Hz, 1H), 7.22-7.25 (m, 1H), 7.16 (s, 1H), 7.04-7.09 (m, 1H), 4.82-4.85 (m, 1H), 4.70-4.73 (m, 1H), 4.21-4.27 (m, 1H), 3.16-3.22 (m, 1H), 2.77-2.80 (m, 1H), 2.58-2.64 (m, 2H) and 1.75-1.84 (m, 2H)
197		7	14	612.90 (M+H) ⁺ , 97.83%	δ 8.59-8.60 (m, 1H), 8.56 (s, 1H), 8.50 (s, 1H), 7.83 (t, J= 8.4 Hz, 1H), 7.68 (d, J= 8.0 Hz, 1H), 7.58-7.61 (m, 1H), 7.42-7.45 (m, 1H), 7.27 (d, J= 6.4 Hz, 2H), 7.05 (s, 1H), 6.93-

					6.97 (m, 1H), 6.71-6.75 (m, 1H), 4.47-4.52 (m, 2H), 4.00-4.08 (m, 1H), 3.91-3.96 (m, 2H), 3.76 (s, 3H), 3.62-3.68 (m, 1H), 1.83-1.89 (m, 2H) and 1.40-1.46 (m, 2H)
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Scheme 12



[0386] Preparation of ethyl 5-(pyridin-3-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylate (62): To an ice-cold solution of 4-ethoxy-3,4-dioxo-1-(pyridin-3-yl)but-1-en-1-

olate lithium salt **56** (10.0 g, 45.23 mmol) in IPA (50 mL) was added (3,4,5-trifluorophenyl)hydrazine hydrochloride **61** (10.77 g, 54.28 mmol) and TFA (6.9 mL, 90.46 mmol). The resulting reaction mixture was warm up to room temperature and then stirred at 90°C for 4 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified over silica gel (100-200 M, 10-15% EtOAc-hexane) to get the desired product **62** (5.50 g, 35%).

[0387] ¹H-NMR (400 MHz, CDCl₃): δ 8.68 (m, 1H), 8.61 (s, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.42 (m, 1H), 7.14 (s, 1H), 7.03 (m, 2H), 4.48 (q, *J* = 7.2 Hz, 2H) and 1.41 (t, *J* = 7.2 Hz, 3H).

MS: 348.15 (M+H)⁺.

[0388] Preparation of 5-(pyridin-3-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylic acid (63): To an ice-cold solution of ethyl 5-(pyridin-3-yl)-1-(3,4,5-

trifluorophenyl)-1H-pyrazole-3-carboxylate **62** (5.50 g, 15.82 mmol) in EtOH (40 mL) was added drop wise an aqueous solution of sodium hydroxide (1.26 g, 31.64 mmol). The

resulting solution was stirred at room temperature for 2 h. After completion of the reaction (TLC monitoring), the solvent was evaporated, added H₂O to the residue followed by extraction with EtOAc (2 x 100 mL). The organic layer was discarded and the pH of the aqueous layer was adjusted to ~4 by adding 1N HCl. The resulting precipitate was filtered and dried under vacuum to get the desired product **63** (3.0 g, 59%) as a white solid.

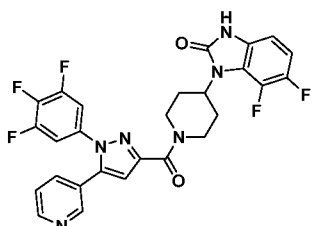
[0389] ¹H-NMR (400 MHz, DMSO-d₆): δ 13.13 (br s, 1H), 8.59 (s, 2H), 7.65 (d, *J*= 8.4 Hz, 1H), 7.52 (m, 2H), 7.41 (m, 1H) and 7.25 (s, 1H). LCMS: 320.14 (M+H)⁺, 95.20 %.

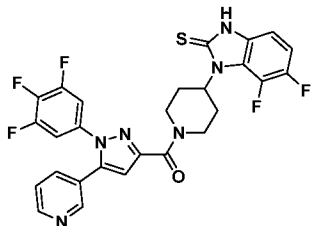
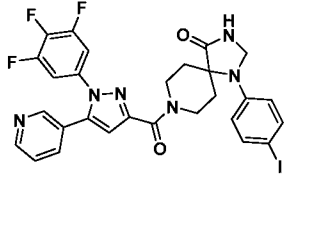
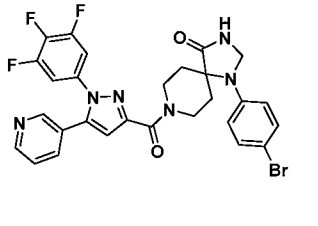
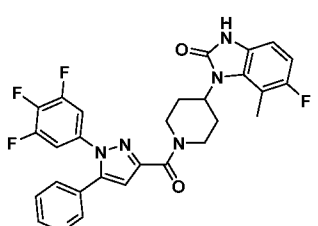
[0390] **General procedure for the preparation of final compounds (General structure**

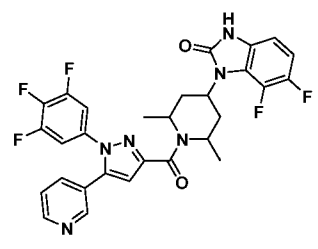
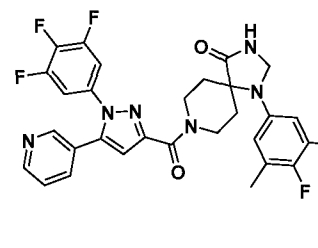
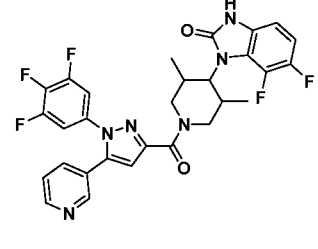
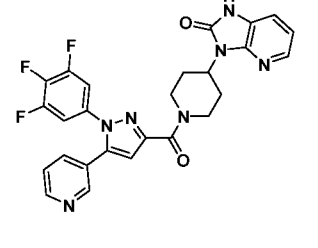
64): The final compounds were prepared following the **general method N**. To an ice cold solution of carboxylic acid **63** (125-150 mg), in DMF (2.0 mL) was added DIPEA (2.5 eq) and HATU (1.50 eq). The resulting mixture was stirred under nitrogen atmosphere at 0°C for 15 min followed by addition of respective amines (1.20 eq). The reaction mixture was then stirred at room temperature for 16 h. After the completion of the reaction (TLC monitoring), the solution was diluted with ice cold water (30 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organics was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified via prep-HPLC.

[0391] Please refer to **Table 6.2** for individual yields and the analytical data of the final compounds.

Table 6.2: Tabulated data of the final compounds including the individual yields obtained.

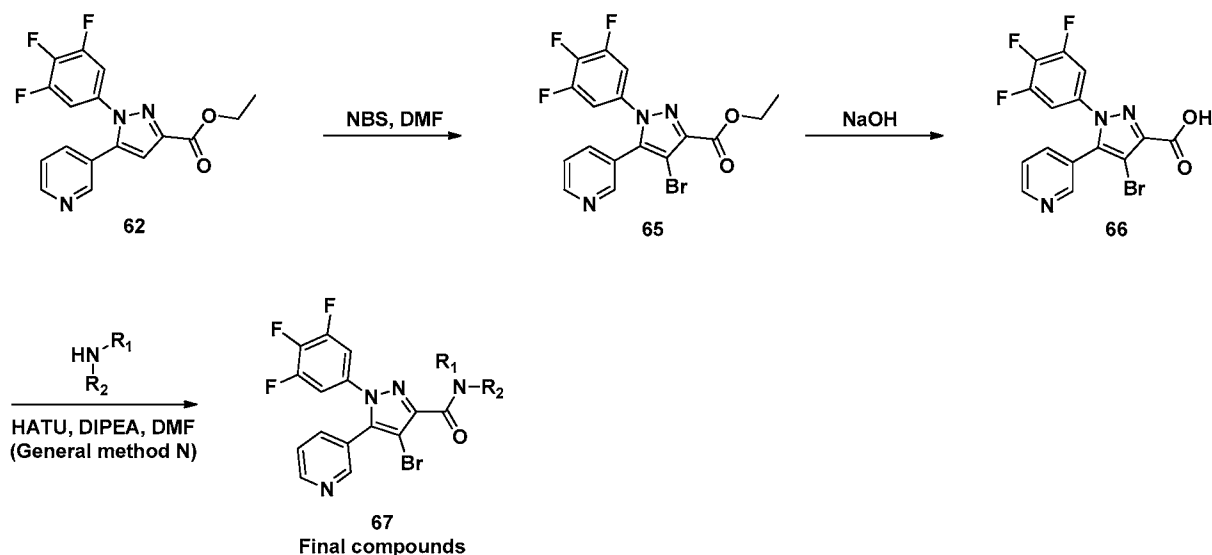
No.	Structure	Amine intermediate used	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz)
198		16	32	555.11 (M+H) ⁺ , 95.55%	δ 11.25 (br s, 1H), 8.60 (s, 2H), 7.67 (d, <i>J</i> = 8.0 Hz, 1H), 7.50-7.53 (m, 2H), 7.39-7.42 (m, 1H), 7.14 (s, 1H), 7.00-7.05 (m, 1H), 6.77-6.80 (m, 1H), 4.80-4.84 (m, 1H), 4.67-4.70 (m, 2H), 3.32 (s, 1H), 2.92-2.98 (m, 1H), 2.11-2.16 (m, 2H) and 1.85-1.88 (m, 2H)

199		Commercial	10	569.31 (M-H) ⁺ , 88.55%	δ 13.11 (br s, 1H), 8.60 (s, 2H), 7.70 (d, J = 8.56 Hz, 1H), 7.50-7.53 (m, 2H), 7.41-7.44 (m, 1H), 7.24-7.29 (m, 1H), 7.16 (s, 1H), 7.00-7.01 (m, 1H), 4.87-4.90 (m, 1H), 4.72-4.74 (m, 2H), 3.32 (s, 1H), 2.92-2.98 (m, 1H), 2.07-2.11 (m, 2H) and 1.86-1.90 (m, 2H)
200		10	22	659.50 (M+H) ⁺ , 97.37%	δ 8.87 (s, 1H), 8.62-8.63 (m, 2H), 7.71 (t, J = 8.2 Hz, 1H), 7.44-7.51 (m, 5H), 7.17 (s, 1H), 6.58-6.60 (m, 2H), 4.59-4.60 (m, 2H), 4.49-4.50 (m, 2H), 3.82-3.87 (m, 2H), 3.49-3.55 (m, 1H), 2.42-2.45 (m, 1H) and 1.70-1.79 (m, 2H)
201		9	25	609.29 (M-H) ⁺ , 99.91%	δ 8.88 (s, 1H), 8.60-8.61 (m, 2H), 7.66 (t, J = 8.04 Hz, 1H), 7.36-7.50 (m, 5H), 7.17 (s, 1H), 6.69-6.72 (m, 2H), 4.59-4.60 (m, 2H), 4.47-4.50 (m, 2H), 3.82-3.88 (m, 1H), 3.50-3.55 (m, 1H), 2.42-2.49 (m, 2H) and 1.70-1.80 (m, 2H)
202		18	18	551.37 (M+H) ⁺ , 99.88%	δ 10.84 (br s, 1H), 8.60 (s, 2H), 7.68 (t, J = 7.92 Hz, 1H), 7.50-7.56 (m, 2H), 7.42-7.45 (m, 1H), 7.13 (s, 1H), 6.74-6.82 (m, 2H), 4.76-4.79 (m, 1H), 4.66-4.69 (m, 2H), 3.25-3.28 (m, 1H), 2.88-2.94 (m, 1H), 2.55-2.58 (m, 2H), 2.50 (s, 3H) and 1.84-1.90 (m, 2H)

203		21	5	583.21 (M+H) ⁺ , 97.96%	δ 11.25 (br s, 1H), 8.59-8.60 (m, 2H), 7.67 (d <i>J</i> = 8.0 Hz, 1H), 7.47-7.50 (m, 2H), 7.41-7.44 (m, 1H), 7.10 (s, 1H), 7.00-7.07 (m, 1H), 6.76-6.79 (m, 1H), 4.80 (s, 1H), 4.67 (s, 1H), 3.90 (s, 1H), 2.23-2.30 (m, 2H), 1.80-1.90 (m, 2H), 1.51 (d, <i>J</i> = 6.4 Hz, 3H) and 1.42 (d, <i>J</i> = 6.8 Hz, 3H)
204		6	18	579.13 (M+H) ⁺ , 99.12%	δ 8.74 (s, 1H), 8.58- 8.60 (m, 2H), 7.66 (d, <i>J</i> = 8.0 Hz, 1H), 7.41-7.48 (m, 3H), 7.10 (s, 1H), 6.58- 6.59 (m, 2H), 4.55 (s, 2H), 4.38-4.41 (s, 2H), 3.79-3.85 (m, 1H), 3.47-3.53 (m, 1H), 2.21-2.25 (m, 2H), 2.12 (s, 6H) and 1.72-1.79 (m, 2H)
207		22	6	583.37 (M+H) ⁺ , 97.90%	δ 11.31 (br s, 1H), 8.60-8.61 (m, 2H), 7.69 (d, <i>J</i> = 8.4 Hz, 1H), 7.43-7.52 (m, 3H), 7.10 (s, 1H), 6.99-7.07 (m, 1H), 6.77-6.79 (m, 1H), 4.65 (s, 1H), 4.31- 4.34 (m, 2H), 3.87- 3.90 (m, 1H), 3.51- 3.54 (m, 1H), 2.26- 2.33 (m, 2H), 0.85 (d, <i>J</i> = 6.4 Hz, 3H) and 0.77 (d, <i>J</i> = 6.8 Hz, 3H)
208		19	12	518.13 (M-H) ⁺ , 97.02%	δ 11.12 (br s, 1H), 8.59-8.60 (m, 2H), 7.92 (d, <i>J</i> = 4.4 Hz, 1H), 7.67 (d <i>J</i> = 8.0 Hz, 1H), 7.50-7.54 (m, 2H), 7.41-7.44 (m, 1H), 7.28 (d <i>J</i> = 6.8 Hz, 1H), 7.15 (s, 1H), 6.97 (t, <i>J</i> =

					7.6 Hz, 1H), 4.79-4.82 (m, 1H), 4.69-4.72 (m, 1H), 4.55-4.57 (m, 1H), 3.28-3.32 (m, 1H), 2.90-2.96 (m, 1H), 2.50-2.55 (m, 2H) and 1.76-1.84 (m, 2H)
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Scheme 13



- 5 [0392] **Preparation of Ethyl 4-bromo-5-(pyridin-3-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylate (65):** To a solution of ethyl 5-(pyridin-3-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylate **62** (1.0 g, 2.88 mmol) in DMF (15 mL) was added NBS (0.77 g, 4.32 mmol). The resulting reaction mixture was heated at 50°C for 4 h. After completion of the reaction (TLC monitoring), the solvent was ice-cold water and
- 10 extracted with ethyl acetate (3 times). The combined organics was washed with ice-cold water, brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified over silica gel (100-200 M, 3-5% EtOAc-hexane) to get the desired product **65** (0.99 g, yield: 81%)

- [0393] ¹H-NMR (400 MHz, CDCl₃): δ 8.71-8.72 (m, 1H), 8.53 (s, 1H), 7.66 (d, *J* = 7.88 Hz, 1H), 7.42-7.45 (m, 1H), 6.93-6.99 (m, 2H), 4.50 (q, *J* = 7.12 Hz, 2H) and 1.39 (t, *J* = 7.2 Hz, 3H). MS: 426.18 (M+H)⁺.
- 15

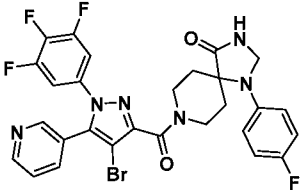
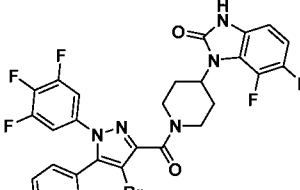
- [0394] **4-bromo-5-(pyridin-3-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylic acid (66):** To an ice-cold solution of ethyl 4-bromo-5-(pyridin-3-yl)-1-(3,4,5-

trifluorophenyl)-1H-pyrazole-3-carboxylate **65** (0.99 g, 2.33 mmol) in EtOH (20 mL) was added drop wise an aqueous solution of sodium hydroxide (0.19 g, 4.66 mmol). The resulting solution was stirred at room temperature for 2 h. After completion of the reaction (TLC monitoring), the solvent was evaporated, added H₂O to the residue followed by extraction with EtOAc (2 x 100 mL). The organic layer was discarded and the pH of the aqueous layer was adjusted to ~4 by adding 1N HCl. The resulting precipitate was filtered and dried under vacuum to get the desired product **66** (0.35 g, yield: 39%) as a white solid.

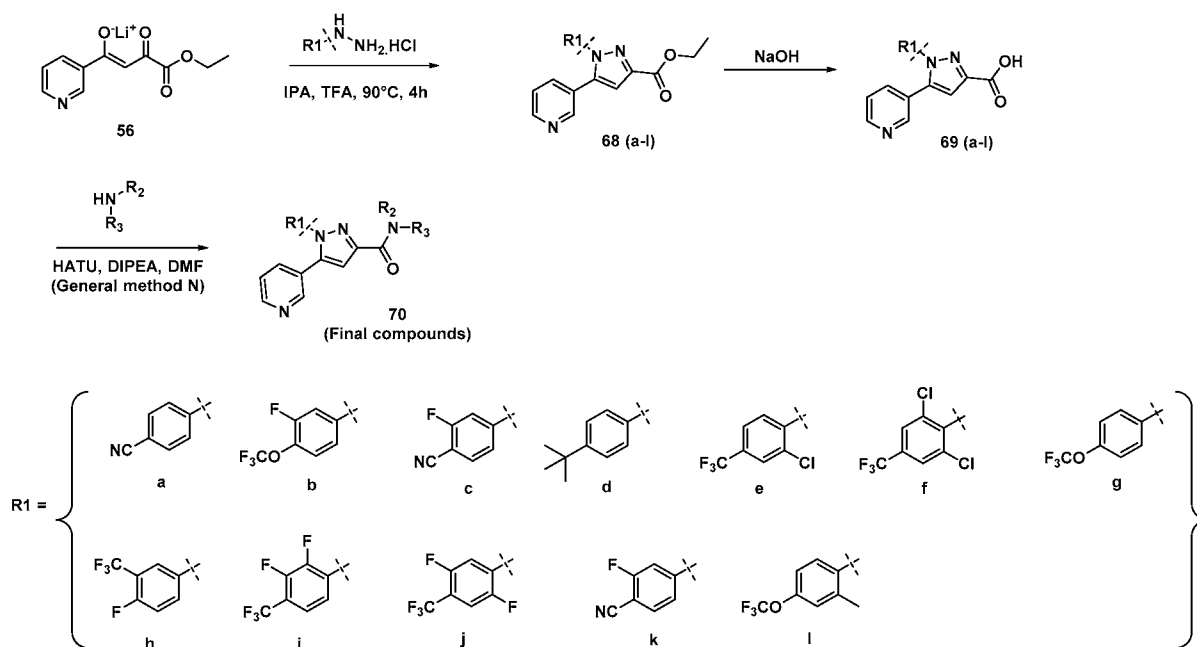
[0395] ¹H-NMR (400 MHz, DMSO-d₆): δ 13.45 (br s, 1H), 8.64-8.65 (m, 1H), 8.57 (s, 1H), 7.77 (d, *J* = 7.96 Hz, 1H) and 7.48-7.52 (m, 3H). LCMS: 397.94 (M+H)⁺, 86.45 %.

- 10 [0396] **General procedure for the preparation of final compounds (General structure 67):** The final compounds were prepared following the **general method N** on 100-150 mg scale. Please refer to **Table 6.3** for individual yields and the analytical data of the final compounds.

Table 6.3: Tabulated data of the final compounds including the individual yields obtained.

No.	Structure	Amine intermediate used	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz)
210		1	13	629.42 (M+H) ⁺ , 99.53%	δ 8.84 (s, 1H), 8.65-8.66 (m, 1H), 8.58 (s, 1H), 7.77 (d, J = 7.84 Hz, 1H), 7.50-7.53 (m, 1H), 7.42-7.45 (m, 2H), 7.10-7.14 (m, 2H), 6.83-6.86 (m, 2H), 4.58-4.61 (m, 2H), 4.45-4.48 (m, 1H), 3.80-3.90 (m, 2H), 3.52-3.58 (m, 1H), 2.27-2.32 (m, 2H), 1.80-1.84 (m, 1H) and 1.71-1.75 (m, 1H)
211		16	26	633.38 (M+H) ⁺ , 97.73%	δ 10.50 (br s, 1H), 8.65-8.66 (m, 1H), 8.59 (s, 1H), 7.78 (d, J = 7.88 Hz, 1H), 7.44-7.52 (m, 3H), 7.00-7.07 (m, 1H), 6.78-6.80 (m, 1H), 4.60-4.70 (m, 2H), 4.10-4.13 (m, 1H), 3.32 (s, 1H), 2.97-3.03 (m, 1H), 2.12-2.18 (m, 2H) and 1.75-1.90 (m, 2H)

Scheme 14



[0397] **General procedure for the preparation of compounds 68 (a-l):** To an ice-cold solution of 4-ethoxy-2-methyl-3,4-dioxo-1-(pyridin-3-yl)but-1-en-1-olate lithium salt **56** (3.0 g, 13.21 mmol) in IPA was added respective hydrazine hydrochloride (1.2 eq) and TFA (2.0 eq). The resulting reaction mixture was warm up to room temperature and then stirred at 90°C for 4-5 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified over silica gel (100-200 M, 10-15% EtOAc-hexane) to get the desired product **68 (a-l)**.

[0398] **Ethyl 1-(4-cyanophenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (68-a):** ¹H-NMR (400 MHz, CDCl₃): δ 9.17 (m, 1H), 8.80-8.81 (m, 1H), 8.22-8.24 (m, 1H), 7.61-7.63 (m, 2H), 7.42-7.45 (m, 2H), 7.14 (s, 1H), 7.05-7.09 (m, 1H), 4.44 (q, *J* = 7.2 Hz, 2H) and 1.35 (t, *J* = 7.2 Hz, 3H). MS: 319.03 (M+H)⁺. Yield: 13%.

[0399] **Ethyl 1-(3-fluoro-4-(trifluoromethoxy)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (68-b):** ¹H-NMR (400 MHz, CDCl₃): δ 8.62-8.68 (m, 2H), 7.61-7.63 (m, 1H), 7.41-7.44 (m, 1H), 7.29-7.34 (m, 2H), 7.14 (s, 1H), 7.07-7.10 (m, 1H), 4.44 (q, *J* = 7.6 Hz, 2H) and 1.38 (t, *J* = 7.2 Hz, 3H). MS: 396.14 (M+H)⁺. Yield: 41%.

[0400] **Ethyl 1-(4-cyano-3-fluorophenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (68-c):** ¹H-NMR (400 MHz, CDCl₃): δ 8.71-8.72 (m, 1H), 8.62 (s, 1H), 7.61-7.64 (m, 2H),

7.44-7.47 (m, 1H), 7.35-7.38 (m, 1H), 7.19 (s, 1H), 7.15-7.17 (m, 1H), 4.42 (q, J = 7.6 Hz, 2H) and 1.36 (t, J = 7.6 Hz, 3H). LCMS: 337.13 (M+H)⁺, 96.65%. Yield: 26%.

[0401] Ethyl 1-(4-(tert-butyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (68-d): ¹H-NMR (400 MHz, CDCl₃): δ 8.58-8.62 (m, 1H), 8.54-8.58 (m, 1H), 7.52-7.54 (m, 1H), 7.39-7.41 (m, 2H), 7.22-7.28 (m, 3H), 7.11 (s, 1H), 4.44 (q, J = 7.2 Hz, 2H), 1.37 (t, J = 7.6 Hz, 3H) and 1.25 (s, 9H). MS: 350.23 (M+H)⁺. Yield: 23%.

[0402] Ethyl 1-(2-chloro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (68-e): ¹H-NMR (400 MHz, CDCl₃): δ 8.57-8.58 (m, 1H), 8.48 (s, 1H), 7.65-7.70 (m, 3H), 7.48-7.50 (m, 1H), 7.24-7.27 (m, 1H), 7.14 (s, 1H), 4.44 (q, J = 7.2 Hz, 2H) and 1.36 (t, J = 7.2 Hz, 3H). MS: 396.27 (M+H)⁺. Yield: 30%.

[0403] Ethyl 1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (68-f): ¹H-NMR (400 MHz, CDCl₃): δ 8.71-8.76 (m, 1H), 8.62-8.65 (m, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.69 (s, 2H), 7.46-7.49 (m, 1H), 7.21 (s, 1H), 4.45 (q, J = 7.6 Hz, 2H) and 1.38 (t, J = 7.2 Hz, 3H). MS: 430.08 (M+H)⁺. Yield: 31%.

[0404] Ethyl 5-(pyridin-3-yl)-1-(4-(trifluoromethoxy)phenyl)-1H-pyrazole-3-carboxylate (68-g): ¹H-NMR (400 MHz, CDCl₃): δ 8.73-8.81 (m, 2H), 8.39-8.41 (m, 1H), 7.72-7.74 (m, 1H), 7.52-7.54 (m, 1H), 7.45-7.47 (m, 2H), 7.33-7.35 (m, 2H), 4.52 (q, J = 7.6 Hz, 2H) and 1.51 (t, J = 7.2 Hz, 3H). LC-MS: 378.28 (M+H)⁺, 88.27% Yield: 40%.

[0405] Ethyl 1-(4-fluoro-3-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (68-h): ¹H-NMR (400 MHz, CDCl₃): δ 8.59-8.66 (m, 1H), 7.77-7.78 (m, 1H), 7.56 (d, J = 8.04 Hz, 1H), 7.38-7.41 (m, 2H), 7.23-7.25 (m, 1H), 7.21 (s, 1H), 7.07-7.10 (m, 1H), 4.48 (q, J = 7.2 Hz, 2H) and 1.38 (t, J = 7.6 Hz, 3H). MS: 380.22 (M+H)⁺. Yield: 35%.

[0406] Ethyl 1-(2,3-difluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (68-i): ¹H-NMR (400 MHz, CDCl₃): δ 8.75-8.79 (m, 1H), 8.50-8.51 (m, 1H), 7.52-7.57 (m, 3H), 7.26 (s, 1H), 7.15 (s, 1H), 4.44 (q, J = 6.92 Hz, 2H) and 1.39 (t, J = 7.16 Hz, 3H). MS: 397.94 (M+H)⁺. Yield: 16%.

[0407] Ethyl 1-(2,5-difluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (68-j): ¹H-NMR (400 MHz, CDCl₃): δ 8.66-8.73 (m, 2H), 7.80 (d, J = 8.0 Hz, 1H), 7.62-7.66 (m, 1H), 7.55-7.58 (m, 1H), 7.35-7.35 (m, 1H), 7.21 (s, 1H), 4.48 (q, J = 7.20 Hz, 2H) and 1.42 (t, J = 7.20 Hz, 3H). MS: 398.15 (M+H)⁺. Yield: 35%.

[0408] **Ethyl 1-(4-cyano-3-fluorophenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (68-k):** $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.71-8.72 (m, 1H), 8.62 (s, 1H), 7.61-7.64 (m, 2H), 7.44-7.47 (m, 1H), 7.36 (d, $J = 7.6$ Hz, 1H), 7.26 (s, 1H), 7.15-7.17 (m, 1H), 4.50 (q, $J = 7.16$ Hz, 2H) and 1.43 (t, $J = 7.24$ Hz, 3H). MS: 337.14 ($\text{M}+\text{H}$) $^+$. Yield: 26%.

5 [0409] **Ethyl 1-(2-methyl-4-(trifluoromethoxy)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (68-l):** $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.51-8.55 (m, 2H), 8.40-8.42 (m, 1H), 7.32-7.34 (m, 1H), 7.20-7.24 (m, 1H), 7.17 (s, 1H), 6.94-6.99 (m, 2H), 4.43 (q, $J = 7.20$ Hz, 2H), 1.98 (s, 3H) and 1.42 (t, $J = 7.24$ Hz, 3H). MS: 392.54 ($\text{M}+\text{H}$) $^+$. Yield: 29%.

[0410] **General procedure for the preparation of compounds 69 (a-l):** To an ice-cold solution of compound **68 (a-l)** (0.80-1.5 g, 1.0 eq) in EtOH was added drop wise an aqueous solution of sodium hydroxide (3.0 eq). The resulting solution was stirred at room temperature for 2-3 h. After completion of the reaction (TLC monitoring), the solvent was evaporated, added H_2O to the residue followed by extraction with EtOAc (2 x 100 mL). The organic layer was discarded and the pH of the aqueous layer was adjusted to ~ 4 by adding 1N HCl. The resulting precipitate was filtered and dried under vacuum to get the desired product **69 (a-l)** as a white solid.

[0411] **1-(4-Cyanophenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (69-a):** LC-MS: 291.27($\text{M}+\text{H}$) $^+$, 85.5%. Yield: 66%.

20 [0412] **1-(3-Fluoro-4-(trifluoromethoxy)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (69-b):** $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 13.15 (br s, 1H), 8.56-8.59 (m, 2H), 7.68-7.71 (m, 3H), 7.41-7.44 (m, 1H), 7.25-7.29 (m, 1H) and 7.17 (s, 1H). LCMS: 368.29 ($\text{M}+\text{H}$) $^+$, 94.25%. Yield: 61%.

[0413] **1-(4-Cyano-3-fluorophenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (69-c):** $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 13.18 (br s, 1H), 8.59-8.91 (m, 2H), 7.67-7.68 (m, 2H), 7.41-7.44 (m, 1H), 7.25-7.27 (m, 2H) and 7.22 (s, 1H). MS: 309.11 ($\text{M}+\text{H}$) $^+$. Yield: 30%.

[0414] **1-(4-(Tert-butyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (69-d):** $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 13.0 (br s, 1H), 8.54-8.55 (m, 1H), 8.48 (s, 1H), 7.66-7.68 (m, 1H), 7.47-7.49 (m, 2H), 7.39-7.42 (m, 1H), 7.26-7.28 (m, 2H), 7.20 (s, 1H) and 1.29 (s, 9H). LCMS: 322.0 ($\text{M}+\text{H}$) $^+$, 98.33%. Yield: 30%.

[0415] **1-(2-Chloro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (69-e):** $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 13.19 (br s, 1H), 8.50-8.54 (m, 2H), 8.14 (s, 1H), 8.04 (d, J = 8.16 Hz, 1H), 7.96 (d, J = 8.20 Hz, 1H), 7.62-7.63 (m, 1H), 7.37-7.43 (m, 1H) and 7.33 (s, 1H). LCMS: 368.12 (M+H) $^+$, 97.38%. Yield: 81%.

5 [0416] **1-(2,6-dichloro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (69-f):** $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 13.33 (br s, 1H), 8.57 (d, J = 1.6 Hz, 1H), 8.52 (s, 1H), 8.28 (s, 2H), 7.60-7.62 (m, 1H) and 7.41-7.44 (m, 2H). LCMS: 402.08 (M+H) $^+$, 96.28%. Yield: 84%.

10 [0417] **5-(pyridin-3-yl)-1-(4-(trifluoromethoxy)phenyl)-1H-pyrazole-3-carboxylic acid (69-g):** $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 13.09 (br s, 1H), 8.52-8.57 (m, 2H), 7.66-7.70 (m, 1H), 7.40-7.43 (m, 5H) and 7.23 (s, 1H). LCMS: 350.27 (M+H) $^+$, 91.79%. Yield: 63%.

[0418] **1-(4-fluoro-3-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (69-h):** $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 13.15 (br s, 1H), 8.57-8.58 (m, 2H), 7.84-7.86 (m, 1H), 7.60-7.69 (m, 3H), 7.40-7.45 (m, 1H) and 7.24 (s, 1H). LCMS: 352.24 (M+H) $^+$, 95.84%. Yield: 73%.

[0419] **1-(2,3-Difluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (69-i):** $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 13.30 (br s, 1H), 8.60-8.61 (m, 2H), 7.80-7.83 (m, 1H), 7.63-7.73 (m, 2H), 7.41-7.44 (m, 1H) and 7.25 (s, 1H). MS: 370.08 (M+H) $^+$, Yield: 86%.

20 [0420] **1-(2,5-Difluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (69-j):** $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 13.34 (br s, 1H), 8.60 (s, 2H), 7.99-8.10 (m, 2H), 7.72 (d, J = 7.0 Hz, 1H), 7.43 (s, 1H) and 7.33 (s, 1H). LCMS: 370.27 (M+H) $^+$, 97.55%. Yield: 68%.

25 [0421] **1-(4-cyano-3-fluorophenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (69-k):** $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 13.18 (br s, 1H), 8.59 (s, 2H), 8.01-8.05 (m, 1H), 7.81 (d, J = 8.32 Hz, 1H), 7.67-7.70 (m, 2H), 7.25-7.27 (m, 1H) and 7.22 (s, 1H). MS: 309.11 (M+H) $^+$. Yield: 30%.

[0422] **1-(2-methyl-4-(trifluoromethoxy)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (69-l):** $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 13.08 (br s, 1H), 8.51-8.57 (m,

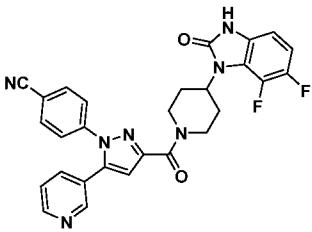
1H), 8.47 (s, 1H), 7.55-7.62 (m, 2H), 7.44 (s, 1H), 7.34-7.38 (m, 2H), 7.29 (s, 1H) and 1.93 (s, 3H). LCMS: 364.26 (M+H)⁺, 92.06%. Yield: 75%.

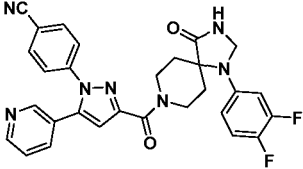
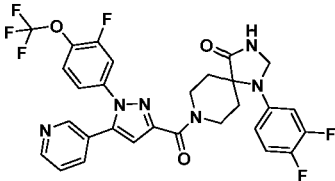
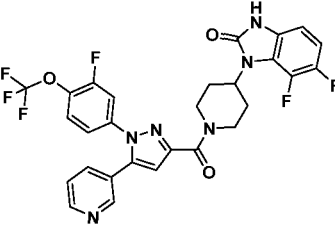
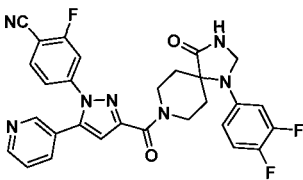
[0423] General procedure for the preparation of final compounds (General structure

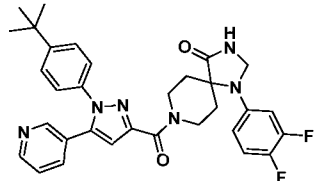
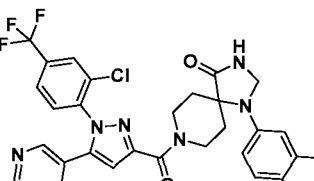
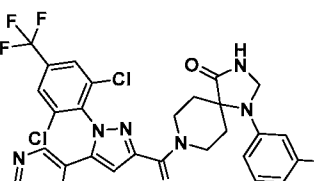
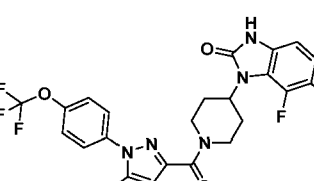
70): The final compounds were prepared following the **general method N**. To an ice cold solution of carboxylic acids **69 (a-l)** (125-150 mg), in DMF (2.0 mL) was added DIPEA (2.5 eq) and HATU (1.50 eq). The resulting mixture was stirred under nitrogen atmosphere at 0°C for 15 min followed by addition of respective amines (1.20 eq). The reaction mixture was then stirred at room temperature for 16 h. After the completion of the reaction (TLC monitoring), the solution was diluted with ice cold water (30 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organics was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The final compounds were purified via prep-HPLC.

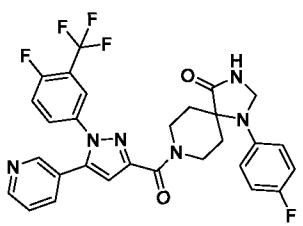
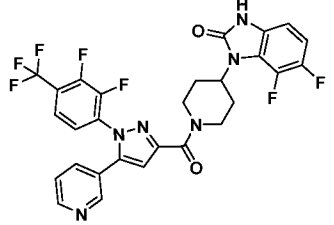
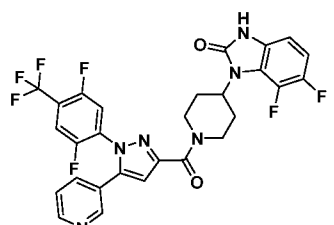
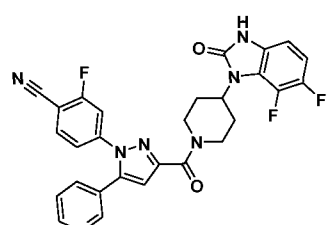
[0424] Please refer to **Table 6.4** for individual yields and the analytical data of the final compounds.

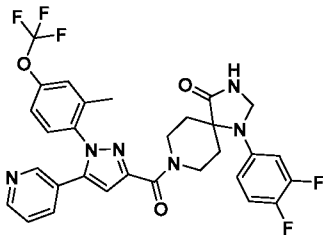
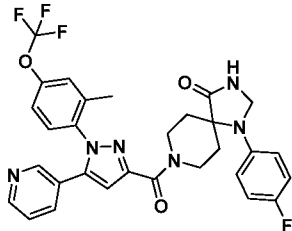
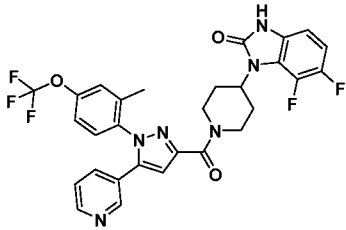
Table 6.4: Tabulated data of the final compounds including the individual yields obtained.

No.	Structure	Amine intermediate used	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz)
212		16	15	524.35 (M-H) ⁺ , 99.78%	δ 11.15 (br s, 1H), 8.60 (d, J= 1.12 Hz, 1H), 8.56 ((d, J= 1.68 Hz, 1H), 7.93 (d, J= 8.52 Hz, 2H), 7.68 ((d, J= 8.0 Hz, 1H), 7.54 ((d, J= 8.52 Hz, 2H), 7.41-7.45 (m, 1H), 7.15 (s, 1H), 7.00-7.07 (m, 1H), 6.77-6.80 (m, 1H), 4.80-4.83 (m, 1H), 4.63-4.71 (m, 2H), 3.32 (s, 1H), 2.93-2.99 (m, 1H), 2.07-2.17 (m, 2H) and 1.85-1.88 (m, 2H)

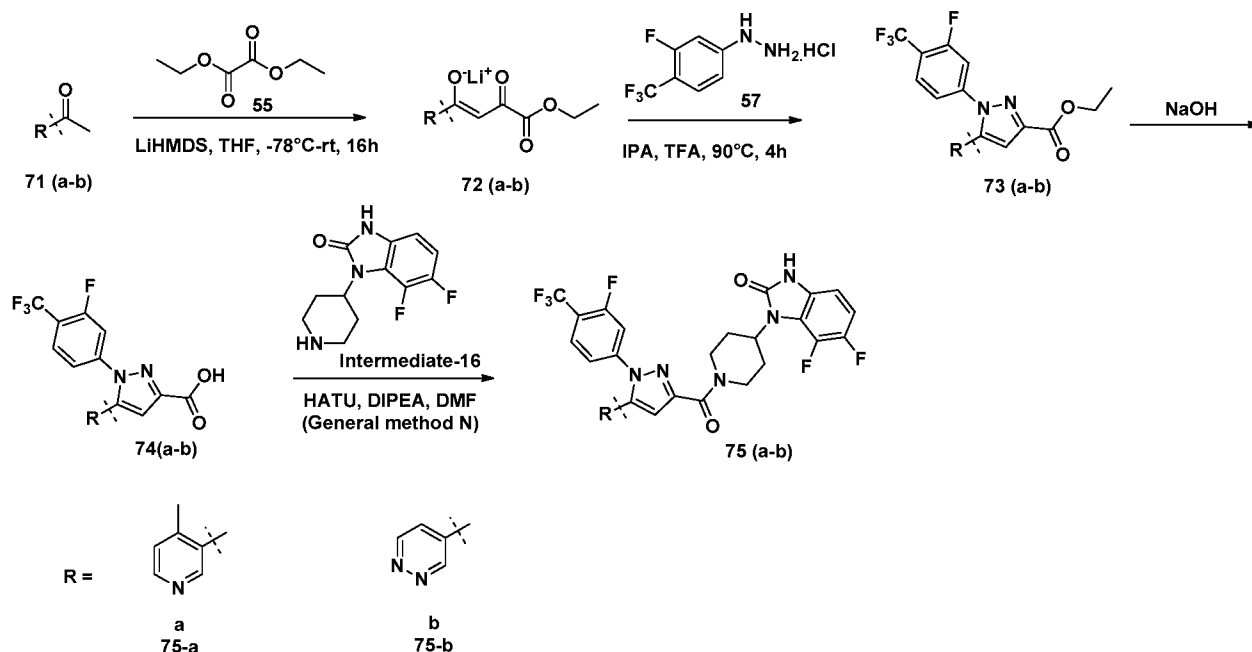
213		2	13	538.35 (M-H) ⁺ , 98.24%	δ 8.89 (s, 1H), 8.56-8.61 (m, 2H), 7.91 (t, <i>J</i> = 8.52 Hz, 1H), 7.73 (d, <i>J</i> = 8.0 Hz, 1H), 7.67 (d, <i>J</i> = 8.12 Hz, 1H), 7.51-7.54 (m, 2H), 7.42-7.45 (m, 1H), 7.26-7.31 (m, 1H), 7.15 (s, 1H), 6.74-6.79 (m, 1H), 6.57-6.59 (m, 1H), 4.59 (s, 2H), 4.47-4.52 (m, 2H), 3.84-3.90 (m, 1H), 3.49-3.55 (m, 1H), 2.35-2.39 (m, 2H) and 1.73-1.81 (m, 2H)
214		2	31	615.38 (M-H) ⁺ , 99.36%	δ 8.88 (s, 1H), 8.58-8.61 (m, 2H), 7.63-7.72 (m, 3H), 7.47-7.47 (m, 1H), 7.24-7.34 (m, 2H), 7.15 (s, 1H), 6.74-6.79 (m, 1H), 6.57-6.59 (m, 1H), 4.60 (s, 2H), 4.47-4.52 (m, 2H), 3.83-3.89 (m, 1H), 3.45-3.55 (m, 1H), 2.33-2.44 (m, 2H) and 1.73-1.77 (m, 2H)
215		16	22	603.42 (M+H) ⁺ , 96.04%	δ 11.25 (br s, 1H), 8.57-8.59 (m, 2H), 7.68-7.72 (m, 3H), 7.42-7.45 (m, 1H), 7.28 (d, <i>J</i> = 8.6 Hz, 1H), 7.14 (s, 1H), 7.00-7.04 (m, 1H), 6.77-6.80 (m, 1H), 4.82-4.85 (m, 1H), 4.67-4.71 (m, 2H), 3.32 (s, 1H), 2.92-2.98 (m, 1H), 2.11-2.17 (m, 2H) and 1.85-1.92 (m, 2H)
216		2	6	556.41 (M-H) ⁺ , 99.04%	δ 8.89 (s, 1H), 8.61-8.63 (m, 2H), 7.97 (d, <i>J</i> = 7.92 Hz, 1H), 7.71 (d, <i>J</i> = 7.92 Hz, 1H), 7.62-7.65 (m, 1H), 7.43-7.47 (m, 1H), 7.28-7.33 (m, 2H), 7.17 (s, 1H), 6.74-6.78 (m, 1H), 6.57-6.59 (m, 1H), 4.60 (s, 2H), 4.45-4.49 (m, 2H), 3.83-3.89 (m, 1H), 3.50-3.55 (m, 1H), 2.36-2.43 (m, 2H) and 1.73-1.82 (m, 2H)

217		2	27	571.51 (M+H) ⁺ , 99.10%	δ 8.87 (s, 1H), 8.51-8.57 (m, 2H), 7.70 (d, <i>J</i> = 8.0 Hz, 1H), 7.43-7.46 (m, 3H), 7.20-7.26 (m, 3H), 7.11 (s, 1H), 6.74-6.78 (m, 1H), 6.56-6.59 (m, 1H), 4.59 (s, 3H), 4.47-4.49 (m, 1H), 3.78-3.82 (m, 1H), 3.48-3.54 (m, 1H), 2.38-2.40 (m, 2H), 1.72-1.80 (m, 2H) and 1.27 (s, 9H)
218		2	40	617.47 (M+H) ⁺ , 99.59%	δ 8.87 (s, 1H), 8.54 (d, <i>J</i> = 4.44 Hz, 1H), 8.50 (s, 1H), 8.13 (s, 1H), 7.96-7.98 (m, 1H), 7.90-7.92 (m, 1H), 7.61-7.63 (m, 1H), 7.38-7.41 (m, 1H), 7.23-7.27 (m, 2H), 6.71-6.76 (m, 1H), 6.54-6.56 (m, 1H), 4.58 (s, 2H), 4.47-4.50 (m, 2H), 3.81-3.87 (m, 1H), 3.49-3.54 (m, 1H), 2.32-2.40 (m, 2H) and 1.70-1.81 (m, 2H)
219		2	42	649.35 (M-H) ⁺ , 98.81%	δ 8.87 (s, 1H), 8.57 (d, <i>J</i> = 4.16 Hz, 1H), 8.52 (s, 1H), 8.24 (d, <i>J</i> = 7.56 Hz, 2H), 7.60-7.62 (m, 1H), 7.41-7.44 (m, 1H), 7.28 (s, 1H), 7.21-7.25 (m, 1H), 6.71-6.75 (m, 1H), 6.53-6.55 (m, 1H), 4.58 (s, 2H), 4.46-4.49 (m, 1H), 4.46-4.54 (m, 1H), 3.80-3.86 (m, 1H), 3.49-3.54 (m, 1H), 2.32-2.40 (m, 2H) and 1.69-1.81 (m, 2H)
220		16	58	583.39 (M-H) ⁺ , 99.73%	δ 11.18 (br s, 1H), 8.56 (d, <i>J</i> = 4.08 Hz, 1H), 8.54 (s, 1H), 7.67 (d, <i>J</i> = 7.84 Hz, 1H), 7.40-7.52 (m, 5H), 7.13 (s, 1H), 6.99-7.06 (m, 1H), 6.77-6.80 (m, 1H), 4.85-4.89 (m, 1H), 4.65-4.71 (m, 2H), 3.31 (s, 1H), 2.92-2.98 (m, 1H), 2.07-2.17 (m, 2H) and 1.84-1.91 (m, 2H)

221		1	23	581.12 (M-H) ⁺ , 98.65%	δ 8.80 (s, 1H), 8.57 (s, 2H), 7.81 (s, 1H), 7.57-7.68 (m, 3H), 7.42 (s, 1H), 7.09-7.13 (m, 3H), 6.86-6.91 (m, 2H), 4.59 (s, 2H), 4.45 (s, 2H), 3.86-3.89 (m, 1H), 3.50-3.56 (m, 1H), 2.23-2.32 (m, 2H) and 1.72-1.82 (m, 2H)
222		16	28	603.10 (M-H) ⁺ , 99.06%	δ 11.22 (br s, 1H), 8.59-8.63 (m, 2H), 7.75-7.81 (m, 2H), 7.64 (t, <i>J</i> = 7.6 Hz, 1H), 7.41-7.44 (m, 1H), 7.24 (s, 1H), 7.00-7.07 (m, 1H), 6.77-6.80 (m, 1H), 4.85-4.89 (m, 1H), 4.65-4.71 (m, 2H), 3.31 (s, 1H), 2.92-2.98 (m, 1H), 2.07-2.17 (m, 2H) and 1.84-1.91 (m, 2H)
223		16	34	603.10 (M-H) ⁺ , 98.00%	δ 11.24 (br s, 1H), 8.59-8.62 (m, 2H), 8.07-8.11 (m, 1H), 7.99-8.03 (m, 1H), 7.74 (t, <i>J</i> = 8.0 Hz, 1H), 7.42-7.45 (m, 1H), 7.22 (s, 1H), 7.00-7.07 (m, 1H), 6.77-6.80 (m, 1H), 4.65-4.77 (m, 3H), 3.32-3.37 (m, 1H), 2.93-2.99 (m, 1H), 2.12-2.20 (m, 2H) and 1.84-1.92 (m, 2H)
224		16	26	544.34 (M+H) ⁺ , 97.34%	δ 10.60 (br s, 1H), 8.61-8.62 (m, 2H), 7.99-8.02 (m, 1H), 7.71-7.73 (m, 1H), 7.65-7.68 (m, 1H), 7.43-7.46 (m, 1H), 7.32-7.34 (m, 1H), 7.17 (s, 1H), 7.00-7.07 (m, 1H), 6.76-6.79 (m, 1H), 4.61-4.70 (m, 2H), 3.32-3.33 (m, 1H), 2.93-2.99 (m, 1H), 2.07-2.21 (m, 2H) and 1.85-1.92 (m, 2H)

225		2	19	613.18 (M+H) ⁺ , 96.25%	δ 8.87 (s, 1H), 8.51-8.53 (m, 1H), 8.46-8.47 (m, 1H), 7.59 (d, J= 6.4 Hz, 1H), 7.44-7.49 (m, 2H), 7.36-7.39 (m, 1H), 7.23-7.30 (m, 2H), 7.19 (s, 1H), 6.70-6.75 (m, 1H), 6.54-6.56 (m, 1H), 4.47-4.59 (m, 4H), 3.81-3.86 (m, 1H), 3.48-3.54 (m, 1H), 2.32-2.36 (m, 2H), 2.00 (s, 3H) and 1.71-1.80 (m, 2H)
226		1	10	595.38 (M+H) ⁺ , 93.90%	δ 8.79 (s, 1H), 8.51-8.52 (m, 1H), 8.46-8.47 (m, 1H), 7.59 (d, J= 6.4 Hz, 1H), 7.47 (d, J= 8.8 Hz, 1H), 7.44 (s, 1H), 7.35-7.38 (m, 1H), 7.29-7.31 (m, 1H), 7.18 (s, 1H), 7.05-7.09 (m, 2H), 6.82-6.85 (m, 2H), 4.57-4.58 (m, 2H), 4.42-4.48 (m, 2H), 3.82-3.85 (m, 1H), 3.50-3.55 (m, 1H), 2.18-2.22 (m, 2H), 2.00 (s, 3H) and 1.73-1.78 (m, 2H)
227		16	38	599.17 (M+H) ⁺ , 96.76%	δ 11.24 (br s, 1H), 8.47-8.53 (m, 2H), 7.61 (d, J= 8.0 Hz, 1H), 7.51 (d, J= 6.8 Hz, 1H), 7.44 (s, 1H), 7.36 (t, J= 8.0 Hz, 1H), 7.30-7.32 (m, 1H), 7.18 (s, 1H), 6.99-7.06 (m, 1H), 6.76-6.79 (m, 1H), 4.81-4.84 (m, 1H), 4.61-4.68 (m, 2H), 3.29-3.32 (m, 1H), 2.91-2.97 (m, 1H), 2.07-2.20 (m, 2H) and 1.82-1.91 (m, 2H)

Scheme 15



[0425] **General procedure for the preparation of compounds 72 (a-b):** A solution of compound 71 (a-b) (2.5 g) in di-ethyl ether was cooled to -78°C followed by addition of LiHMDS (1.10 eq). The resulting reaction mixture was stirred at -78°C for 45 min followed by drop wise addition of diethyl oxalate 55 (1.20 eq) in about 30 min. The reaction mixture was then left to stir at room temperature for 16 h. After completion of the reaction (TLC and MS monitoring), the solution was then cooled 0°C and the resulting precipitate was filtered to get the desired product 72 (a-b) as an off-white solid, which was carried forward to the next step without purification.

[0426] **4-Ethoxy-1-(4-methylpyridin-3-yl)-3,4-dioxobut-1-en-1-olate lithium salt (72-a):** ¹H-NMR (400 MHz, DMSO-d₆): δ 8.44 (s, 1H), 8.38-8.39 (m, 1H), 7.21-7.22 (m, 1H), 5.93 (s, 1H), 4.10 (q, *J* = 7.16 Hz, 2H), 2.36 (s, 3H) and 1.20 (t, *J* = 7.6 Hz, 3H). MS: 236.0 (M+H)⁺. Yield: quantitative.

[0427] **4-ethoxy-3,4-dioxo-1-(pyridazin-4-yl)but-1-en-1-olate lithium salt (72-b):** ¹H-NMR (400 MHz, DMSO-d₆): δ 9.48-9.56 (m, 2H), 9.20-9.21 (m, 1H), 6.46 (s, 1H), 4.10 (q, *J* = 7.20 Hz, 2H) and 1.21 (t, *J* = 7.6 Hz, 3H). MS: 223.04 (M+H)⁺. Yield: 76%.

[0428] **General procedure for the preparation of compounds 73 (a-b):** To an ice-cold solution of compound 72 (a-b) (2.50-3.0 g, 1.0 eq) in IPA was added (3-fluoro-4-(trifluoromethyl)phenyl)hydrazine hydrochloride 57 (1.10 eq) and TFA (2.0 eq). The

resulting reaction mixture was warm up to room temperature and then stirred at 90°C for 4-5 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified over silica gel (100-200 M, 10-15% EtOAc-hexane) to get the desired product **73 (a-b)**.

[0429] Ethyl 1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(4-methylpyridin-3-yl)-1H-pyrazole-3-carboxylate (73-a): ¹H-NMR (400 MHz, CDCl₃): δ 8.60-8.66 (m, 2H), 7.53-7.55 (m, 1H), 7.46-7.47 (m, 1H), 7.21-7.28 (m, 1H), 7.08 (s, 1H), 6.99-7.05 (m, 1H), 4.45 (q, *J*=7.2 Hz, 2H), 2.15 (s, 3H) and 1.42 (t, *J*= 7.6 Hz, 3H). MS: 394.33 (M+H)⁺. Yield: 22%.

[0430] Ethyl 1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(pyridazin-4-yl)-1H-pyrazole-3-carboxylate (73-b): ¹H-NMR (400 MHz, CDCl₃): δ 7.61-7.71 (m, 2H), 7.41-7.55 (m, 4H), 7.11 (s, 1H), 4.46 (q, *J*= 7.16 Hz, 2H) and 1.42 (t, *J*= 7.24 Hz, 3H). MS: 381.25 (M+H)⁺. Yield: 27%.

[0431] General procedure for the preparation of compounds 74 (a-b): To an ice-cold solution of compound **73 (a-b)**, (1.0-1.2 g) (1.0 eq) in EtOH was added drop wise an aqueous solution of sodium hydroxide (3.0 eq). The resulting solution was stirred at room temperature for 2-3 h. After completion of the reaction (TLC monitoring), the solvent was evaporated, added H₂O to the residue followed by extraction with EtOAc (2 x 100 mL). The organic layer was discarded and the pH of the aqueous layer was adjusted to ~4 by adding 1N HCl. The resulting precipitate was filtered and dried under vacuum to get the desired product **74 (a-b)** as a white solid.

[0432] 1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(4-methylpyridin-3-yl)-1H-pyrazole-3-carboxylic acid (74-a): ¹H-NMR (400 MHz, DMSO-d₆): δ 13.20 (br s, 1H), 8.50 (d, *J*= 4.12 Hz, 1H), 8.39 (s, 1H), 7.82 (t, *J*= 7.88 Hz, 1H), 7.51-7.53 (m, 1H), 7.35-7.37 (m, 1H), 7.24-7.26 (m, 1H), 7.17 (s, 1H) and 2.08 (s, 3H). LCMS: 366.22 (M+H)⁺, 99.72%. Yield: 60%.

[0433] 1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(pyridazin-4-yl)-1H-pyrazole-3-carboxylic acid (74-b): ¹H-NMR (400 MHz, DMSO-d₆): δ 13.20 (br s, 1H), 9.24-9.27 (m, 2H), 7.89-7.90 (m, 1H), 7.75-7.77 (m, 1H), 7.53-7.54 (m, 1H) and 7.40-7.46 (m, 2H). LCMS: 353.19 (M+H)⁺, 93.39%. Yield: 70%.

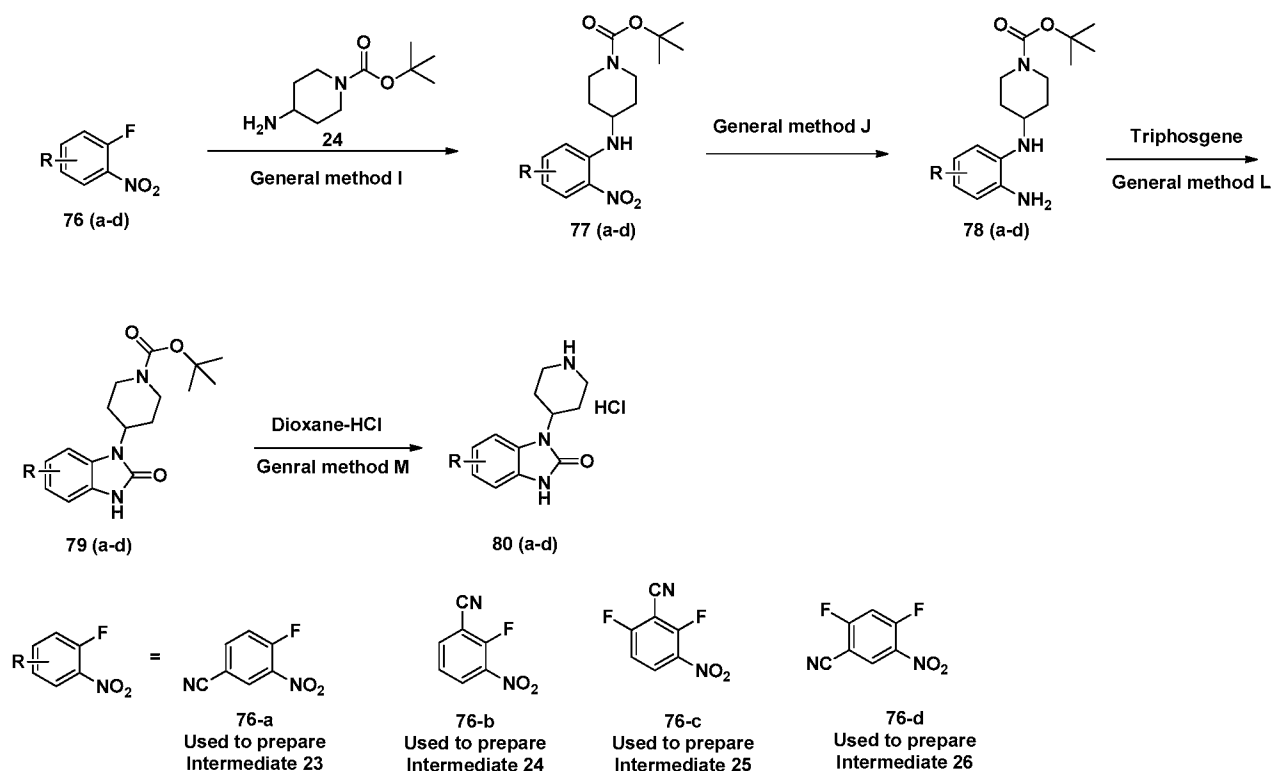
[0434] General procedure for the preparation of final compounds (75-a and 75-b):

The final compounds were prepared following the general **method N**. To an ice cold solution of carboxylic acids **74 (a-b)**, (125 mg, 1.0 eq), in DMF (2.0 mL) was added DIPEA (3.0 eq) and HATU (1.50 eq). The resulting mixture was stirred under nitrogen atmosphere at 0°C for 15 min followed by addition of 6,7-difluoro-1-(piperidin-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one **Intermediate 16** (1.20 eq). The reaction mixture was then stirred at room temperature for 16 h. After the completion of the reaction (TLC monitoring), the solution was diluted with ice cold water (30 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organics was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified via prep-HPLC.

[0435] 6,7-difluoro-1-(1-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(4-methylpyridin-3-yl)-1H-pyrazole-3-carbonyl)piperidin-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (75-a): ¹H-NMR (400 MHz, DMSO-d₆): δ 11.25 (br s, 1H), 8.50-8.52 (m, 1H), 8.42 (s, 1H), 7.80 (t, *J* = 8.12 Hz, 1H), 7.51-7.53 (m, 1H), 7.37 (d, *J* = 4.92 Hz, 1H), 7.22 (d, *J* = 8.92 Hz, 1H), 7.07 (s, 1H), 7.00-7.05 (m, 1H), 6.77-6.80 (m, 1H), 4.81-4.84 (m, 1H), 4.64-4.72 (m, 2H), 3.38-3.41 (m, 1H), 2.94-3.00 (m, 1H), 2.10-2.22 (m, 5H), and 1.87-1.90 (m, 2H). LCMS: 601.17 (M+H)⁺, 99.94 %. Yield: 24%.

[0436] 6,7-difluoro-1-(1-(1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(pyridazin-4-yl)-1H-pyrazole-3-carbonyl)piperidin-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one (75-b): ¹H-NMR (400 MHz, DMSO-d₆): δ 11.25 (br s, 1H), 9.26-9.29 (m, 2H), 7.89-7.93 (m, 1H), 7.75-7.78 (m, 1H), 7.57 (d, *J* = 4.04 Hz, 1H), 7.42-7.44 (m, 2H), 7.00-7.06 (m, 1H), 6.78-6.79 (m, 1H), 4.67-4.77 (m, 3H), 3.32 (s, 1H), 2.95-3.00 (m, 1H), 2.08-2.15 (m, 2H) and 1.85-1.92 (m, 2H). LCMS: 588.26 (M+H)⁺, 99.30 %. Yield: 32%.

Scheme 16



General procedure for the preparation of 80 (a-d):

- 5 [0437] **General method I:** To an ice-cold solution of tert-butyl 4-aminopiperidine-1-carboxylate **24** (1.0-2.5 g, 1.0 eq) in DMF was added DIPEA (1.5 eq) and respective nitro compounds **76 (a-d)** (1.0 eq). The resulting reaction mixture was stirred at RT for 2-3 h. After completion of the reaction (TLC monitoring), the reaction mass was diluted with ice-cold water and extracted with EtOAc (3 times). The combined organics was washed with
- 10 brine, dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude was purified over silica gel (100-200 M, 10-15% EtOAc-hexane) to get the desired product **77 (a-d)**.

[0438] **Tert-butyl 4-((4-cyano-2-nitrophenyl)amino)piperidine-1-carboxylate (77-a):**

- $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.42 (d, J = 6.8 Hz, 1H), 7.58 (dd, J = 2.0 & 8.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 4.04-4.06 (m, 2H), 3.67-3.74 (m, 1H), 3.01-3.06 (m, 2H), 2.04-2.07 (m, 2H), 1.59-1.63 (m, 3H) and 1.47 (s, 9H). LCMS: 345.53 (M-H^+), 92.45%. Yield: 57%.
- 15

[0439] **Tert-butyl 4-((2-cyano-6-nitrophenyl)amino)piperidine-1-carboxylate (77-b):**

$^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.37-8.40 (m, 1H), 7.73-7.75 (m, 1H), 6.72-6.76 (m, 1H), 4.47-4.54 (m, 1H), 4.04-4.06 (m, 2H), 3.01-3.03 (m, 2H), 2.12-2.15 (m, 2H), 1.50-1.56 (m, 3H) and 1.44 (s, 9H). LCMS: 345.28 (M-H^+), 95.79%. Yield: 77%.

[0440] **Tert-butyl 4-((2-cyano-3-fluoro-6-nitrophenyl)amino)piperidine-1-carboxylate (77-c):** $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.81-8.83 (m, 1H), 8.44-8.48 (m, 1H), 6.49-6.54 (m, 1H), 4.53-4.60 (m, 1H), 4.07-4.10 (m, 2H), 3.00-3.06 (m, 2H), 2.14-2.17 (m, 2H), 1.62-1.67 (m, 2H) and 1.40 (s, 9H). LCMS: 363.32 (M-H) $^+$, 97.61%. Yield: 59%.

5 [0441] **Tert-butyl 4-((4-cyano-5-fluoro-2-nitrophenyl)amino)piperidine-1-carboxylate (77-d):** $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.51-8.56 (m, 2H), 8.60-8.63 (m, 1H), 4.04-4.07 (m, 2H), 3.57-3.61 (m, 1H), 3.01-3.07 (m, 2H), 2.03-2.06 (m, 2H), 1.56-1.60 (m, 2H) and 1.47 (s, 9H). MS: 363.37 (M-H) $^+$. Yield: 77%.

General procedure for the preparation of 78 (a-d):

10 [0442] **General method J:** To a solution of compound 77 (a-d) (1.0-2.5 g, 1.0 eq) in EtOAc were added Pd-C (w/w, 10 mol %) and the resulting solution was stirred under hydrogen atmosphere (1 atm) at ambient temperature for 16 h. The reaction mixture was filtered through celite bed and the filtrate was concentrated under reduced pressure to get the desired product 78 (a-d).

15 [0443] **Tert-butyl 4-((2-amino-4-cyanophenyl)amino)piperidine-1-carboxylate (78-a):** $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 6.89 (d, J = 6.8 Hz, 1H), 6.77 (s, 1H), 6.54-6.56 (m, 1H), 5.11-5.12 (m, 1H), 4.98 (br s, 2H), 3.89-3.91 (m, 2H), 3.52 (br s, 1H), 2.89 (s, 2H), 1.88-1.90 (m, 2H) and 1.17-1.29 (m, 11H). MS: 315.18 (M-H) $^+$. Yield: 78%.

[0444] **Tert-butyl 4-((2-amino-6-cyanophenyl)amino)piperidine-1-carboxylate (78-b):**
20 $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 6.95-6.96 (m, 1H), 6.88-6.91 (m, 2H), 4.11-4.12 (m, 2H), 3.48-3.49 (m, 1H), 3.34-3.37 (m, 1H), 2.73-2.79 (m, 2H), 1.89-1.92 (m, 2H), 1.59-1.61 (m, 2H) and 1.45-1.49 (m, 11H). MS: 315.55 (M-H) $^+$. Yield: 40%.

[0445] **Tert-butyl 4-((6-amino-2-cyano-3-fluorophenyl)amino)piperidine-1-carboxylate (78-c):** $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 6.81-6.84 (m, 1H), 6.54-6.58 (m, 1H), 4.09-4.14 (m, 2H), 3.78-3.82 (m, 1H), 3.66-3.68 (m, 1H), 3.44-3.48 (m, 2H), 2.80-2.85 (m, 2H), 1.95-1.98 (m, 2H) and 1.43-1.48 (m, 11H). LCMS: 333.56 (M-H) $^+$, 82.07%. Yield: 88%.

[0446] **Tert-butyl 4-((2-amino-4-cyano-5-fluorophenyl)amino)piperidine-1-carboxylate (78-d):** $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 6.92-6.94 (m, 1H), 6.30-6.36 (m, 1H), 4.39-4.41 (br s,

1H), 4.06-4.10 (m, 2H), 3.38-3.40 (m, 2H), 2.91-2.97 (m, 2H), 2.00-2.03 (m, 2H) and 1.48 (s, 12H). MS: 333.56 (M-H)⁺. Yield: 62%.

[0447] General procedure for the preparation of 79 (a-d):

[0448] General method L: To an ice-cold solution of compound **78 (a-d)** (0.50-1.50 g, 1.0 eq) in THF was added Et₃N (2.0 eq) and triphosgene (1.5 eq). The resulting reaction mixture was stirred at RT for 4 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was purified over silica gel (100-200 M, 30-40% EtOAc-hexane) to get the desired product **79 (a-d)**.

[0449] Tert-butyl 4-(5-cyano-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-1-carboxylate (79-a):

[0450] ¹H-NMR (400 MHz, DMSO-d₆): δ 10.08 (br s, 1H), 7.38-7.40 (m, 2H), 7.18-7.20 (m, 1H), 4.43-4.46 (m, 1H), 4.32-4.36 (m, 2H), 2.87-2.87 (m, 2H), 2.25-2.28 (m, 2H), 1.83-1.85 (m, 2H) and 1.44 (s, 9H). LCMS: 343.41 (M+H)⁺, 93.09%. Yield: 90%.

[0451] Tert-butyl 4-(7-cyano-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-1-carboxylate (79-b): LCMS: 341.14 (M-H)⁺, 83.61%. Yield: 75%.

[0452] Tert-butyl 4-(7-cyano-6-fluoro-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-1-carboxylate (79-c): LCMS: 359.32 (M-H)⁺, 83.11%. Yield: 48%.

[0453] Tert-butyl 4-(5-cyano-6-fluoro-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-1-carboxylate (79-d): LCMS: 359.57 (M-H)⁺, 81.30%. Yield: 82%.

[0454] General procedure for the preparation of 80 (a-d):

[0455] General method M: An ice-cold solution of compound **79 (a-d)** (0.5 g-1.0 g, 1.0 eq) in dioxane-HCl (~4N) was stirred at RT for 2h. After completion of the reaction (TLC monitoring), the reaction mass was dried under reduced pressure. The crude was triturated with diethyl ether to get desired product **80 (a-d)** as off solid.

[0456] 2-Oxo-1-(piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazole-5-carbonitrile hydrochloride (80-a): Intermediate 23

[0457] ¹H-NMR (400 MHz, DMSO-d₆): δ 11.45 (br s, 1H), 9.11 (br s, 2H), 7.64 (d, *J*=8.0 Hz, 1H), 7.50-7.52 (m, 1H), 7.40-7.41 (m, 1H), 4.56-4.62 (m, 1H), 3.34-3.41 (m, 2H), 3.03-3.08 (m, 2H), 2.58-2.64 (m, 2H) and 1.83-1.90 (m, 2H). LCMS: 243.16 (M+H)⁺, 98.94%. Yield: 89%.

5 [0458] **2-Oxo-3-(piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile hydrochloride (80-b): Intermediate 24**

[0459] ¹H-NMR (400 MHz, DMSO-d₆): δ 11.50 (br s, 1H), 9.13 (br s, 1H), 8.62 (br s, 1H), 7.40-7.42 (m, 1H), 7.32-7.36 (m, 1H), 7.28-7.30 (m, 1H), 4.72-4.78 (m, 1H), 3.35-3.48 (m, 2H), 2.86-2.95 (m, 2H), 2.67-2.72 (m, 2H) and 2.06-2.09 (m, 2H). LCMS: 241.05 (M-H)⁺, 89.68%. Yield: 95%.

10 [0460] **5-Fluoro-2-oxo-3-(piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazole-4-carbonitrile hydrochloride (80-c): Intermediate 25**

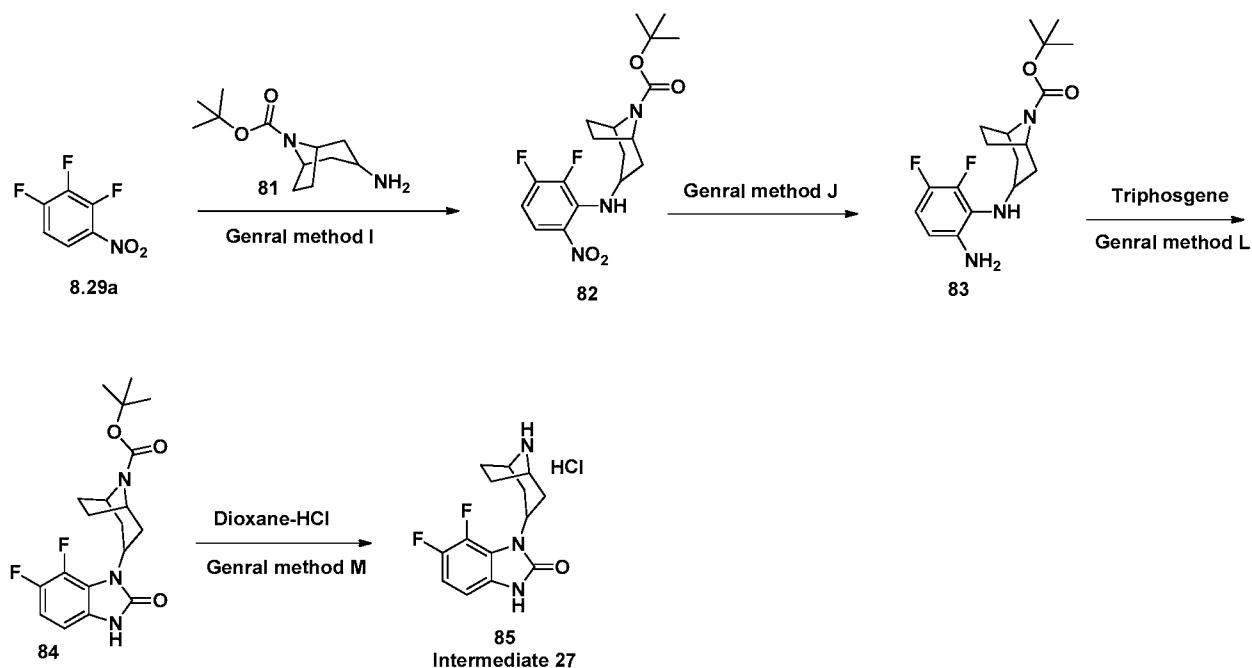
[0461] ¹H-NMR (400 MHz, DMSO-d₆): δ 11.58 (br s, 1H), 9.35 (br s, 1H), 8.76 (br s, 1H), 7.20-7.25 (m, 1H), 7.06-7.11 (m, 1H), 4.65-4.71 (m, 1H), 3.56-3.63 (m, 2H), 2.85-2.90 (m, 2H), 2.67-2.73 (m, 2H) and 2.08-2.11 (m, 2H). LCMS: 260.96 (M+H)⁺, 95.41%. Yield: 28%.

15 [0462] **6-Fluoro-2-oxo-1-(piperidin-4-yl)-2,3-dihydro-1H-benzo[d]imidazole-5-carbonitrile hydrochloride (80-d): Intermediate 26**

[0463] ¹H-NMR (400 MHz, DMSO-d₆): δ 10.51 (br s, 1H), 9.13-9.24 (m, 2H), 7.76 (d, *J*=8.8 Hz, 1H), 7.40 (d, *J*=5.2 Hz, 1H), 4.55-4.61 (m, 1H), 3.31-3.35 (m, 2H), 3.04-3.07 (m, 2H), 2.60-2.66 (m, 2H) and 1.84-1.87 (m, 2H). LCMS: 259.2 (M-H)⁺, 97.74%. Yield: 91%.

20

Scheme 17



[0464] Preparation of tert-butyl 3-((2,3-difluoro-6-nitrophenyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (82):

[0465] Prepared following the general **method I**.

[0466] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.61 (d, $J = 6.0$ Hz, 1H), 8.01-8.04 (m, 1H), 6.45-6.51 (m, 1H), 4.21-4.31 (m, 3H), 2.29-2.35 (m, 2H), 2.07-2.09 (m, 2H), 1.94-1.96 (m, 2H), 1.68-1.73 (m, 2H) and 1.47 (s, 9H). LCMS: 384.36 ($\text{M}+\text{H}$) $^+$, 99.35%. Yield: 78%.

[0467] Preparation of tert-butyl 3-((6-amino-2,3-difluorophenyl)amino)-8-azabicyclo[3.2.1]octane-8-carboxylate (83):

[0468] Prepared following the general **method J**.

[0469] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 6.57-6.60 (m, 1H), 6.39-6.41 (m, 1H), 4.70 (br s, 2H), 4.17-4.19 (m, 1H), 4.01-4.08 (m, 2H), 3.64 (br s, 1H), 1.98-2.06 (m, 4H), 1.84-1.86 (m, 2H), 1.61-1.64 (m, 2H) and 1.38 (s, 9H). MS: 354.13 ($\text{M}+\text{H}$) $^+$. Yield: 95%.

[0470] Preparation of tert-butyl 3-(6,7-difluoro-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)-8-azabicyclo[3.2.1]octane-8-carboxylate (84):

[0471] Prepared following the general **method L**.

[0472] $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 10.03 (br s, 1H), 6.85-6.97 (m, 1H), 6.74-6.75 (m, 1H), 4.52-4.59 (m, 1H), 4.34-4.46 (m, 2H), 2.52-2.54 (m, 2H), 2.06-2.10 (m, 2H), 1.80-1.89 (m, 4H) and 1.52 (s, 9H). LCMS: 378.13 (M-H) $^+$, 96.51%. Yield: 85%.

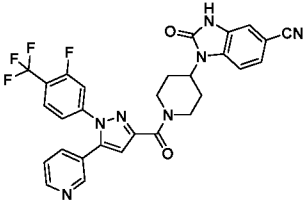
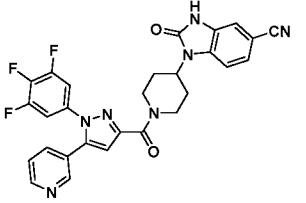
[0473] **Preparation of 1-(8-azabicyclo[3.2.1]octan-3-yl)-6,7-difluoro-1,3-dihydro-2H-benzo[d]imidazol-2-one hydrochloride (85): Intermediate 27:**

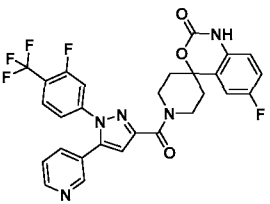
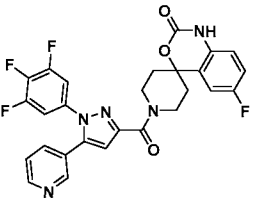
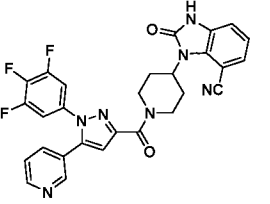
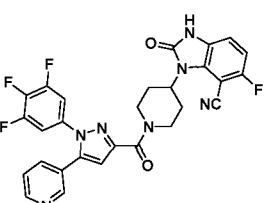
[0474] Prepared following the general **method L**.

[0475] $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 11.34 (br s, 1H), 9.02 (br s, 1H), 8.87 (br s, 1H), 7.03-7.10 (m, 1H), 6.80-6.81 (m, 1H), 4.89-4.93 (m, 1H), 4.08-4.10 (m, 2H), 2.49-2.52 (m, 2H), 2.08-2.09 (m, 2H) and 1.90-1.97 (m, 4H). LCMS: 278.06 (M-H) $^+$, 99.73%. Yield: 94%.

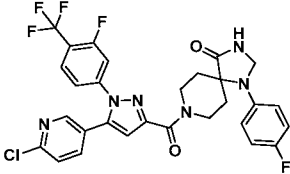
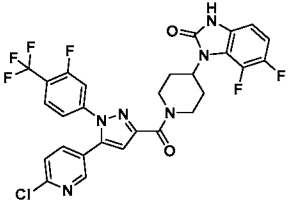
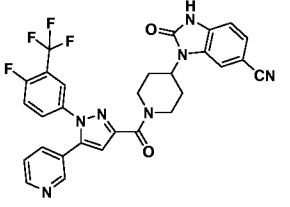
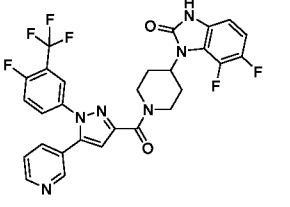
10 [0476] Preparation of final targets

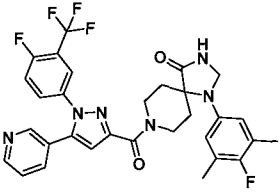
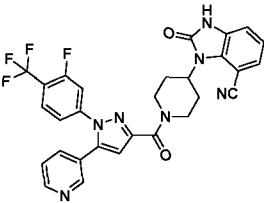
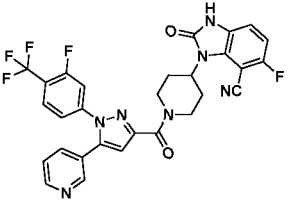
Table 6.5: Tabulated data of the final compounds including the individual yields obtained.

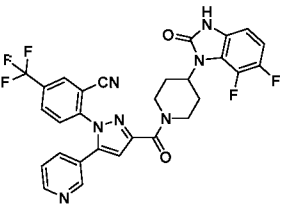
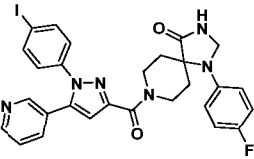
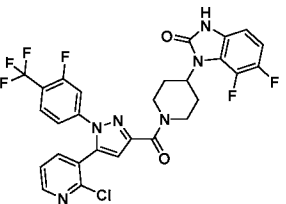
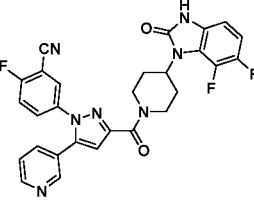
No.	Structure	Amine intermediate used	Yield (%)	LCMS	$^1\text{H-NMR}$ data (DMSO-d_6 , 400 MHz), unless otherwise specified
228		23	38	573.86 (M-H) $^+$, 98.22%	δ 11.31 (br s, 1H), 8.60-8.62 (m, 2H), 7.85 (t, J =8.40 Hz, 1H), 7.73 (d, J =8.0 Hz, 1H), 7.64-7.67 (m, 1H), 7.44-7.47 (m, 3H), 7.37 (s, 1H), 7.32 (d, J =8.4 Hz, 1H), 7.17 (s, 1H), 4.70-4.78 (m, 2H), 4.54-4.57 (m, 1H), 3.28-3.32 (m, 1H), 2.92-2.98 (m, 1H), 2.25-2.28 (m, 2H) and 1.79-1.83 (m, 2H)
229		23	35	541.85 (M-H) $^+$, 98.34%	δ 11.36 (br s, 1H), 8.60-8.61 (m, 2H), 7.67-7.69 (m, 1H), 7.41-7.53 (m, 5H), 7.37 (s, 1H), 7.15 (s, 1H), 4.69-4.77 (m, 2H), 4.53-4.56 (m, 1H), 3.29-3.32 (m, 1H), 2.92-2.97 (m, 1H), 2.25-2.29 (m, 2H) and 1.79-1.87 (m, 2H)

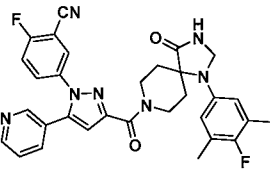
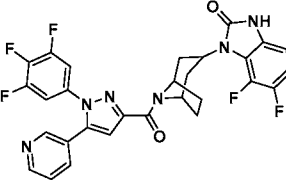
No.	Structure	Amine intermediate used	Yield (%)	LCMS	¹ H-NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
230		Commercial	23	569.82 (M+H) ⁺ , 98.81%	δ 10.36 (br s, 1H), 8.61-8.63 (m, 2H), 7.84 (t, J= 8.0 Hz, 1H), 7.73 (d, J= 7.6 Hz, 1H), 7.66-7.69 (m, 1H), 7.44-7.48 (m, 1H), 7.30-7.34 (m, 2H), 7.17 (s, 1H), 7.10-7.15 (m, 1H), 6.90-6.93 (m, 1H), 4.58-4.68 (m, 2H), 3.50-3.56 (m, 1H), 3.11-3.18 (m, 1H) and 2.02-2.18 (m, 4H)
231		Commercial	21	537.86 (M+H) ⁺ , 97.64%	δ 10.36 (br s, 1H), 8.60-8.61 (m, 2H), 7.67 (d, J= 8.0 Hz, 1H), 7.49-7.53 (m, 2H), 7.42-7.45 (m, 1H), 7.29-7.31 (m, 1H), 7.14 (s, 1H), 7.11-7.13 (m, 1H), 6.89-6.93 (m, 1H), 4.57-4.67 (m, 2H), 3.48-3.52 (m, 1H), 3.10-3.17 (m, 1H) and 2.01-2.13 (m, 4H)
232		24	10	542.41 (M-H) ⁺ , 97.92%	δ 11.25 (br s, 1H), 8.60-8.61 (m, 2H), 7.68 (d, J= 7.6 Hz, 1H), 7.51 (t, J= 8.4 Hz, 2H), 7.39-7.45 (m, 2H), 7.26 (d, J= 8.0 Hz, 1H), 7.11-7.13 (m, 2H), 4.85-4.85 (m, 2H), 4.74-4.77 (m, 1H), 3.78-3.81 (m, 1H), 3.22-3.26 (m, 2H), 2.76-2.77 (m, 1H) and 1.94-1.96 (m, 2H)
233		25	11	560.43 (M-H) ⁺ , 95.31%	δ 11.48 (br s, 1H), 8.61-8.62 (m, 2H), 7.70 (d, J= 7.6 Hz, 1H), 7.47-7.55 (m, 2H), 7.44-7.46 (m, 1H), 7.23-7.27 (m, 1H), 7.13 (s, 1H), 7.05-7.08 (m, 1H), 4.83-4.85 (m, 2H), 4.73-4.80 (m, 1H), 3.76-3.81 (m, 1H), 3.22-3.26 (m, 2H), 2.80-2.86 (m, 1H) and 1.96-1.99 (m, 2H)

No.	Structure	Amine intermediate used	Yield (%)	LCMS	¹ H-NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
234		26	19	592.11 (M-H) ⁺ , 98.27%	δ 11.45 (br s, 1H), 8.60-8.62 (m, 2H), 7.85 (t, J= 8.0 Hz, 1H), 7.75 (d, J= 8.00 Hz, 1H), 7.62-7.67 (m, 2H), 7.46-7.49 (m, 1H), 7.33-7.38 (m, 2H), 7.17 (s, 1H), 4.70-4.78 (m, 2H), 4.50-4.56 (m, 1H), 3.27-3.33 (m, 1H), 2.89-2.92 (m, 1H), 2.30-2.35 (m, 2H) and 1.78-1.86 (m, 2H)
235		26	48	560.42 (M-H) ⁺ , 98.73%	δ 11.39 (br s, 1H), 8.59-8.60 (m, 2H), 7.67 (d, J= 8.0 Hz, 1H), 7.61-7.64 (m, 1H), 7.49 (t, J= 8.4 Hz, 2H), 7.41-7.43 (m, 1H), 7.37 (d, J= 5.6 Hz, 1H), 7.14 (s, 1H), 4.69-4.80 (m, 2H), 4.49-4.55 (m, 1H), 2.87-2.94 (m, 1H), 2.25-2.36 (m, 3H) and 1.78-1.86 (m, 2H)
236		16	28	635.45 (M-H) ⁺ , 99.95%	δ 11.21 (br s, 1H), 8.51-8.54 (m, 2H), 8.33 (s, 1H), 8.20 (d, J= 8.40 Hz, 1H), 7.90 (d, J= 8.40 Hz, 1H), 7.59 (d, J= 8.0 Hz, 1H), 7.36-7.40 (m, 1H), 7.25 (s, 1H), 6.98-7.05 (m, 1H), 6.76-6.79 (m, 1H), 4.62-4.76 (m, 3H), 3.21-3.25 (m, 1H), 2.92-2.98 (m, 1H), 2.07-2.12 (m, 2H) and 1.79-1.91 (m, 2H)
237		16	20	627.09 (M+H) ⁺ , 99.86%	δ 11.25 (br s, 1H), 8.56-8.60 (m, 2H), 7.80 (d, J= 8.40 Hz, 2H), 7.71-7.73 (m, 1H), 7.45-7.48 (m, 1H), 7.18 (d, J= 8.4 Hz, 1H), 7.13 (s, 1H), 7.06-7.09 (m, 1H), 7.01-7.03 (m, 1H), 6.77-6.80 (m, 1H), 4.83-4.86 (m, 1H), 4.62-4.70 (m, 2H), 3.33-3.36 (m, 1H), 2.94-2.97 (m, 1H), 2.13-2.17 (m,

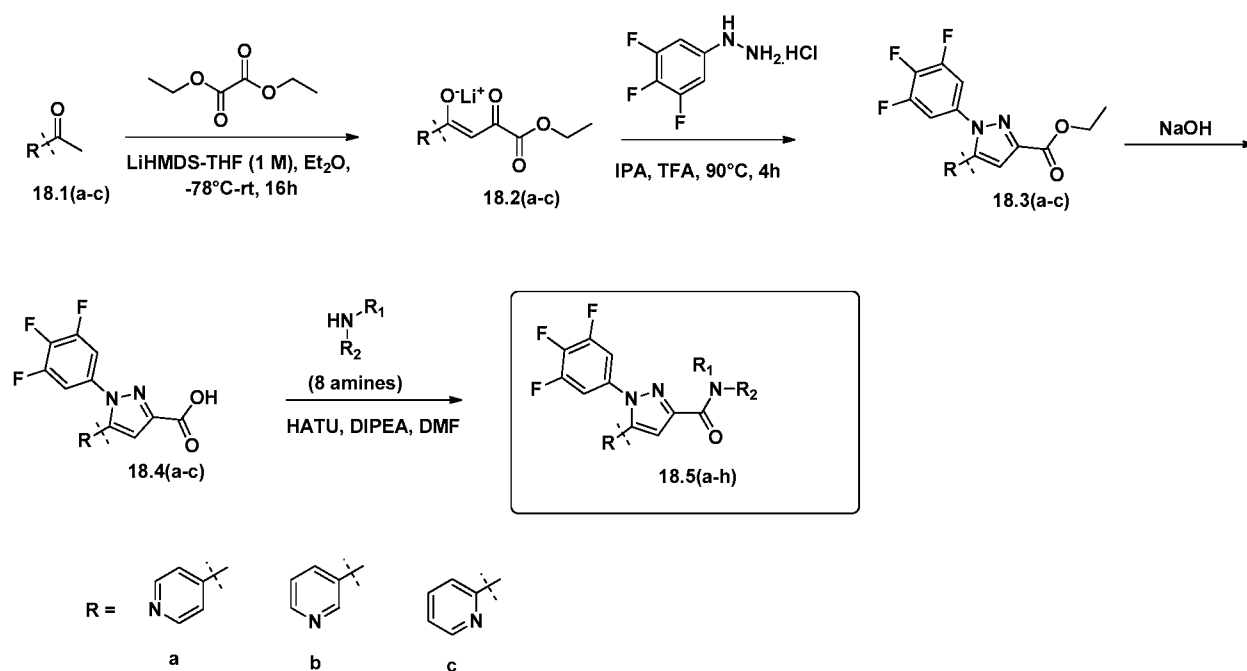
No.	Structure	Amine intermediate used	Yield (%)	LCMS	¹ H-NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
					2H) and 1.83-1.90 (m, 2H)
238		1	13	617.16 (M+H) ⁺ , 95.05%	δ 8.83-8.85 (m, 1H), 8.44-8.47 (m, 1H), 7.86 (t, <i>J</i> = 8.4 Hz, 1H), 7.75-7.77 (m, 1H), 7.66-7.69 (m, 1H), 7.58 (d, <i>J</i> = 7.6 Hz, 1H), 7.30-7.32 (m, 1H), 7.16 (s, 1H), 7.08-7.12 (m, 2H), 6.84-6.88 (m, 2H), 4.59-4.60 (m, 2H), 4.38-4.44 (m, 2H), 3.88-3.90 (m, 1H), 3.51-3.54 (m, 1H), 2.26-2.30 (m, 2H) and 1.78-1.83 (m, 2H)
239		16	8	621.24 (M+H) ⁺ , 98.56%	δ 11.25 (br s, 1H), 8.48-4.49 (m, 1H), 7.88 (t, <i>J</i> = 8.0 Hz, 1H), 7.78 (d, <i>J</i> = 8.4 Hz, 1H), 7.76-7.77 (m, 1H), 7.58 (d, <i>J</i> = 8.0 Hz, 1H), 7.36 (d, <i>J</i> = 7.20 Hz, 1H), 7.21 (s, 1H), 7.02-7.05 (m, 1H), 6.77-6.80 (m, 1H), 4.77-4.80 (m, 1H), 4.66-4.70 (m, 2H), 3.33-3.36 (m, 1H), 2.94-2.97 (m, 1H), 2.11-2.17 (m, 2H) and 1.85-1.88 (m, 2H)
240		20	9	576.41 (M+H) ⁺ , 99.91%	δ 11.45 (br s, 1H), 8.58-8.59 (m, 2H), 7.81-7.84 (m, 2H), 7.73-7.76 (m, 2H), 7.60-7.64 (m, 1H), 7.43-7.45 (m, 2H), 7.10-7.14 (m, 2H), 4.71-4.79 (m, 2H), 4.51-4.54 (m, 1H), 3.23-3.27 (m, 1H), 2.89-2.95 (m, 1H), 2.32-2.35 (m, 2H) and 1.77-1.85 (m, 2H)
241		16	18	587.46 (M+H) ⁺ , 97.82%	δ 11.25 (br s, 1H), 8.58-8.59 (m, 2H), 7.82-7.83 (m, 1H), 7.72-7.75 (m, 2H), 7.59 (t, <i>J</i> =8.4 Hz, 1H), 7.43-7.46 (m, 1H), 7.14 s, 1H), 7.04-

No.	Structure	Amine intermediate used	Yield (%)	LCMS	¹ H-NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
					7.07 (m, 1H), 6.77-6.80 (m, 1H), 4.78-4.81 (m, 1H), 4.67-4.80 (m, 2H), 3.31-3.34 (m, 1H), 2.92-2.99 (m, 1H), 2.11-2.17 (m, 2H) and 1.84-1.87 (m, 2H)
242		6	16	611.24 (M+H) ⁺ , 96.86%	δ 8.74 (br s, 1H), 8.60-8.61 (m, 2H), 7.79-7.80 (m, 1H), 7.58-7.73 (m, 3H), 7.44-7.47 (m, 1H), 7.10 (s, 1H), 6.57 (d, J=5.6 Hz, 2H), 4.55 (s, 2H), 4.36-4.39 (m, 2H), 3.79-3.85 (m, 1H), 3.47-3.53 (m, 1H), 2.29-2.32 (m, 1H), 2.17-2.20 (m, 1H), 2.10 (s, 6H) and 1.70-1.76 (m, 2H)
243		24	12	576.15 (M+H) ⁺ , 91.27%	δ 11.24 (br s, 1H), 8.61-8.62 (m, 2H), 7.85 (t, J=8.4 Hz, 1H), 7.74 (d, J=7.6 Hz, 1H), 7.66-7.69 (m, 1H), 7.40-7.46 (m, 2H), 7.28-7.35 (m, 2H), 7.15 (s, 1H), 7.10-7.11 (m, 1H), 4.83-4.86 (m, 2H), 4.74-4.77 (m, 1H), 3.32-3.40 (m, 1H), 3.21-3.27 (m, 2H), 2.95-3.00 (m, 1H) and 1.98-2.01 (m, 2H)
244		25	10	592.04 (M-H) ⁺ , 97.13%	δ 11.24 (br s, 1H), 8.60-8.62 (m, 2H), 7.85 (t, J=8.80 Hz, 1H), 7.73 (d, J=7.2 Hz, 1H), 7.66-7.69 (m, 1H), 7.44-7.47 (m, 1H), 7.33 (d, J=8.0 Hz, 1H), 7.23-7.27 (m, 1H), 7.15 (s, 1H), 7.05-7.10 (m, 1H), 4.73-4.87 (m, 3H), 3.15-3.20 (m, 2H), 2.81-2.84 (m, 1H) and 1.92-2.02 (m, 3H)

No.	Structure	Amine intermediate used	Yield (%)	LCMS	¹ H-NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
245		16	12	594.16 (M+H) ⁺ , 95.67%	δ 11.25 (br s, 1H), 9.41 (s, 1H), 8.84-8.85 (m, 1H), 8.70-8.72 (m, 1H), 8.65 (s, 1H), 8.07-8.10 (m, 2H), 7.91-7.93 (m, 1H), 7.72-7.75 (m, 1H), 7.03-7.08 (m, 1H), 6.79-6.81 (m, 1H), 4.69-4.76 (m, 2H), 4.09-4.13 (m, 1H), 3.07-3.15 (m, 2H), 1.97-2.00 (m, 2H) and 1.74-1.82 (m, 2H)
246		1	10	623.08 (M+H) ⁺ , 90.04%	δ 8.79 (br s, 1H), 8.56-8.57 (m, 1H), 8.51 (s, 1H), 7.78-7.80 (m, 2H), 7.64-7.66 (m, 1H), 7.40-7.43 (m, 1H), 7.07-7.14 (m, 5H), 6.84-6.86 (m, 2H), 4.53 (s, 2H), 4.41-4.43 (m, 2H), 3.84-3.89 (m, 1H), 3.49-3.55 (m, 1H), 2.14-2.21 (m, 2H) and 1.73-1.77 (m, 2H)
247		16	13	619.03 (M-H) ⁺ , 95.97%	δ 11.10 (br s, 1H), 8.55-8.56 (m, 1H), 8.13-8.15 (m, 1H), 7.83 (t, J= 8.0 Hz, 1H), 7.56-7.63 (m, 2H), 7.22 (d, J= 8.8 Hz, 1H), 7.12 (s, 1H), 7.01-7.05 (m, 1H), 6.77-6.81 (m, 1H), 4.79-4.82 (m, 1H), 4.68-4.71 (m, 2H), 3.37-3.41 (m, 1H), 2.95-3.01 (m, 1H), 2.12-2.21 (m, 2H) and 1.91-1.99 (m, 2H)
248		16	20	544.12 (M+H) ⁺ , 98.99%	δ 11.25 (br s, 1H), 8.58-8.59 (m, 2H), 8.11-8.13 (m, 1H), 7.75-7.80 (m, 1H), 7.60-7.67 (m, 2H), 7.40-7.43 (m, 1H), 7.15 (s, 1H), 6.96-7.03 (m, 1H), 6.75-6.78 (m, 1H), 4.82-4.85 (m, 1H), 4.68-4.70 (m, 2H), 3.33 (s, 1H), 2.91-2.98 (m, 1H), 2.13-2.15 (m, 2H) and

No.	Structure	Amine intermediate used	Yield (%)	LCMS	¹ H-NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
					1.83-1.90 (m, 2H)
249		6	10	566.08 (M-H) ⁺ , 99.21%	δ 8.76 (br s, 1H), 8.56-8.59 (m, 2H), 8.05-8.07 (m, 1H), 7.70-7.74 (m, 1H), 7.59-7.66 (m, 2H), 7.40-7.43 (m, 1H), 7.10 (s, 1H), 6.57 (d, J = 6.4 Hz, 2H), 4.55 (s, 2H), 4.38-4.40 (m, 2H), 3.79-3.86 (m, 1H), 3.47-3.53 (m, 1H), 2.27-2.29 (m, 1H), 2.17-2.18 (m, 1H), 2.11 (s, 6H) and 1.71-1.79 (m, 2H)
250		27	25	581.12 (M+H) ⁺ , 95.59%	δ 11.20 (br s, 1H), 8.58-8.60 (m, 2H), 7.69-7.70 (m, 1H), 7.52-7.55 (m, 2H), 7.42-7.45 (m, 1H), 7.22 (s, 1H), 7.01-7.08 (m, 1H), 6.77-6.79 (m, 1H), 5.34 (m, 1H), 4.86 (m, 1H), 4.36-4.38 (m, 1H), 2.49 (m, 1H), 2.00-2.11 (m, 2H) and 1.84-1.92 (m, 5H)

Scheme 18:



[0477] **General procedure for the preparation of compounds 18.2 (a-c):** A solution of compound 18.1 (a-c) (1 eq) in di-ethyl ether was cooled to -78°C followed by addition of LiHMDS-THF (1M solution, 1.10 eq). The resulting reaction mixture was stirred at -78°C for 45 min followed by drop wise addition of diethyl oxalate (1.20 eq) in about 30 min. The reaction mixture was then left to stir at room temperature for 16 h. After completion of the reaction (TLC and MS monitoring), the solution was then cooled 0°C and the resulting precipitate was filtered to get the desired product as an off-white solid 18.2 (a-c), which was carried forward to the next step without purification.

[0478] **4-Ethoxy-3,4-dioxo-1-(pyridin-4-yl)but-1-en-1-olate lithium salt (18.2a):** ¹H-NMR (400 MHz, DMSO-d₆): δ 8.93 (s, 1H), 8.62 (m, 1H), 8.10 (m, 1H), 7.40 (m, 1H), 6.38 (m, 1H), 4.11 (q, *J* = 7.20 Hz, 2H) and 1.22 (t, *J* = 7.2 Hz, 3H). MS: 221.96 (M+H)⁺. Yield: 90%.

[0479] **4-Ethoxy-3,4-dioxo-1-(pyridin-3-yl)but-1-en-1-olate lithium salt (18.2b):** ¹H-NMR (400 MHz, DMSO-d₆): δ 8.97 (s, 1H), 8.63 (d, *J* = 4.0 Hz, 1H), 8.14 (m, 1H), 7.43 (m, 1H), 6.41 (m, 1H), 4.13 (q, *J* = 7.20 Hz, 2H) and 1.23 (t, *J* = 7.2 Hz, 3H). MS: 221.92 (M+H)⁺. Yield: 76%.

[0480] **4-Ethoxy-3,4-dioxo-1-(pyridin-2-yl)but-1-en-1-olate lithium salt (18.2c):** ¹H-NMR (400 MHz, DMSO-d₆): δ 8.60 (d, *J* = 4.4 Hz, 1H), 7.98 (m, 1H), 7.87 (m, 1H), 7.45 (m, 1H), 6.48 (s, 1H), 4.15 (q, *J* = 7.20 Hz, 2H) and 1.19 (t, *J* = 6.8 Hz, 3H). MS: 221.97 (M+H)⁺. Yield: 96%.

- 5 [0481] **General procedure for the preparation of compounds 18.3 (a-c):** To an ice-cold solution of compound 18.2 (a-c), (1.0 eq) in IPA was added 3,4,5-trifluorophenyl hydrazine HCl (1.10 eq) and TFA (2.0 eq). The resulting reaction mixture was warm up to room temperature and then stirred at 90°C for 4-5 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted
10 with ethyl acetate (3 times). The combined organics was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified over silica gel (100-200 M, 10-15% EtOAc-hexane) to get the desired products 18.3 (a-c).

- [0482] **Ethyl 5-(pyridin-4-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylate (18.3a):** ¹H-NMR (400 MHz, CDCl₃): δ 8.70 (m, 1H), 8.65 (s, 1H), 7.62 (d, *J* = 8.0 Hz, 1H),
15 7.42 (m, 1H), 7.15 (s, 1H), 7.03 (m, 2H), 4.49 (q, *J* = 7.2 Hz, 2H) and 1.45 (t, *J* = 7.2 Hz, 3H). MS: 348.09 (M+H)⁺. Yield: 28%.

- [0483] **Ethyl 5-(pyridin-3-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylate (18.3b):** ¹H-NMR (400 MHz, CDCl₃): δ 8.67 (m, 1H), 8.60 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 1H),
20 7.41 (m, 1H), 7.12 (s, 1H), 7.00 (m, 2H), 4.47 (q, *J* = 7.2 Hz, 2H) and 1.43 (t, *J* = 7.2 Hz, 3H). MS: 348.15 (M+H)⁺. Yield: 22%.

[0484] **Ethyl 5-(pyridin-2-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylate (18.3c):** ¹H-NMR (400 MHz, CDCl₃): δ 8.53 (m, 1H), 7.75 (m, 1H), 7.45 (d, *J* = 8.0 Hz, 1H),
7.30 (m, 1H), 7.23 (s, 1H), 7.03 (m, 2H), 4.39 (q, *J* = 6.8 Hz, 2H) and 1.41 (t, *J* = 7.2 Hz, 3H). MS: 347.88 (M+H)⁺. Yield: 23%.

- 25 [0485] **General procedure for the preparation of compounds 18.4 (a-c):** To an ice-cold solution of compound 18.3 (a-c) (1.0 eq) in EtOH was added dropwise an aqueous solution of sodium hydroxide (3.0 eq). The resulting solution was stirred at room temperature for 2-3 h. After completion of the reaction (TLC monitoring), the solvent was evaporated, added H₂O to the residue followed by extraction with EtOAc (2 x 100 mL). The organic layer was
30 discarded and the pH of the aqueous layer was adjusted to ~4 by adding 1N HCl. The

resulting precipitate was filtered and dried under vacuum to get the desired products 18.4 (a-c) as a white solid.

[0486] 5-(pyridin-4-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylic acid

(18.4a): $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 13.40 (br s, 1H), 8.62 (m, 2H), 7.68 (d, J = 8.0 Hz, 1H), 7.56 (m, 2H), 7.45 (m, 1H) and 7.22 (s, 1H). LCMS: 320.17 ($\text{M}+\text{H}$) $^+$, 96.12%. Yield: 65%.

[0487] 5-(pyridin-3-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylic acid

(18.4b): $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 13.12 (br s, 1H), 8.58 (s, 2H), 7.64 (d, J = 8.4 Hz, 1H), 7.50 (m, 2H), 7.40 (m, 1H) and 7.24 (s, 1H). LCMS: 320.14 ($\text{M}+\text{H}$) $^+$, 94.25 %. Yield: 61%.

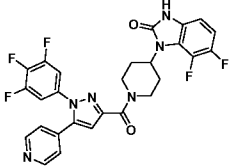
[0488] 5-(pyridin-2-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylic acid

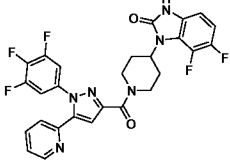
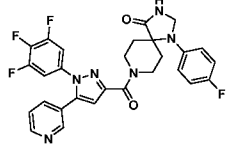
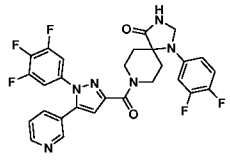
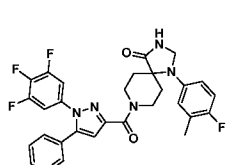
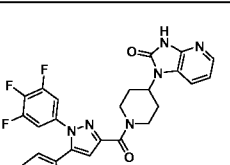
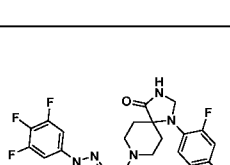
(18.4c): $^1\text{H-NMR}$ (400 MHz, DMSO- d_6): δ 8.45 (d, J = 5.4 Hz, 1H), 7.87 (m, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.35 (m, 3H) and 7.25 (s, 1H). LCMS: 320.12 ($\text{M}+\text{H}$) $^+$, 98.46 %. Yield: 55%.

[0489] General procedure for the preparation of final compounds 5 (18.a-h): To an ice cold solution of carboxylic acids 18.4 (a-c) (1.0 eq), in DMF (2.0 mL) was added DIPEA (3.0 eq) and HATU (1.50 eq). The resulting mixture was stirred under nitrogen atmosphere at 0°C for 15 min followed by addition of respective amines (1.20 eq). The reaction mixture was then stirred at room temperature for 16 h. After the completion of the reaction (TLC monitoring), the solution was diluted with ice cold water (30 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure. The crude residue was purified via prep-HPLC.

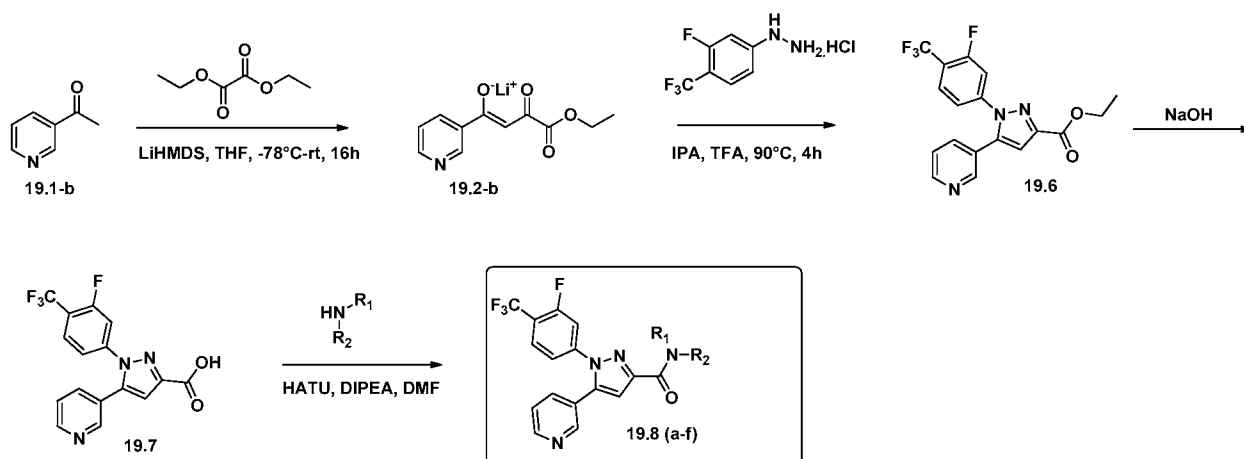
[0490] Individual yields and the analytical data of the final compounds synthesized via scheme 18 are set forth in Table 6.6.

Table 6.6: Tabulated data of the final compounds including the individual yields obtained via scheme 18.

Compound No.	Structure	Yield (%)	LCMS	NMR data (DMSO- d_6 , 400 MHz), unless otherwise specified
251		23	555.11 ($\text{M}+\text{H}$) $^+$, 99.32%	δ 11.19 (br s, 1H), 8.59 (d, J = 6.0 Hz, 2H), 7.54 (t, J = 7.6 Hz, 2H), 7.31 (d, J = 5.6 Hz, 2H), 7.23 (s, 1H), 7.00-7.07 (m, 1H), 6.77-6.80 (m, 1H), 4.78-4.81 (m, 1H), 4.67-4.70 (m, 2H), 3.29 (s, 1H), 2.92-2.98 (m, 1H), 2.07-2.13 (m, 2H) and 1.84-

				1.87 (m, 2H)
252		15	555.09 (M+H) ⁺ , 99.89%	δ 11.25 (br s, 1H), 8.47 (s, 1H), 7.91 (s, 1H), 7.71 (s, 1H), 7.48 (s, 2H), 7.38 (s, 1H), 7.25 (s, 1H), 7.04-7.09 (m 1H), 6.79 (s, 1H), 4.81-4.83 (m, 1H), 4.67-4.74 (m, 2H), 3.17 (s, 1H), 2.94-2.98 (m, 1H), 2.14-2.16 (m, 2H) and 1.83-1.87 (m, 2H)
253		20	551.13 (M+H) ⁺ , 99.86%	δ 8.80 (s, 1H), 8.59-8.60 (m, 2H), 7.66 (d, J= 7.6 Hz, 1H), 7.41-7.48 (m, 3H), 7.08-7.15 (m, 3H), 6.84-6.87 (m, 2H), 4.59 (s, 2H), 4.41-4.49 (m, 2H), 3.83-3.89 (m, 1H), 3.50-3.56 (m, 1H), 2.20-2.28 (m, 2H) and 1.74-1.83 (m, 2H)
254		19	567.12 (M-H) ⁺ , 98.45%	δ 8.89 (s, 1H), 8.62 (s, 2H), 7.70-7.72 (m, 1H), 7.45-7.50 (m, 3H), 7.28-7.31 (m, 1H), 7.15 (s, 1H), 6.74-6.79 (m, 1H), 6.57-6.59 (m, 1H), 4.59 (s, 2H), 4.47-4.49 (m, 2H), 3.82-3.85 (m, 1H), 3.49-3.53 (m, 1H), 2.33-2.36 (m, 2H) and 1.72-1.76 (m, 2H)
255		23	565.34 (M+H) ⁺ , 97.49%	δ 8.78 (s, 1H), 8.59-8.60 (m, 2H), 7.66 (d, J= 7.6 Hz, 1H), 7.41-7.48 (m, 3H), 7.12 (s, 1H), 7.01-7.05 (m, 1H), 6.68-6.74 (m, 2H), 4.57 (s, 2H), 4.40-4.43 (m, 2H), 3.81-3.84 (m, 1H), 3.49-3.51 (m, 1H), 2.23-2.26 (m, 2H), 2.14 (s, 3H) and 1.72-1.76 (m, 2H)
256		9.8	520.10 (M+H) ⁺ , 99.67%	δ 11.55 (br s, 1H), 8.60 (s, 2H), 7.89 (d, J= 4.4 Hz, 1H), 7.67 (d, J= 7.6 Hz, 1H), 7.57 (d, J= 7.6 Hz, 1H), 7.50 (d, J= 7.6 Hz, 2H), 7.41-7.45 (m, 1H), 7.15 (s, 1H), 6.97-7.01 (m, 1H), 4.70-4.79 (m, 2H), 4.49-4.55 (m, 1H), 2.90-2.96 (m, 1H), 2.22-2.26 (m, 3H) and 1.80-1.84 (m, 2H)
257		15	569.31 (M+H) ⁺ , 99.50%	δ 8.65 (s, 1H), 8.59-8.60 (m, 2H), 7.62 (d, J= 8.0 Hz, 1H), 7.43-7.48 (m, 4H), 7.27-7.30 (m, 1H), 7.07-7.10 (m, 1H), 7.04 (s, 1H), 4.53-4.57 (m, 2H), 4.22-4.26 (m, 1H), 4.10-4.14 (m, 1H), 3.87-3.93 (m, 1H), 3.55-3.61 (m, 1H), 1.87-1.94 (m, 2H) and 1.37-1.42 (m, 2H)

Scheme 19:

**[0491] Preparation of 4-ethoxy-3,4-dioxo-1-(pyridin-3-yl)but-1-en-1-olate lithium salt**

(19.2-b): A solution of 3-acetyl pyridine 19.1-b (25 g, 206.37 mmol) in di-ethyl ether (300 mL) was cooled to -78°C followed by addition of LiHMDS (1.0 M in THF, 250 mL, 227.01 mmol). The resulting reaction mixture was stirred at -78°C for 45 min followed by drop wise addition of diethyl oxalate (33.8 mL, 247.64 mL) in about 30 min. The reaction mixture was then left to stir at room temperature for 16 h. After completion of the reaction (TLC and MS monitoring), the solution was then cooled to 0°C and the resulting precipitate was filtered to get the desired product as an off-white solid 2 (34 g, 76%), which was carried forward to the next step without purification. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 8.97 (s, 1H), 8.63 (d, $J=4.0$ Hz, 1H), 8.14 (m, 1H), 7.43 (m, 1H), 6.41 (m, 1H), 4.13 (q, $J=7.20$ Hz, 2H) and 1.23 (t, $J=7.2$ Hz, 3H). MS: 221.92 ($\text{M}+\text{H}$) $^{+}$.

[0492] Preparation of ethyl 1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (19.6):

To an ice-cold solution of 4-ethoxy-3,4-dioxo-1-(pyridin-3-yl)but-1-en-1-olate lithium salt 19.2-b (10 g, 45.23 mmol) in IPA (60 mL) was added (3-fluoro-4-(trifluoromethyl)phenyl)hydrazine hydrochloride 10.5 g, 54.28 mmol) and TFA (7.25 mL, 90.46 mL). The resulting reaction mixture was warm up to room temperature and then stirred at 90°C for 4-5 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified over silica gel (100-200 M, 10-15% EtOAc-hexane) to get the desired product 19.6 (7.5 g, 41%). $^1\text{H-NMR}$ (400 MHz,

CDCl₃): δ 8.70 (m, 2H), 7.73 (m, 3H), 7.48 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 7.6 Hz, 1H), 7.13 (s, 1H), 4.47 (q, J = 6.8 Hz, 2H) and 1.43 (t, J = 7.2 Hz, 3H). MS: 379.88 (M+H)⁺.

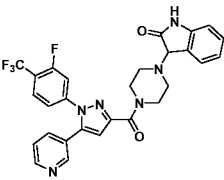
[0493] Preparation of 1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid 19.7: To an ice-cold solution of ethyl 1-(3-fluoro-4-

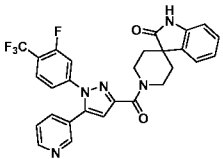
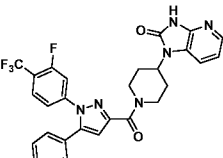
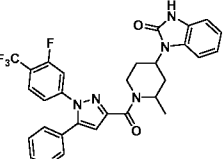
(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate 19.6 (7.5 g, 19.77 mmol) in EtOH (50 mL) was added drop wise an aqueous solution of sodium hydroxide (1.6 g in 5 mL H₂O). The resulting solution was stirred at room temperature for 2 h. After completion of the reaction (TLC monitoring), the solvent was evaporated, added H₂O to the residue followed by extraction with EtOAc (2 x 100 mL). The organic layer was discarded and the pH of the aqueous layer was adjusted to ~4 by adding 1N HCl. The resulting precipitate was filtered and dried under vacuum to get the desired product 19.7 (4.0 g, 58%) as a white solid. ¹H-NMR (400 MHz, DMSO-d₆): δ 8.58 (m, 2H), 7.86 (t, J = 8.0 Hz, 1H), 7.70 (d, J = 7.6 Hz, 1H), 7.63 (m, 1H), 7.43 (m, 1H), 7.33 (d, J = 8.4 Hz, 1H) and 7.24 (s, 1H). LCMS: 351.96 (M+H)⁺, 90.40%.

[0494] General procedure for the preparation of final compounds 19.8 (a-f): To an ice cold solution of 1-(3-fluoro-4-(trifluoromethyl) phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid 19.7 (1.0 eq), in DMF (2.0 mL) was added DIPEA (3.0 eq) and HATU (1.50 eq). The resulting mixture was stirred under nitrogen atmosphere at 0°C for 15 min followed by addition of respective amines (1.20 eq). The reaction mixture was then stirred at room temperature for 16 h. After the completion of the reaction (TLC monitoring), the solution was diluted with ice cold water (30 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified via prep-HPLC.

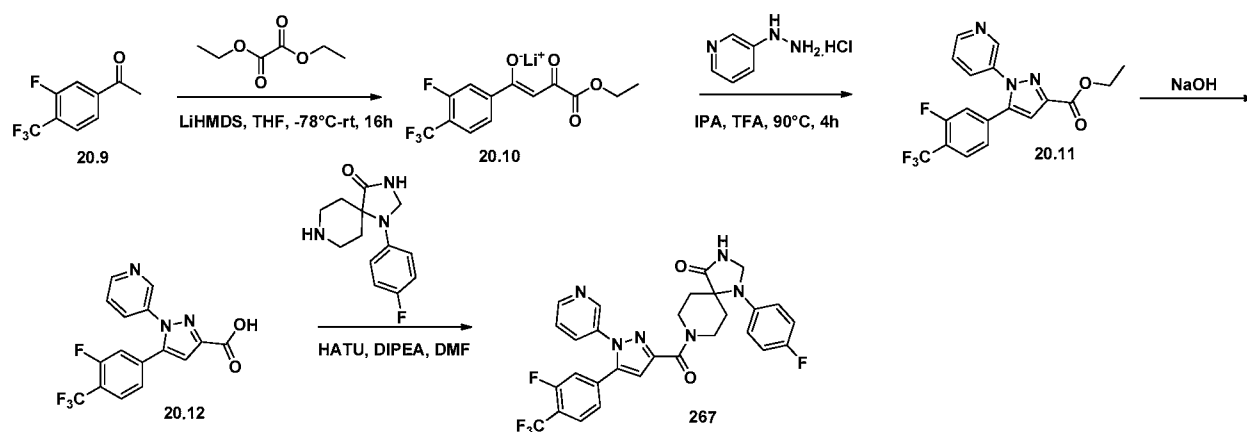
[0495] Yields and the analytical data of the final compounds synthesized via scheme 19 are set forth in Table 6.7.

Table 6.7: Tabulated data of the final compounds including the individual yields obtained via scheme 19.

Compound No.	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
258		20	551.15 (M+H) ⁺ , 98.86%	δ 10.39 (br s, 1H), 8.58-8.61 (m, 2H), 7.83 (t, J = 8.4 Hz, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.65-7.67 (m, 1H), 7.43-7.46 (m, 1H), 7.29-7.32 (m, 2H), 7.19 (d, J = 7.6 Hz, 1H), 7.12 (s, 1H), 6.96 (t, J = 7.6 Hz, 1H), 6.78 (d, J = 7.6 Hz, 1H), 4.43 (s, 1H), 3.96-

				3.98 (m, 2H), 3.65-3.67 (m, 2H), 2.81-2.86 (m, 2H) and 2.67-2.68 (m, 2H)
259		21	536.12 (M+H) ⁺ , 96.33%	δ 10.48 (br s, 1H), 8.61-8.62 (m, 2H), 7.85 (t, J= 8.4 Hz, 1H), 7.73 (d, J= 8.0 Hz, 1H), 7.64-7.67 (m, 1H), 7.50 (d, J= 7.6 Hz, 1H), 7.44-7.46 (m, 1H), 7.32-7.34 (m, 1H), 7.18-7.22 (m, 2H), 7.95 (t, J= 8.4 Hz, 1H), 6.86 (t, J= 8.0 Hz, 1H), 4.22-4.23 (m, 2H), 4.00-4.05 (m, 2H) and 1.81-1.83 (m, 4H)
260		12	552.11 (M+H) ⁺ , 95.74%	δ 10.57 (br s, 1H), 8.61-8.62 (m, 2H), 7.85-7.89 (m, 2H), 7.73 (d, J= 8.0 Hz, 1H), 7.64-7.67 (m, 1H), 7.58 (d, J= 8.0 Hz, 1H), 7.44-7.46 (m, 1H), 7.32-7.35 (m, 1H), 7.17 (s, 1H), 6.97-7.01 (m, 1H), 4.70-4.74 (m, 2H), 4.50-4.53 (m, 1H), 3.35-3.37 (m, 1H), 2.92-2.95 (m, 1H), 2.23-2.28 (m, 2H) and 1.81-1.86 (m, 2H)
261		19	565.21 (M+H) ⁺ , 99.87%	δ 10.87 (br s, 1H), 8.61-8.62 (m, 2H), 7.84-7.88 (m, 1H), 7.73 (d, J= 8.0 Hz, 1H), 7.64-7.68 (m, 1H), 7.44-7.48 (m, 1H), 7.32-7.34 (m, 2H), 7.18 (s, 1H), 6.98-7.01 (m, 3H), 4.37-4.42 (m, 3H), 3.70 (s, 1H), 2.11-2.15 (m, 2H), 1.88-1.90 (m, 2H) and 1.31-1.33 (d, J= 6.0 Hz, 3H)

Scheme 20:



- 5 [0496] **Preparation of 4-ethoxy-1-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4-dioxobut-1-en-1-olate lithium salt (20.10):** A solution of 1-(3-fluoro-4-(trifluoromethyl)phenyl)ethan-1-one 20.9 (5 g, 24.25 mmol) in diethyl ether (60 mL) was cooled to -78°C followed by addition of LiHMDS (1.0 M in THF, 27 mL, 26.68 mmol). The resulting reaction mixture was stirred at -78°C for 45 min followed by drop wise addition of diethyl oxalate (4.0 mL,

29.10 mmol) in about 30 min. The reaction mixture was then left to stir at room temperature for 16 h. After completion of the reaction (TLC and MS monitoring), the solution was then cooled 0°C and the resulting precipitate was filtered to get the desired product as an off-white solid 20.10 (7.4 g, 99%), which was carried forward to the next step without purification. ¹H-NMR (400 MHz, DMSO-d₆): δ 7.76 (m, 3H), 6.44 (s, 1H), 4.14 (q, J= 7.20 Hz, 2H) and 1.23 (t, J= 7.2 Hz, 3H). MS: 306.98 (M+H)⁺.

[0497] Preparation of ethyl 5-(3-fluoro-4-(trifluoromethyl)phenyl)-1-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (20.11):

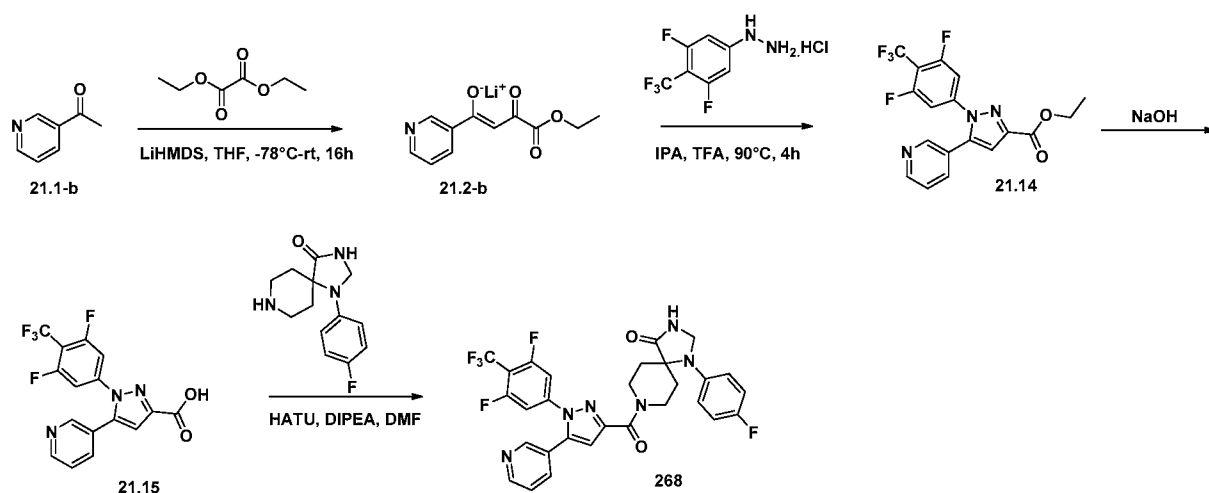
To an ice-cold solution of 4-ethoxy-1-(3-fluoro-4-(trifluoromethyl)phenyl)-3,4-dioxobut-1-en-1-olate lithium salt 20.10 (2.5 g, 8.01 mmol) in IPA (20 mL) was added 3-hydrazinylpyridine hydrochloride 1.5 g, 8.01 mmol) and TFA (1.2 mL, 16.03 mmol). The resulting reaction mixture was warmed up to room temperature and then stirred at 90°C for 4-5 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified over silica gel (100-200 M, 10-15% EtOAc-hexane) to get the desired product 20.11 (1.0 g, 34%). ¹H-NMR (400 MHz, CDCl₃): δ 8.65 (m, 1H), 8.56 (s, 1H), 7.74 (d, J= 7.6 Hz, 1H), 7.56 (t, J= 7.6 Hz, 1H), 7.39 (m, 1H), 7.14 (s, 1H), 7.00 (m, 2H), 4.39 (q, J= 7.6 Hz, 2H) and 1.42 (t, J= 7.2 Hz, 3H). MS: 380.17 (M+H)⁺.

[0498] Preparation of 5-(3-fluoro-4-(trifluoromethyl)phenyl)-1-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (20.12):

To an ice-cold solution of ethyl 5-(3-fluoro-4-(trifluoromethyl)phenyl)-1-(pyridin-3-yl)-1H-pyrazole-3-carboxylate 20.11 (1.0 g, 2.63 mmol) in EtOH (30 mL) was added drop wise an aqueous solution of sodium hydroxide (0.22 g in 3 mL H₂O). The resulting solution was stirred at room temperature for 2 h. After completion of the reaction (TLC monitoring), the solvent was evaporated, added H₂O to the residue followed by extraction with EtOAc (2 x 100 mL). The organic layer was discarded and the pH of the aqueous layer was adjusted to ~4 by adding 1N HCl. The resulting precipitate was filtered and dried under vacuum to get the desired product 20.12 (0.8 g, 86%) as a white solid. ¹H-NMR (400 MHz, DMSO-d₆): δ 13.23 (br s, 1H), 8.66 (t, J= 4.0 Hz, 1H), 8.60 (m, 1H), 7.84 (d, J= 8.4 Hz, 1H), 7.77 (t, J= 7.6 Hz, 1H), 7.54 (m, 2H), 7.34 (s, 1H) and 7.23 (d, J= 8.0 Hz, 1H). LCMS: 352.00 (M+H)⁺, 95.49%.

[0499] Preparation of 8-(5-(3-fluoro-4-(trifluoromethyl)phenyl)-1-(pyridin-3-yl)-1H-pyrazole-3-carbonyl)-1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (Compound 267): To an ice cold solution of 5-(3-fluoro-4-(trifluoromethyl)phenyl)-1-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid 20.12 (0.15 g, 0.43 mmol) in DMF (2.0 mL) was added DIPEA (0.22 mL, 1.29 mmol) and HATU (0.25 g, 0.65 mmol). The resulting mixture was stirred under nitrogen atmosphere at 0°C for 15 min followed by addition of 1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (0.11 g, 0.43 mmol). The reaction mixture was then stirred at room temperature for 16 h. After the completion of the reaction (TLC monitoring), the solution was diluted with ice cold water (30 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified via prep-HPLC (0.045 g, 18%). ¹H-NMR (400 MHz, DMSO-d₆): δ 8.80 (s, 1H), 8.60-8.63 (m, 2H), 7.78-7.83 (m, 2H), 7.53-7.56 (m, 1H), 7.50-7.52 (m, 1H), 7.24 (d, J= 8.0 Hz, 1H), 7.22 (s, 1H), 7.07 (d, J= 8.8 Hz, 2H), 6.84-6.87 (m, 2H), 4.58-4.59 (m, 2H), 4.42-4.48 (m, 2H), 3.84-.387 (m, 1H), 3.51-3.56 (m, 1H), 2.19-2.23 (m, 2H) and 1.74-1.79 (m, 2H). LCMS: 583.14 (M+H)⁺, 96.73 %.

Scheme 21:



[0500] Preparation of 4-ethoxy-3,4-dioxo-1-(pyridin-3-yl)but-1-en-1-olate lithium salt (21.2-b): Intermediate 21.2-b was prepared as per the procedure mentioned in scheme 19.

[0501] Preparation of ethyl 1-(3,5-difluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (21.14): To an ice-cold solution of 4-ethoxy-3,4-dioxo-1-(pyridin-3-yl)but-1-en-1-olate lithium salt 21.2-b (1.5 g, 6.78 mmol) in IPA (20 mL) was

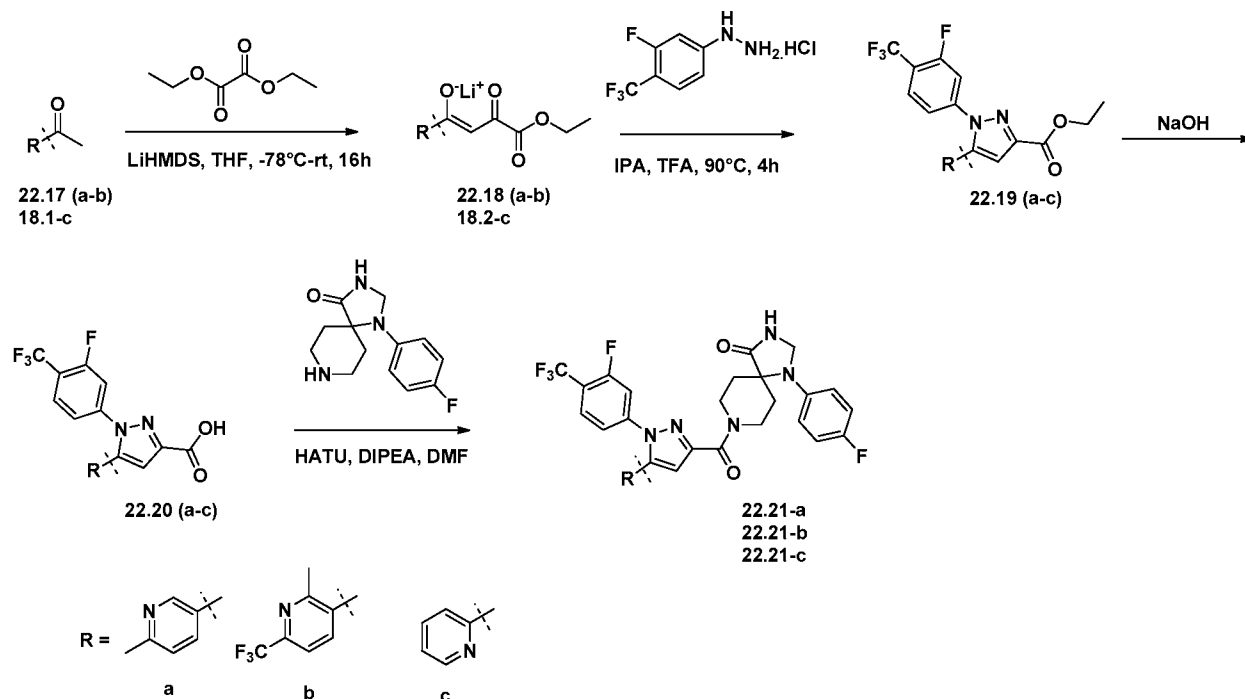
added (3,5-difluoro-4-(trifluoromethyl)phenyl)hydrazine hydrochloride (1.68 g, 6.78 mmol) and TFA (1.0 mL, 13.56 mL). The resulting reaction mixture was warm up to room temperature and then stirred at 90°C for 4-5 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated. The crude was purified over silica gel (100-200 M, 10-15% EtOAc-hexane) to get the desired product 21.14 (0.66 g, 25%). ¹H-NMR (400 MHz, CDCl₃): δ 8.70 (m, 1H), 8.58 (m, 1H), 7.57 (m, 1H), 7.38 (m, 1H), 7.08 (s, 1H), 7.03 (m, 2H), 4.44 (q, J= 6.8 Hz, 2H) and 1.41 (t, J= 6.8 Hz, 3H). MS: 398.16 (M+H)⁺.

[0502] Preparation of 1-(3,5-difluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (2.15): To an ice-cold solution of ethyl 1-(3,5-difluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate 2.14 (0.60 g, 1.65 mmol) in EtOH (20 mL) was added drop wise an aqueous solution of sodium hydroxide (0.13 g in 3 mL H₂O). The resulting solution was stirred at room temperature for 2 h. After completion of the reaction (TLC monitoring), the solvent was evaporated, added H₂O to the residue followed by extraction with EtOAc (2 x 100 mL). The organic layer was discarded and the pH of the aqueous layer was adjusted to ~4 by adding 1N HCl. The resulting precipitate was filtered and dried under vacuum to get the desired product 2.15 (0.3 g, 51%) as a white solid. ¹H-NMR (400 MHz, DMSO-d₆): δ 13.31 (br s, 1H), 8.59 (m, 2H), 7.73 (m, 1H), 7.45 (m, 2H), 7.38 (m, 1H) and 7.04 (m, 1H). MS: 368.14 (M-H)⁺.

[0503] Preparation of 8-(1-(3,5-difluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carbonyl)-1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (Compound 268): To an ice cold solution of 1-(3,5-difluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid 2.15 (0.10 g, 0.27 mmol) in DMF (2.0 mL) was added DIPEA (0.14 mL, 0.81 mmol) and HATU (0.154 g, 0.41 mmol). The resulting mixture was stirred under nitrogen atmosphere at 0°C for 15 min followed by addition of 1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]decan-4-one (0.067 g, 0.27 mmol). The reaction mixture was then stirred at room temperature for 16 h. After the completion of the reaction (TLC monitoring), the solution was diluted with ice cold water (30 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organics was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified via prep-HPLC (0.035 g, 21%). ¹H-NMR (400 MHz, DMSO-d₆ + D₂O): δ 8.59-8.60 (m, 1H), 8.54-8.55 (m, 1H), 7.75 (d, J= 8.0 Hz, 1H) 7.46-7.47 (m, 1H), 7.30-7.32 (m, 2H), 7.05-7.09

(m, 3H), 6.84-6.88 (m, 2H), 4.56 (s, 2H), 4.31-4.35 (m, 2H), 3.79-3.81 (m, 1H), 3.48-3.51 (m, 1H), 2.15-2.19 (m, 2H) and 1.71-1.75 (m, 2H). LCMS: 601.10 (M+H)⁺, 99.21 %.

Scheme 22:



5

[0504] Preparation of 22.18 (a-b) and 18.1-c: These intermediates were prepared following the general procedure mentioned in scheme 18.

[0505] 4-Ethoxy-1-(6-methylpyridin-3-yl)-3, 4-dioxobut-1-en-1-olate lithium salt

(22.18-a): ¹H-NMR (400 MHz, DMSO-d₆): δ 8.85 (s, 1H), 8.03 (d, J= 7.2 Hz, 1H), 7.28 (d, J= 8.0 Hz, 1H), 6.40 (s, 1H), 4.14 (q, J= 6.8 Hz, 2H), 2.45 (s, 3H) and 1.25 (t, J= 7.2 Hz, 3H). MS: 236.14 (M+H)⁺. Yield: 80%.

[0506] 4-Ethoxy-1-(2-methyl-6-(trifluoromethyl) pyridin-3-yl)-3,4-dioxobut-1-en-1-olate lithium salt (22.18-b): ¹H-NMR (400 MHz, DMSO-d₆): δ 7.87 (d, J= 7.6 Hz, 1H),

7.70 (d, J= 7.2 Hz, 1H), 5.91 (s, 1H), 4.17 (q, J= 7.6 Hz, 2H), 2.58 (s, 3H) and 1.16 (t, J= 7.2 Hz, 3H). MS: 304.12 (M+H)⁺. Yield: 93%.

[0507] 4-Ethoxy-3,4-dioxo-1-(pyridin-2-yl)but-1-en-1-olate lithium salt (18.2-c): ¹H-NMR (400 MHz, DMSO-d₆): δ 8.60 (d, J= 4.4 Hz, 1H), 7.98 (m, 1H), 7.87 (m, 1H), 7.45 (m, 1H), 6.48 (s, 1H), 4.15 (q, J= 7.20 Hz, 2H) and 1.19 (t, J= 6.8 Hz, 3H). MS: 221.97 (M+H)⁺. Yield: 96%.

[0508] **Preparation of 22.19 (a-c):** These intermediates were prepared following the general procedure mentioned in scheme 18.

[0509] **Ethyl 1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(6-methylpyridin-3-yl)-1H-pyrazole-3-carboxylate (22.19-a):** $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.61 (m, 1H), 7.60 (t, J= 8.0 Hz, 1H), 7.53 (d, J= 8.0 Hz, 1H), 7.32 (m, 2H), 7.13 (m, 2H), 4.44 (q, J= 7.2 Hz, 2H), 2.68 (s, 3H) and 1.41 (t, J= 7.2 Hz, 3H). MS: 394.17 (M+H) $^+$. Yield: 57%.

[0510] **Ethyl 1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(2-methyl-6-(trifluoromethyl)pyridin-3-yl)-1H-pyrazole-3-carboxylate (22.19-b):** $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 7.69 (d, J= 7.6 Hz, 1H), 7.60 (t, J= 6.8 Hz, 1H), 7.53 (t, J= 8.0 Hz, 1H), 7.30 (m, 2H), 7.03 (s, 1H), 4.46 (q, J= 6.8 Hz, 2H), 2.37 (s, 3H) and 1.38 (t, J= 6.8 Hz, 3H). MS: 462.25 (M+H) $^+$. Yield: 26%.

[0511] **Ethyl 1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-2-yl)-1H-pyrazole-3-carboxylate (22.19-c):** $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.52 (d, J= 4.4 Hz, 1H), 7.77 (t, J= 8.0 Hz, 1H), 7.55 (t, J= 7.6 Hz, 1H), 7.47 (d, J= 7.6 Hz, 1H), 7.29 (m, 2H), 7.25 (m, 1H), 7.19 (m, 1H), 4.43 (q, J= 7.2 Hz, 2H) and 1.39 (t, J= 7.2 Hz, 3H). MS: 380.20 (M+H) $^+$. Yield: 40%.

[0512] **Preparation of 22.20 (a-c):** These intermediates were prepared following the general procedure mentioned in scheme 18.

[0513] **1-(3-fluoro-4-(trifluoromethyl)phenyl)-5-(6-methylpyridin-3-yl)-1H-pyrazole-3-carboxylic acid (22.20-a):** $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 8.44 (s, 1H), 7.87 (m, 1H), 7.64 (d, J= 7.2 Hz, 1H), 7.57 (m, 1H), 7.29 (m, 2H), 7.19 (m, 1H) and 2.50 (s, 3H). MS: 366.15 (M+H) $^+$. Yield: 59%.

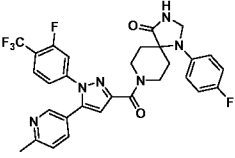
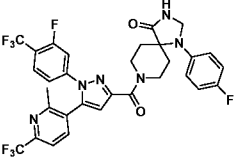
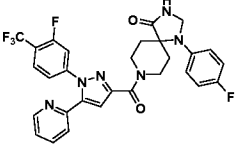
[0514] **1-(3-Fluoro-4-(trifluoromethyl)phenyl)-5-(2-methyl-6-(trifluoromethyl)pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (22.20-b):** $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 7.93 (d, J= 8.0 Hz, 1H), 7.80 (d, J= 8.0 Hz, 1H), 7.76 (m, 1H), 7.62 (m, 1H), 7.27 (m, 1H), 7.08 (m, 1H) and 2.63 (s, 3H). MS: 432.09 (M-H) $^+$. Yield: 83%.

[0515] **1-(3-Fluoro-4-(trifluoromethyl)phenyl)-5-(pyridin-2-yl)-1H-pyrazole-3-carboxylic acid (22.20-c):** $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 8.45 (d, J= 4.0 Hz, 1H), 7.90 (t, J= 8.0 Hz, 1H), 7.76 (m, 2H), 7.54 (d, J= 7.2 Hz, 1H), 7.37 (m, 1H), 7.27 (d, J= 8.0 Hz, 1H) and 7.20 (s, 1H): LC-MS: 351.97 (M+H) $^+$, 99.57%. Yield: 47%.

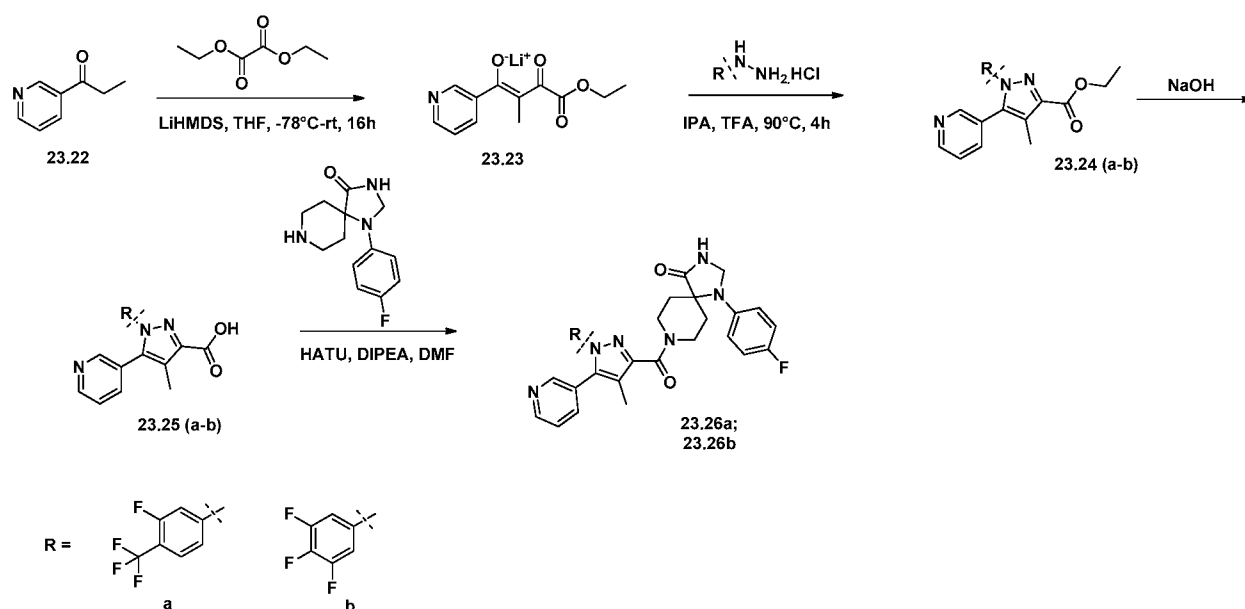
[0516] **Preparation of 22.21 (a-c):** These intermediated were prepared following the general procedure mentioned in scheme 18.

[0517] Yields and the analytical data of the final compounds are set forth in Table 6.8.

Table 6.8: Tabulated data of the final compounds including the individual yields obtained.

Compound No.	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
262		22	597.18 (M+H) ⁺ , 97.44%	δ 8.81 (s, 1H), 8.45-8.46 (m, 1H), 7.83-7.87 (m, 1H), 7.58-7.65 (m, 2H), 7.28-7.32 (m, 2H), 7.08-7.12 (m, 3H), 6.84-6.87 (m, 2H), 4.58-4.59 (m, 2H), 4.42-4.45 (m, 2H), 3.84-3.87 (m, 1H), 3.50-3.54 (m, 1H), 2.50 (s, 3H), 2.20-2.23 (m, 2H) and 1.74-1.79 (m, 2H)
263		26	663.10 (M-H) ⁺ , 98.09%	δ 8.82 (s, 1H), 7.94-7.96 (m, 1H), 7.80-7.83 (m, 2H), 7.60-7.63 (m, 1H), 7.17-7.19 (m, 2H), 7.09-7.11 (m, 2H), 6.85-6.89 (m, 2H), 4.60 (s, 2H), 4.44-4.45 (m, 2H), 3.86-3.89 (m, 1H), 3.53-3.55 (m, 1H), 2.40 (s, 3H), 2.22-2.25 (m, 2H) and 1.75-1.81 (m, 2H)
264		25	583.14 (M+H) ⁺ , 96.24%	δ 8.81 (s, 1H), 8.47-8.48 (m, 1H), 7.92-7.96 (m, 1H), 7.79-7.81 (m, 2H), 7.57-7.60 (m, 1H), 7.39-7.42 (m, 1H), 7.27-7.30 (m, 2H), 7.08-7.12 (m, 2H), 6.84-6.87 (m, 2H), 4.58-4.59 (m, 2H), 4.44-4.45 (m, 2H), 3.84-3.88 (m, 1H), 3.50-3.54 (m, 1H), 2.17-2.21 (m, 2H) and 1.74-1.77 (m, 2H)

Scheme 23:

**[0518] Preparation of 4-ethoxy-2-methyl-3,4-dioxo-1-(pyridin-3-yl)but-1-en-1-olate**

- 5 **lithium salt (23.23):** A solution of 3-propionylpyridine 23.22 (2 g, 14.8 mmol) in di-ethyl ether (20 mL) was cooled to -78°C followed by addition of LiHMDS (1.0 M in THF, 17 mL, 17.0 mmol). The resulting reaction mixture was stirred at -78°C for 45 min followed by drop wise addition of diethyl oxalate (2.32 mL, 17.0 mmol) in about 30 min. The reaction mixture was then left to stir at room temperature for 16 h. After completion of the reaction (TLC and
- 10 MS monitoring), the solution was then cooled 0°C and the resulting precipitate was filtered to get the desired product as an off-white solid 23.23 (3.4 g, 98%), which was carried forward to the next step without purification. $^1\text{H-NMR}$ (400 MHz, DMSO-d_6): δ 8.41 (m, 2H), 7.56 (d, $J = 7.60$ Hz, 1H), 7.25 (d, $J = 7.60$ Hz, 1H), 3.65 (q, $J = 7.20$ Hz, 2H), 3.36 (s, 3H) and 1.08 (t, $J = 6.8$ Hz, 3H). MS: 236.10 ($\text{M}+\text{H}$) $^{+}$.

- 15 **[0519] General procedure for the preparation of compounds 23.24 (a-b):** To an ice-cold solution of 4-ethoxy-2-methyl-3,4-dioxo-1-(pyridin-3-yl)but-1-en-1-olate lithium salt 23.23 (1 eq) in IPA was added respective hydrazine hydrochloride (1 eq) and TFA (2 eq). The resulting reaction mixture was warm up to room temperature and then stirred at 90°C for 4-5 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the
- 20 residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics were washed with brine, dried over anhydrous sodium sulfate, filtered and

concentrated. The crude was purified over silica gel (100-200 M, 10-15% EtOAc-hexane) to get the desired product 23.24 (a-b).

[0520] Ethyl 1-(3-fluoro-4-(trifluoromethyl)phenyl)-4-methyl-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylate (23.24-a): ¹H-NMR (400 MHz, CDCl₃): δ 8.73 (m, 1H), 8.57 (s,

1H), 7.68 (m, 1H), 7.60 (m, 3H), 7.02 (m, 1H), 4.45 (q, J= 7.2 Hz, 2H), 2.33 (s, 3H) and 1.18 (t, J= 7.6 Hz, 3H). MS: 394.08 (M+H)⁺. Yield: 25%.

[0521] Ethyl 4-methyl-5-(pyridin-3-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylate (23.24-b): ¹H-NMR (400 MHz, CDCl₃): δ 8.62 (m, 1H), 8.49 (s, 1H), 7.69 (m, 1H), 7.49 (m, 1H), 7.40 (m, 2H), 4.36 (q, J= 6.8 Hz, 2H), 2.22 (s, 3H) and 1.17 (t, J= 6.8 Hz, 3H). MS: 362.13 (M+H)⁺. Yield: 22%.

[0522] General procedure for the preparation of compounds 23.25 (a-b): To an ice-cold solution of compound 23.24 (a-b) (1.0 eq) in EtOH was added drop wise an aqueous solution of sodium hydroxide (3.0 eq). The resulting solution was stirred at room temperature for 4h. After completion of the reaction (TLC monitoring), the solvent was evaporated, added H₂O to the residue followed by extraction with EtOAc (2 x 100 mL). The organic layer was discarded and the pH of the aqueous layer was adjusted to ~4 by adding 1N HCl. The resulting precipitate was filtered and dried under vacuum to get the desired product 23.25 (a-b) as a white solid.

[0523] 1-(3-Fluoro-4-(trifluoromethyl)phenyl)-4-methyl-5-(pyridin-3-yl)-1H-pyrazole-3-carboxylic acid (23.25-a): ¹H-NMR (400 MHz, DMSO-d₆): δ 13.12 (br s, 1H), 8.64 (m, 1H), 8.50 (s, 1H), 7.81 (t, J= 8.0 Hz, 1H), 7.74 (d, J= 7.6 Hz, 1H), 7.48 (m, 2H), 7.23 (d, J= 8.0 Hz, 1H) and 2.21 (s, 3H). MS: 366.17(M+H)⁺. Yield: 65%.

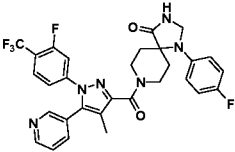
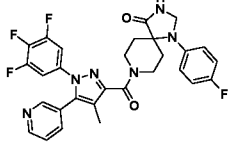
[0524] 4-Methyl-5-(pyridin-3-yl)-1-(3,4,5-trifluorophenyl)-1H-pyrazole-3-carboxylic acid (23.25-b): ¹H-NMR (400 MHz, DMSO-d₆): δ 13.07 (br s, 1H), 8.62 (m, 1H), 8.49 (s, 1H), 7.69 (d, J= 7.6 Hz, 1H), 7.46 (m, 1H), 7.36 (m, 2H) and 2.20 (s, 3H). LCMS: 334.13 (M+H)⁺, 99.66%. Yield: 55%.

[0525] General procedure for the preparation of final compounds 23.26 (a-b): To an ice cold solution of carboxylic acids 23.25 (a-b) (1.0 eq), in DMF (2.0 mL) was added DIPEA (3.0 eq) and HATU (1.50 eq). The resulting mixture was stirred under nitrogen atmosphere at 0°C for 15 min followed by addition of respective amines (1.20 eq). The reaction mixture was then stirred at room temperature for 16 h. After the completion of the

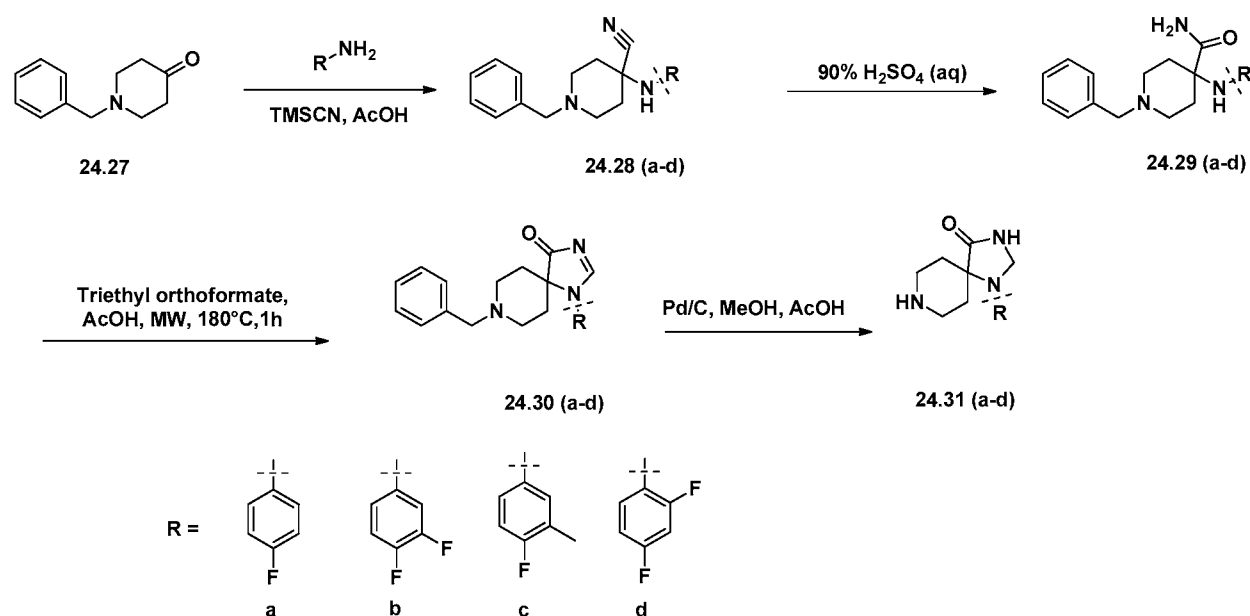
reaction (TLC monitoring), the solution was diluted with ice cold water (30 mL) followed by extraction with EtOAc (3 x 50 mL). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The crude residue was purified via prep-HPLC.

5 [0526] Yields and the analytical data of the final compounds are set forth in Table 6.9.

Table 6.9: Tabulated data of the final compounds including the individual yields obtained.

Compound No.	Structure	Yield (%)	LCMS	NMR data (DMSO-d ₆ , 400 MHz), unless otherwise specified
265		13	597.18 (M+H) ⁺ , 99.21%	δ 8.82 (s, 1H), 8.64-8.66 (m, 1H), 8.53-8.54 (m, 1H), 7.75-7.80 (m, 2H), 7.46-7.53 (m, 2H), 7.07-7.16 (m, 3H), 6.85-6.88 (m, 2H), 4.59-4.60 (m, 2H), 4.45-4.48 (m, 1H), 4.10-4.13 (m, 1H), 3.79-3.85 (m, 1H), 3.51-3.57 (m, 1H), 2.36-2.38 (m, 1H), 2.27-2.29 (m, 1H), 2.09 (s, 3H), 1.80-1.84 (m, 1H) and 1.72-1.75 (m, 1H)
266		12	565.14 (M+H) ⁺ , 99.90%	δ 8.81 (s, 1H), 8.62-8.63 (m, 1H), 8.50-8.51 (m, 1H), 7.70 (d, J= 8.0 Hz, 1H), 7.47-7.49 (m, 1H), 7.29-7.31 (m, 2H), 7.07-7.12 (m, 2H), 6.84-6.87 (m, 2H), 4.59 (s, 2H), 4.43-4.46 (m, 1H), 4.12-4.15 (m, 1H), 3.78-3.83 (m, 1H), 3.50-3.53 (m, 1H), 2.26-2.30 (m, 2H), 2.08 (s, 3H) and 1.71-1.83 (m, 2H)

Scheme 24:



[0527] General procedure for the preparation of 24.28 (a-d): To an ice-cold solution of 1-benzylpiperidin-4-one 24.27 (1 eq) in acetic acid was added respective aryl amines (1.1 eq) and trimethylsilyl cyanide (1.5 eq). The resulting reaction mass was stirred at RT for 18 h. After completion of the reaction (TLC monitoring), the reaction mass was cooled to 0°C and the pH adjusted to ~10 using 5.0 N sodium hydroxide solution. The aqueous part was extracted with DCM (3 x 250 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was triturated with diethyl ether to get the desired product 24.28 (a-d) as off white solid.

[0528] 1-Benzyl-4-((4-fluorophenyl)amino)piperidine-4-carbonitrile (24.28-a): ¹H-NMR (400 MHz, CDCl₃): δ 7.32 (m, 5H), 6.91-6.94 (m, 4H), 3.55 (s, 2H), 3.47 (br s, 1H), 2.81-2.84 (m, 2H), 2.39 (m, 2H), 2.21-2.24 (m, 2H) and 1.87-1.94 (m, 2H). LC-MS: 310.13 (M+H)⁺, 96.16%. Yield: 84%

[0529] 1-Benzyl-4-((3,4-difluorophenyl)amino)piperidine-4-carbonitrile (24.28-b): ¹H-NMR (400 MHz, CDCl₃): δ 7.28 (m, 5H), 7.00 (m, 1H), 6.73 (m, 1H), 6.61 (m, 1H), 3.58 (br s, 1H), 3.55 (s, 2H), 2.80 (m, 2H), 2.41 (m, 2H), 2.26 (m, 2H) and 1.87 (m, 2H). LC-MS: 328.42 (M+H)⁺, 94.27%. Yield: 50%

[0530] 1-Benzyl-4-((4-fluoro-3-methylphenyl)amino)piperidine-4-carbonitrile (24.28-c): ¹H-NMR (400 MHz, CDCl₃): δ 7.31 (m, 5H), 6.87 (m, 1H), 6.74 (m, 2H), 3.55 (s, 2H), 3.40 (s, 1H), 2.81-2.84 (m, 2H), 2.39 (m, 2H), 2.23 (s, 3H), 2.21 (m, 2H) and 1.87 (m, 2H). LC-MS: 324.40 (M+H)⁺, 92.13%. Yield: 77%

[0531] 1-Benzyl-4-((2,4-difluorophenyl)amino)piperidine-4-carbonitrile (24.28-d): ¹H-NMR (400 MHz, CDCl₃): δ 7.28 (m, 5H), 7.12 (m, 1H), 6.69 (m, 2H), 3.71 (br s, 1H), 3.62 (s, 2H), 2.81 (m, 2H), 2.41 (m, 2H), 2.19 (m, 2H) and 1.91 (m, 2H). LC-MS: 328.26 (M+H)⁺, 95.96%. Yield: 36%

[0532] General procedure for the preparation of 24.29 (a-d): To an ice cold solution of 24.28 (a-d) (1.0 eq) was added 90% aqueous sulphuric acid and the resulting reaction mixture was stirred at room temperature for 16 h. After completion of the reaction (TLC monitoring), the reaction mass was cooled to 0°C and the pH adjusted to ~10 using 5.0 N sodium hydroxide solution. The aqueous part was extracted with DCM. The combined organics was dried over anhydrous sodium sulphate, filtered and concentrated. The crude was triturated with diethyl ether to get the desired product 24.29 (a-d) as off-white solid.

[0533] 1-Benzyl-4-(4-fluorophenylamino)piperidine-4-carboxamide (24.29-a): ¹H-NMR (400 MHz, CDCl₃): δ 7.23 (m, 5H), 6.87 (m, 3H), 6.55 (m, 2H), 5.47 (br s, 1H), 3.93 (s, 1H), 3.48 (s, 2H), 2.72 (m, 2H), 2.28 (m, 2H), 2.04 (m, 2H) and 1.86 (m, 2H). LCMS: 328.12 (M+H)⁺, 99.60%. Yield: 84%

5 **[0534] 1-Benzyl-4-((3,4-difluorophenyl)amino)piperidine-4-carboxamide (24.29-b):** ¹H-NMR (400 MHz, CDCl₃): δ 7.30 (m, 5H), 6.88 (m, 1H), 6.78 (br s, 1H), 6.42 (m, 1H), 6.29 (m, 1H), 5.51 (br s, 1H), 3.98 (s, 1H), 3.48 (s, 2H), 2.73 (m, 2H), 2.28 (m, 2H), 2.04 (m, 2H) and 1.85 (m, 2H). LCMS: 346.14 (M+H)⁺, 92.24%. Yield: 66%

10 **[0535] 1-Benzyl-4-((3-fluoro-4-methylphenyl)amino)piperidine-4-carboxamide (24.29-c):** ¹H-NMR (400 MHz, DMSO-d₆): δ 7.24 (m, 5H), 7.18 (s, 1H), 7.02 (br s, 1H), 6.81 (m, 1H), 6.45 (m, 1H), 6.35 (m, 1H), 5.34 (br s, 1H), 3.41 (s, 2H), 2.50 (m, 2H), 2.24 (m, 2H), 2.09 (s, 3H), 1.95 (m, 2H) and 1.81 (m, 2H). LCMS: 342.33 (M+H)⁺, 97.83%. Yield: 59%

15 **[0536] 1-Benzyl-4-((2,4-difluorophenyl)amino)piperidine-4-carboxamide (24.29-d):** ¹H-NMR (400 MHz, DMSO-d₆): δ 7.20 (m, 6H), 7.10 (m, 1H), 7.07 (br s, 1H), 6.82 (m, 1H), 6.46 (m, 1H), 4.78 (s, 1H), 3.41 (s, 2H), 2.52 (m, 2H), 2.13 (m, 2H), 1.98 (m, 2H) and 1.83 (m, 2H). LCMS: 346.25 (M+H)⁺, 96.72%. Yield: 46.9%

[0537] General procedure for the preparation of 24.30 (a-d): A solution of compounds 24.29 (a-d) in triethylorthoformate and AcOH (3:1) was irradiated by microwave in a sealed tube to 190°C for 2h. The reaction mixture was diluted with water and extracted with EtOAc.
20 The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified over silica gel (100-200 M, 2-4% MeOH-DCM) to get the desired product 24.30 (a-d) as off-white solid.

25 **[0538] 8-Benzyl-1-(4-fluorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (24.30-a):** ¹H-NMR (400 MHz, DMSO-d₆): δ 8.65 (s, 1H), 7.44 (m, 2H), 7.34 (m, 2H), 7.13 (m, 5H), 3.41 (s, 2H), 2.66 (m, 2H), 2.41 (m, 2H) and 1.75 (m, 4H). MS: 338.22 (M+H)⁺. Yield: 48%.

[0539] 8-Benzyl-1-(3,4-difluorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (24.30-b): LCMS: 356.29 (M+H)⁺, 82.22%. Yield: 22%.

[0540] 8-Benzyl-1-(4-fluoro-3-methylphenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (24.30-c): MS: 352.13 (M+H)⁺. Yield: 31%.

[0541] **8-Benzyl-1-(2,4-difluorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (24.30-d):**

MS: 356.19 (M+H)⁺. Yield: 18%.

[0542] **General procedure for the preparation of 24.31 (a-d):** To a solution of compounds 24.30 (a-d) (1.0 eq) in MeOH and AcOH (40:1, 20 mL) was added Pd-C (w/w, 10 mol %) and the resulting solution was stirred under hydrogen atmosphere (1 atm) at ambient temperature for 16 h. The reaction mixture was filtered through celite bed and the filtrate was concentrated under reduced pressure. The residue was purified over silica gel (basic alumina, 2-4% MeOH-DCM) to get the desired product 24.31 (a-d) as off-white solid.

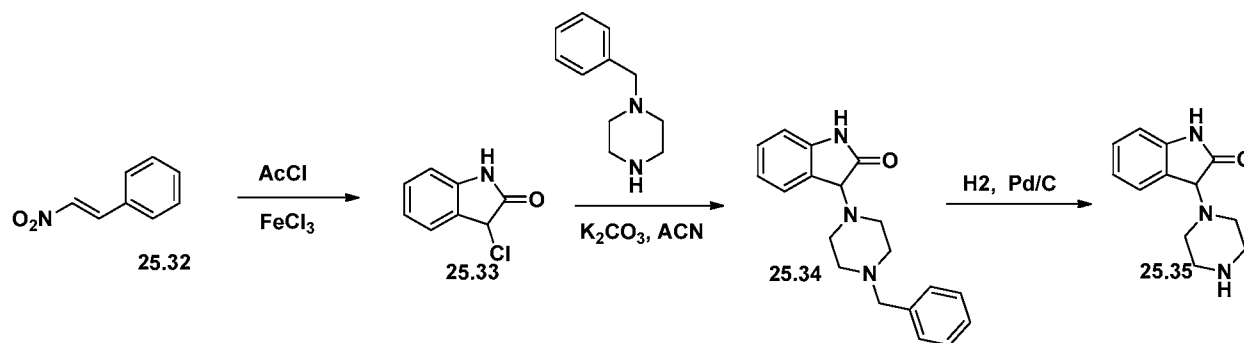
[0543] **1-(4-Fluorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (24.31-a):** ¹H-NMR (400 MHz, DMSO-d₆): δ 8.79 (br s, 1H), 7.03 (m, 2H), 6.95 (m, 2H), 4.56 (s, 2H), 3.37 (m, 3H), 2.95 (m, 2H), 2.33 (m, 2H) and 1.62 (m, 2H). LCMS: 250.13 (M+H)⁺, 81.19%. Yield: 70%

[0544] **1-(3,4-Difluorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (24.31-b):** MS: 268.20 (M+H)⁺. Yield: 25%

[0545] **1-(4-Fluoro-3-methylphenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (24.31-c):** ¹H-NMR (400 MHz, DMSO-d₆): δ 8.58 (br s, 1H), 6.96 (m, 1H), 6.83 (m, 2H), 4.52 (s, 2H), 3.40 (m, 1H), 3.17 (m, 2H), 2.83 (m, 2H), 2.15 (m, 3H), 2.09 (m, 2H) and 1.49 (m, 2H). MS: 264.14 (M+H)⁺. Yield: 50%

[0546] **1-(2,4-Difluorophenyl)-1,3,8-triazaspiro[4.5]dec-2-en-4-one (24.31-d):** ¹H-NMR (400 MHz, DMSO-d₆): δ 8.66 (br s, 1H), 7.47 (m, 1H), 7.27 (m, 1H), 7.08 (m, 1H), 4.51 (s, 2H), 3.12 (m, 1H), 2.81 (m, 2H), 1.83 (m, 4H) and 1.40 (m, 2H). LCMS: 268.12 (M+H)⁺, 92.83%. Yield: 90%

Scheme 25:

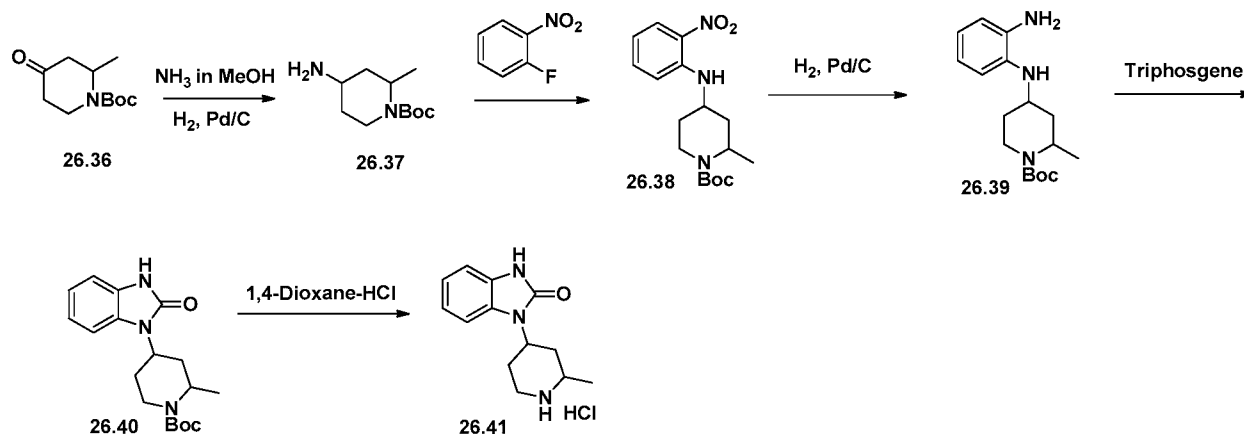


[0547] Preparation of 3-chloroindolin-2-one (25.33): To an ice-cold solution of nitrostyrene 25.32 (5.0 g, 335.55 mmol) in DCM was added acetyl chloride (5.0 mL, 67.11 mmol) and FeCl₃ (13.0 g, 67.11 mmol). The resulting reaction mass was stirred at 0°C for 5 h. After completion of reaction (TLC monitoring), added 0.1M HCl (100 mL) and stirred at RT for 16 h. The resulting reaction mixture was extracted with DCM (3 x 100 mL). The combined organics was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified over silica gel (100-200 M, 25% EtOAc/hexane) to get the desired product 25.33 (2.4 g, 43%) as off-white solid. ¹H-NMR (400 MHz, DMSO-d₆): δ 10.76 (br s, 1H), 7.35 (d, J= 7.6 Hz, 1H), 7.27 (t, J= 7.6 Hz, 1H), 7.03 (t, J= 7.2 Hz, 1H), 6.86 (d, J= 7.6 Hz, 1H) and 5.57 (s, 1H). LCMS: 166.07 (M-H)⁺, 99.70%.

[0548] Preparation of 3-(4-benzylpiperazin-1-yl) indolin-2-one (25.34): To a solution of 3-chloroindolin-2-one 25.33 (1.0 g, 5.97 mmol) in ACN (10 mL) was added potassium carbonate (1.23 g, 8.96 mmol) and 1-benzylpiperazine (1.16 g, 6.57 mmol). The resulting reaction mixture was heated at 80°C for 16 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was purified over silica gel (100-200 M, 40% EtOAc-hexane) to get the desired product 25.34 (0.62 g, 31%). ¹H-NMR (400 MHz, DMSO-d₆): δ 7.84 (br s, 1H), 7.36 (d, J= 7.6 Hz, 1H), 7.20 (m, 6H), 7.01 (t, J= 7.6 Hz, 1H), 6.80 (d, J= 7.6 Hz, 1H), 4.29 (s, 1H), 3.51 (s, 2H), 2.88 (m, 2H), 2.65 (m, 2H) and 2.49 (m, 4H). MS: 308.21 (M+H)⁺.

[0549] Preparation of 3-(piperazin-1-yl) indolin-2-one (25.35): To a solution of 3-(4-benzylpiperazin-1-yl) indolin-2-one 25.34 (0.30 g, 0.98 mmol) in MeOH and AcOH (40:1, 10 mL) was added Pd-C (w/w, 10 mol %) and the resulting solution was stirred under hydrogen atmosphere (1 atm) at ambient temperature for 16 h. The reaction mixture was filtered through celite bed and the filtrate was concentrated under reduced pressure to get the desired product 25.35 (0.16 g, 76%) as off-white solid. ¹H-NMR (400 MHz, DMSO-d₆): δ 10.32 (br s, 1H), 7.23 (d, J= 7.2 Hz, 1H), 7.17 (m, 1H), 6.93 (t, J= 6.8 Hz, 1H), 6.71 (d, J= 8.0 Hz, 1H), 4.25 (s, 1H), 2.53 (m, 1H), 2.50 (m, 4H), 2.38 (m, 2H) and 1.87 (m, 2H). MS: 218.16 (M+H)⁺.

Scheme 26:

**[0550] Preparation of tert-butyl 4-amino-2-methylpiperidine-1-carboxylate (26.37):**

- 5 To a solution of tert-butyl 2-methyl-4-oxopiperidine-1-carboxylate 26.36 (2.0 g, 9.38 mmol) in methanolic ammonia (~4N, 200 mL) was added Pd/C (10 mol%, 0.2 g). The resulting reaction mixture was stirred at 50 PSI for 60 h under hydrogen atmosphere. After completion of the reaction (TLC monitoring), the reaction mass was filtered through celite bed. The filtrate was dried under reduced pressure to get desired product 26.37 (2.0 g, quantitative yield) as semi solid. MS: 215.17 (M+H)⁺.
- 10

[0551] Preparation of tert-butyl 2-methyl-4-((2-nitrophenyl)amino)piperidine-1-carboxylate (26.38):

- To an ice-cold solution of tert-butyl 4-amino-2-methylpiperidine-1-carboxylate 26.37 (1.7 g, 7.93 mmol) in DMF (10 mL) was added DIPEA (2.0 mL, 11.89 mmol) and 1-fluoro-2-nitrobenzene (1.2 g, 7.93 mmol). The resulting reaction mixture was heated at 80°C for 16 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was purified over silica gel (100-200 M, 10% EtOAc-hexane) to get the desired product 26.38 (1.3 g, 50%). ¹H-NMR (400 MHz, CDCl₃): δ 8.38 (m, 1H), 8.18 (d, J= 8.8 Hz, 1H), 7.42 (t, J= 7.2 Hz, 1H), 6.82 (d, J= 8.8 Hz, 1H), 6.40 (t, J= 7.6 Hz, 1H), 4.30 (m, 1H), 3.90 (m, 1H), 3.21 (m, 2H), 1.95 (m, 2H), 1.77 (m, 2H), 1.47 (s, 9H) and 1.30 (d, J= 6.8 Hz, 3H). LCMS: 334.21 (M-H)⁺, 89.85%.
- 15
- 20

[0552] Preparation of tert-butyl 4-((2-aminophenyl)amino)-2-methylpiperidine-1-carboxylate (26.39):

- 25 To a solution of tert-butyl 2-methyl-4-((2-nitrophenyl)amino)piperidine-1-carboxylate 26.38 (1.30 g, 3.87 mmol) in MeOH (10 mL)

was added Pd-C (w/w, 10 mol %) and the resulting solution was stirred under hydrogen atmosphere (1 atm) at ambient temperature for 16 h. The reaction mixture was filtered through celite bed and the filtrate was concentrated under reduced pressure to get the desired product 26.39 (1.15 g, quantitative) as off-white solid. MS: 306.20 (M+H)⁺.

- 5 **[0553] Preparation of tert-butyl 2-methyl-4-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-1-carboxylate (26.40):** To an ice-cold solution of tert-butyl 4-((2-aminophenyl)amino)-2-methylpiperidine-1-carboxylate 26.39 (0.50 g, 1.64 mmol) in THF (20 mL) was added Et₃N (0.34 mL, 2.46 mmol) and triphosgene (0.59 g, 1.96 mmol). The resulting reaction mixture was heated at RT for 4 h. After completion of the reaction (TLC monitoring), the solvent was evaporated and the residue was diluted with water and extracted with ethyl acetate (3 times). The combined organics was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude was purified over silica gel (100-200 M, 40% EtOAc-hexane) to get the desired product 26.40 (0.5 g, 90%). ¹H-NMR (400 MHz, DMSO-d₆): δ 10.86 (br s, 1H), 7.23 (m, 1H), 6.97 (m, 3H), 4.34 (m, 1H), 3.64 (m, 2H), 2.27 (m, 1H), 1.94 (m, 2H), 1.72 (m, 2H), 1.43 (s, 9H) and 1.35 (m, 3H). MS: 330.22 (M-H)⁺.
- 10
- 15

- [0554] Preparation of 1-(2-methylpiperidin-4-yl)-1,3-dihydro-2H-benzo[d]imidazol-2-one hydrochloride salt (26.41):** An ice-cold solution of tert-butyl 2-methyl-4-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)piperidine-1-carboxylate 26.40 (0.25 g, 0.75 mmol) in 1,4-dioxane-HCl (~4N, 10 mL) was stirred at RT for 2h. After completion of the reaction (TLC monitoring), the reaction mass was dried under reduced pressure to get desired product 26.41 (0.2 g, quantitative) as off-white solid. MS: 232.12 (M+H)⁺.
- 20

Example 2. Biological Activity of Compounds of the Invention.

- [0555]** Since TRPA1 functions as a ligand-gated ion channel which is a relatively non-selective cation channel that is calcium permeable, a cell-based functional assay that measured increases in intracellular calcium ([Ca²⁺]_i) upon activation with agonist ligands was employed to test unknown compounds. A stable HEK293 cell line that expresses human TRPA1 in an inducible manner was employed in this assay. These HEK293 cells were grown in Dulbecco's minimal essential medium containing 4.5 mg/ml glucose supplemented with 10% heat-inactivated fetal bovine serum, 50 units/ml of penicillin, 50 µg/ml of streptomycin, supplemented with 5 µg/ml blasticidin and 50 µg/ml hygromycin B at 37°C in 95% air 5% CO₂. The expression of TRPA1 was induced by including 1 µg/ml doxycycline in the culture medium. For the induced cells, ruthenium red (5 µM) was also added to
- 25
- 30

minimize the constitutive TRPA1 channel activity and cells were used 14–18 hrs after induction. To measure $[Ca^{2+}]_i$ changes, cells were seeded in wells of 96-well plates at ~100,000 cells/well and grown for 14–18 hrs to reach confluency. To prevent cell loss from subsequent washing, the wells were treated with 20 μ g/ml polyornithine (MW >30,000, Sigma, St Louis, MO) for >15 min and rinsed once with Hank's balanced salt solution without Mg^{2+} and Ca^{2+} . To load the Ca^{2+} indicator dye, cells were washed once with an extracellular solution (ECS) containing 140 mM NaCl, 5 mM KCl, 1mM $MgCl_2$, 1.8 mM $CaCl_2$, 10 mM glucose, and 15 mM HEPES, pH 7.4 and then incubated in 50 μ L ECS supplemented with 2 μ M Fluo4-AM and 0.05% Pluronic F-127 at 37°C for 60 min. In some experiments, Fluo-8-AM was used instead of Fluo-4-AM as the calcium-sensitive fluorescent probe. Probenecid (2 mM) was included in all solutions to prevent the leakage of Fluo-4 or Fluo-8 from the cells. At the end of the incubation, cells were washed three times with ECS and placed in 80 μ L of the same solution. Fluorescence changes were measured using a fluid handling integrated fluorescence plate reader, FlexStation (Molecular Devices, Sunnyvale, CA). Stock solutions of test compounds were initially solubilized in 100% DMSO and then serially diluted to achieve the desired final concentration. The final concentration of DMSO in the assay did not exceed 0.3% (v/v). Drugs were diluted into ECS at 2x or 3 x the desired final concentrations and delivered to the sample plate by an integrated robotic 8-channel pipettor at preprogrammed time points. The Fluo-4 or Fluo-8 fluorescence was read using the excitation wavelength of 494 nm and emission wavelength of 525 nm from the bottom of the plate at 0.67 Hz. Experiments were performed at 20–25°C. For certain experiments, 0.1% BSA was included with the cells and test compounds.

[0556] The kinetic data obtained at each test concentration of drug represents a series of fluorescent intensities as a function of time. Data were transferred from the Softmax Pro software to construct concentration-response curves for each active compound and curve fitting using the logistic equation (Prism, Graphpad, San Diego, CA) was used to obtain inhibition constants for antagonists (IC_{50} s) or activation constants for agonist ligands (EC_{50} s).

[0557] Using a sequential addition protocol, test compounds were initially applied to the cells loaded with Fluo-4 or Fluo-8 and fluorescence changes in each well monitored for 2.5 min. The plate was read again after a 15-30 min incubation with the test compounds after challenge with a reference TRPA1 agonist. Reference TRPA1 agonists in testing each compound included at least one of flufenamic acid (FFA), allyl isothiocyanate (AITC) and 4-hydroxynonenal (4-HNE). Compounds that demonstrated antagonist activity showed a

concentration dependent reduction in initial rate and/or reduction in the magnitude of activity stimulated by the reference agonist.

[0558] Antagonist activity can be expressed in terms of IC_{50} with respect to TRPA1 and agonist activity can be expressed in terms of EC_{50} with respect to TRPA1. Results for the

5 TRPA1 modulatory activity of the disclosed compounds are found below in Table 7; the IC_{50} values shown in Table 7 were determined from data collected during the time period initiated by addition of the reference TRPA1 agonist to the mixture containing TRPA1 and the test compound. For each compound, the activity is classified as A, B or C wherein A is an IC_{50} of 0.05-5 μM ; B is an IC_{50} of 5-25 μM ; and C is an IC_{50} of >25 μM . One of skill in the art will

10 appreciate that other analytical techniques (*e.g.*, patch clamp experiments as described below) can be used to characterize compound activity, and that the IC_{50} or the EC_{50} value observed for a particular compound can vary depending on the technique employed

Table 7. TRPA1 modulatory activity of compounds of the disclosure.

Cpd #	human TRPA1-HEK Activity
6	C
31	C
4	C
12	C
16	B
25	C
28	C
13	C
18	C
29	C
30	C
8	B
143	B
144	B
145	B
146	B
147	C
148	C
152	C
153	C
154	C
155	C
156	C
157	C
158	B
159	B

Cpd #	human TRPA1-HEK Activity
160	C
161	B
162	B
163	B
164	B
165	C
166	C
170	C
171	C
172	C
174	C
149	B
150	B
151	C
167	B
168	B
169	C
173	C
54	C
55	A
56	C
57	C
58	C
61	C
62	C
63	C
66	C
67	C
68	C
71	C
74	C
75	C
76	C
79	C
80	C
83	C
84	C
85	C
60	B
65	C
70	B
72	B
73	C
77	A
78	C
82	C

Cpd #	human TRPA1-HEK Activity
87	C
88	B
89	C
90	C
92	C
93	C
94	C
95	C
96	C
98	B
100	C
101	C
105	C
106	C
107	C
97	C
99	A
102	C
103	C
104	C
108	C
109	C
110	C
111	C
114	C
119	C
120	B
121	C
122	C
123	C
124	C
125	C
126	C
127	C
128	C
129	C
130	B
131	C
132	C
135	C
136	B
137	C
138	C
139	C
140	B
141	B

Cpd #	human TRPA1-HEK Activity
142	C
69	C
91	C
112	C
113	C
115	C
116	C
117	C
118	C
133	C
134	C
177	A
178	B
175	A
176	B
49	A
45	C
52	C
32	C
33	C
34	C
35	C
37	C
38	B
39	C
40	C
179	C
180	A
264	B
259	B
260	A
262	B
198	A
252	B
253	A
256	C
267	B
268	A
266	A
263	C
181	A
254	A
255	A
258	C
261	A
257	C

Cpd #	human TRPA1-HEK Activity
265	A
182	A
199	A
212	A
213	A
218	A
219	A
220	A
189	A
185	B
202	A
217	A
184	C
201	A
214	A
215	A
183	C
186	A
187	A
200	A
190	A
188	A
191	A
192	A
193	A
205	A
216	A
196	A
206	B
210	A
211	A
194	B
195	A
204	A
221	A
197	B
209	C
203	C
208	A
222	A
223	A
224	A
207	C
75-b	A
75-a	A
225	A

Cpd #	human TRPA1-HEK Activity
226	A
227	A
228	A
229	A
230	A
231	A
232	A
233	A
234	A
235	A
236	A
237	A
238	A
239	A
240	A
241	A
242	A
243	C
244	B
245	C
246	A
247	C
248	A
249	A
250	C

Example 3. Electrophysiological Testing of Compounds of the Invention.

[0559] Whole-cell patch clamp experiments permit the detection of currents through the TRPA1 channel in the cell line described above. A glass electrode is brought into contact with a single cell and the membrane is then ruptured, permitting control of the voltage of the cell membrane and measurement of currents flowing across the membrane using an amplifier attached to the electrode. A perfusion system permits control of the extracellular solution, including the rapid addition of TRPA1 agonists and antagonists that either induce or inhibit the current, respectively. The TRPA1 specific current is activated by application of a known agonist, selected from a group which consists of flufenamic acid, allyl isothiocyanate (AITC), or 15-deoxy-PGJ2 prostaglandin at the appropriate concentration to the solution. To determine the activity of compounds of the present invention, a compound is added before the addition of an agonist to determine the effects of pre-incubation on TRPA1 activity or

alternatively the compound is added simultaneously with the agonist to determine the effects of simultaneous addition on TRPA1 activity.

[0560] HEK293 cells expressing human TRPA1 are seeded on polyornithine-treated glass coverslips one day before patching. Recording pipettes are pulled from micropipette glass (World Precision Instruments Inc, Sarasota, FL) to 2–4 M Ω when filled with a pipette solution containing (in mM): 117 CsCl, 9 EGTA, 1.8 MgCl₂, 14 Tris-creatine phosphate, 4 Mg-ATP, 0.3 Tris-GTP, 9 HEPES, pH 7.4 and placed in the bath solution containing (in mM): 150 NaCl, 4 KCl, 2 CaCl₂, 2 MgCl₂, 10 glucose, 10 HEPES, pH 7.4. Isolated cells are voltage-clamped in the whole-cell mode using an EPC10 amplifier with data collected at a sampling rate of 5 kHz using an analog-to-digital converter under the control of PatchMaster (HEKA Instruments). Voltage ramps of 100 ms of –100 mV to +100 mV from the holding potential of –60 mV are applied every 0.5 s. The patched cell is continuously superfused by the bath solution through an 8-channel SmartSquirt perfusion system (AutoMate Scientific, Inc., Berkeley, CA, USA). Compounds are diluted in the final concentration and applied for 10–40 sec as desired. For either kinetic or concentration-response studies, the application of reference agonist is 10 sec and the maximal current densities at –100 and +100 mV are used for calculations. All recordings are performed at room temperature (~23°C).

Example 4. Compound Activity in Freund's Complete Adjuvant Hyperalgesia Model

[0561] The efficacy of compounds of the disclosure in reducing or alleviating inflammatory pain is tested using an established animal model for testing potential analgesic activity of compounds that is widely known as the Freund's Complete Adjuvant (CFA) model of hyperalgesia. The CFA model is a well-established acute inflammatory pain model widely used by the pharmaceutical industry to evaluate the analgesic activity of compounds including TRPA1 antagonists (Eid, SR, *et al.* (2008) "HC-030031, a TRPA1 selective antagonist attenuates inflammatory- and neuropathy-induced mechanical hypersensitivity." *Mol Pain* 4:48-58.)

[0562] Testing employs the Randell-Selitto test or paw pressure test which is a technique for the measurement of the pain response in animals. For this inflammatory pain model, rats are injected with 200 μ l of Complete Freund's Adjuvant (CFA), 1:1 in saline intraplantarly into their left paw (Colpaert, 1987). Animals are tested for hyperalgesia 3 days after CFA administration, using withdrawal threshold to paw pressure (Randal-Selitto test). To investigate whether the anti-hyperalgesic effect of the test compound are observed upon

repeated dosing, the compound is administered for 3 days at a range of doses which include 0.3, 1, 3, 10 and 30 mg/kg by either oral or i.p. administration each day. Reversal of mechanical hyperalgesia is assessed at the time corresponding to the peak plasma levels of each drug (determined in separate pharmacokinetic experiments) after oral or i.p. dosing for the test compound (1-7 hrs) post-dose on day 1, 2 and 3. Either naproxen, indomethacin, and diclofenac (3-30 mg/kg PO) can be included as a positive control test agent. Compounds of the disclosure which have efficacy in this model diminish pain responses compared to responses in the absence of the compound.

Example 5. Compound Activity in Spinal Nerve Ligation Neuropathic Pain Model

[0563] This example describes the use of an animal model for testing compounds of the disclosure for their ability to reduce neuropathic pain. For the neuropathic pain model (spinal nerve ligation, SNL) also known as the Chung model, rats are anesthetized with isoflurane and placed on a heating pad. Using aseptic techniques, the L5 and L6 spinal nerves are exposed, ligated and transected (Kim, S.H. and Chung, J.M, (1992), *Pain*, 50 (3): 355-363).

Muscle and skin are closed with 4-0 Polydioxone and wound clips, respectively. Allodynia is assessed 2-4 weeks post SNL surgery and only rats that develop allodynia as defined by a significant decrease in their mechanical threshold using von Frey filaments are used. Tactile allodynia is assessed with calibrated von Frey filaments (Stoelting Co, Wood Dale, IL), using an up-down paradigm (Chaplan, S.R., *et al.* (1994) *J. Neurosci. Methods*, 53 (1): 55-63).

Pregabalin (3-30 mg/kg PO) or gabapentin (50-100 mg/kg PO or 100-150 mg I.P) is included as a positive control.

[0564] Test compounds are administered to the surgically treated rats either orally or I.P, and pain measurements are assessed at post-dosing intervals that correspond to near-maximal peak plasma concentrations for the test compound and specific mode of administration.

[0565] The action of test compounds 175, 180, and 198 was evaluated in the Chung model after surgery to induce neuropathy. Test compounds were administered to the surgically treated rats 18 days after L5-L6 spinal nerve injury at 30mg/kg i.p (10ml/kg). Gabapentin at 150mg/kg i.p. (10ml/kg) was administered as a positive control group. Vehicle and test compounds were dissolved in 10% DMSO, 20% Tween-80 and 40% PEG-400. On the day before treatment, the neuropathic pain basal response was measured by von Frey test and the rats were randomized based on PWT responses. A cut-off of <4.0g was considered before selection of animals for treatment. On the day of treatment, the test compounds were

administered at 30mg/kg i.p. (10ml/kg) dissolved in 10% DMSO, 20% Tween-80, 40% PEG-400. Additional test groups included vehicle control and gabapentin at 150mg/kg i.p. (10ml/kg). The mechanical allodynia was measured at 2 hrs post-dose. Results for compound 175 are shown in FIGS. 1 and 2 where data are presented as paw withdrawal threshold (PWT in g) (FIG. 1) and percentage of maximal possible effect (%MPE) (FIG. 2). Each bar represents the mean $\pm$ SEM of 8 rats. The test compounds demonstrated significant anti-allodynic effect on paw withdrawal threshold and %MPE ($p < 0.001$). Statistical analysis was completed using one-way ANOVA followed by Dunnett's post-test. %MPE values exhibited by the test compounds are set forth in Table 8.

Table 8. Efficacy of Algomedix Compounds in the Spinal Nerve Ligation Model of Neuropathic Pain

Compound No.	Dose	% MPE
175	30 mg/kg, i.p.	59 $\pm$ 10 (3)
180	30 mg/kg, i.p.	65 (1)
198	30 mg/kg, i.p.	41 (1)

%MPE = % Maximum Possible Effect
() number of experiments

[0566] The test compounds inhibited allodynia and hyperalgesia while the vehicle administered group did not show any improvement. Statistical analysis showed the differences between the vehicle and test compound group to be highly significant. From these results, the test compounds showed a high level of effectiveness (41-65% of maximal possible effect) for reducing neuropathic pain.

Example 6. Compound Activity in Incisional Pain Model

[0567] The effects of compounds of the disclosure on post-surgical pain are assessed using an incisional pain model, as described previously by Brennan et al. (1996). In the incisional pain model, Sprague-Dawley rats (weighing 200-300g) undergo surgery by having a 1 cm longitudinal incision made through skin and fascia of the plantar aspect of the paw. Unoperated rats serve as controls. Hind paw withdrawal thresholds (PWTs) to a noxious mechanical stimulus are determined using an analgesimeter. Withdrawal responses to punctuate mechanical stimulation are determined by using calibrated von Frey filaments. Cut-off is set at 250g and the endpoint is taken as complete paw withdrawal. Twenty-four hours following plantar incision, predrug PWTs are measured, and the rats (9-20/group) receive a single dose of 3, 10 or 30 mg/kg p.o. or i.p. the test compound, 30 mg/kg p.o. celecoxib as a

positive control, or vehicle. PWTs are determined again at multiple intervals (eg. at 1, 3, 5 and 24 hours) postdrug administration. The percent reversal of hyperalgesia for each animal is calculated by $(\text{Postdose threshold} - \text{predose threshold}) / (\text{Baseline threshold} - \text{predose threshold}) \times 100$.

5 **Example 7. Compound Activity in Iodoacetate Osteoarthritic Pain Model**

[0568] An established animal model of osteoarthritis related pain has been termed the iodoacetate model since it is based upon the progressive joint destruction which occurs after injection of iodoacetate into the articular space of the knee of the rat (Marker and Pomonis, 2012). Pain related behaviors that can be measured include both hind limb weight bearing
10 and primary mechanical hyperalgesia. In the rat model of osteoarthritis, iodoacetate (IOA, 2 mg/25 μL per rat in pH 7.4 saline) is administered under brief isoflurane anesthesia into the rat left knee joint and hypersensitivity to von Frey filaments and changes in weight bearing is assessed 6 weeks post-IOA administration. Rats receive a single dose of 1, 3, 10 or 30 mg/kg p.o. or i.p. of the test compound administered prior to testing at an interval determined by the
15 time required to reach peak plasma levels for the individual test agent. Percent reversal of hypersensitivity is calculated as: $(\text{post-drug} - \text{post-IOA injection}) / (\text{pre-IOA injection} - \text{post-IOA injection}) \times 100$, where 100% is equivalent to complete reversibility.

Example 8. Compound Activity in Formalin Nociceptive Pain Model

[0569] The formalin model is widely used for evaluating the effects of analgesic
20 compounds in laboratory animals. It is a useful model for nociceptive pain. In this test, a dilute (0.5–5%) formalin solution (in which formaldehyde is the active ingredient) is injected into the paw of a rodent, and pain-related behaviors are assessed over two temporally distinct phases, including an initial robust phase in which paw lifting, licking, and flinching are scored during the first 10 min, followed by a transient decline in these behaviors and a
25 subsequent second phase of behavior lasting 30–60 min.

[0570] For the formalin-induced model, mice or rats are administered with formalin and/or one of the disclosed compounds. Test compounds are either injected intradermally, delivered orally or by i.p. administration 30–120 min prior to formalin injection. Formalin is then injected (50 μL of 2.5% formalin, diluted in saline) into the dorsal surface of the right hind
30 paw of the rat, and the animal is put into a chamber of an apparatus where movement of the formalin-injected paw is recorded. The number of paw flinches or paw licking and biting is

tallied by minute over the next 60 min. In some analyses of collected data, the 60 minute observation period is subdivided into various phases.

Example 9. Compound Activity in Chronic Constriction Injury Neuropathic Pain

Model

5 [0571] The rat chronic constriction injury (CCI) model of neuropathic pain developed by Bennett and Xie (1988) is a neuropathic pain model widely used to assess analgesic activity of test compounds. Subsequent to ligation of the sciatic nerve, eventual damage of peripheral nerves occurs in part due to production of several inflammatory mediators (*e.g.*, proinflammatory cytokines and chemokines) which contribute to generation and maintenance
10 of neuropathic pain.

[0572] The surgery protocol used for generating CCI rats is described by Bennett and Xie (Bennett, GJ, Xie, YK (1988) *Pain* 33(1): 87-107.). In brief, male Sprague-Dawley rats (175-250g) are anesthetized, the middle third of the right sciatic nerve is exposed through a 1.5 cm longitudinal incision and three ligatures (5-0 chromic Catgut) are tied loosely around the
15 sciatic nerve proximal to the sciatic trifurcation. Incisions are then sutured and closed, rats are administered antibiotic and general health is evaluated daily during the recovery. Two weeks post-nerve ligation, basal mechanical allodynia is measured as described for the rat Chung model and CCI rats using paw withdrawal thresholds (PWT) < 4 g to qualify rats for inclusion in the study (Kim, SH, Chung, JM (1992). *Pain* 50(3): 355-363; Chaplin, SR, *et al.*
20 (1994) *J Neurosci Methods* 53(1): 55-63).

[0573] On the following day, compounds of the invention are solubilized in a pre-validated vehicle and administered at doses of 1, 3, 10 and 30 mg/kg (oral or i.p.) and PWTs are measured during a period corresponding to peak plasma levels of the compound. Each experimental group consists of 8 rats. Gabapentin is used as a positive control group and the
25 experimenter recording behavior is blinded to the treatment groups. The 50% PWT and % maximal possible effect data are analyzed using one-way ANOVA followed by the Dunnett post-test using Prism (Graphpad).

Example 10. Compound Activity in Streptozotocin Diabetic Neuropathic Pain Model

[0574] Diabetes related damage to sensory nerves (diabetic neuropathy) is a common
30 complication of Type 1 and Type 2 diabetes and people with this neuropathy suffer from chronic pain. The injection of streptozotocin (STZ) into rats is a commonly used chemical

method to induce a diabetic condition leading to diabetic neuropathic pain. The STZ neuropathic pain model is commonly used to evaluate the efficacy of anaglesic compounds, including TRPA1 antagonists (Courteix, C, *et al.* (1994) *Pain* 57(2): 153-160; Wei, H, *et al.* (2009) *Anesthesiology* 111: 147-154.) After STZ administration, hyperglycemia and

hypoinsulinemia appear and persist due to irreversible toxicity.

[0575] The efficacy of compounds of the invention for inhibiting or reducing diabetic neuropathic pain and reducing pain hypersensitivity are determined in this model using the following established procedure. In brief, male Sprague-Dawley rats (175-200) grams are administered STZ (45 mg/kg i.v. in 0.1M citrate buffer) into the dorsal tail vein and,

hyperglycemia is confirmed by measuring glucose levels 3, 10 and 17 days after STZ administration. Mechanical allodynia generally appears three weeks post injection of STZ and lasts for approximately seven weeks. On day 17 after STZ administration, basal mechanical allodynia is measured as described for the rat SNL model and rats displaying 50% PWT values of <5 g qualify for the investigation. The next day, compounds of the invention are solubilized in pre-validated vehicle and administered at doses of 1, 3, 10 and 30 mg/kg (oral or i.p.) to qualified rats. Mechanical allodynia is measured as described for the Chung model at time corresponding to the period when peak plasma levels for the study compound are observed. Each experimental group will include eight rats and tramadol (30 mg/kg, i.p.) will be used as a positive control. The 50% PWT and %MPE data are analyzed using one-way ANOVA and post-hoc Dunnett's test using the computer program, Prism (Graphpad).

Example 11. Compound Activity in Chemotherapy-Induced Neuropathic Pain Model

[0576] Chemotherapy-induced peripheral neuropathy is one of the most serious complications of anti-cancer drug therapy. For example, agents which include paclitaxel (Taxol) or oxaliplatin which are most effective and frequently used chemotherapeutics produce peripheral neurotoxicity with patients reporting neuropathic pain during and often persisting after chemotherapeutic treatment. The TRPA1 antagonist, AD_09, has been reported to reduce neuropathic pain in the oxaliplatin model (Nativi, C, *et al.* (2013) *Scientific Reports* 3, 2005, 1-10.)

[0577] The studies described below provide a method to test compounds of the present invention in the established rat model of paclitaxel-induced neuropathic pain (Flatters, SJ and Bennett, G, *Pain* (2004) 109:150-161). In this procedure, male Sprague-Dawley rats receive

i.p. injections of 1 mg/kg paclitaxel or vehicle solution every other day for a total of 4 injections (Day 0, 2, 4 and 6). After receiving injections on even-number experimental days, the rats are tested for mechanical and cold allodynia on odd-number experimental days.

After the full development of allodynia after the last paclitaxel injection (~day 10), one

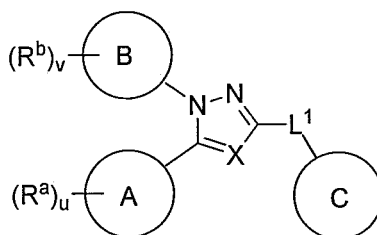
- 5 subgroup of the rats (12 rats per treatment group) receive an oral dose or i.p. injection of compound of the present invention (1, 3, 10 or 30 mg/kg) or its vehicle solution. Mechanical allodynia is measured using the von Frey assay to assess the effects of compounds to reduce pain. The rats are initially tested for mechanical and cold allodynia 1 hour after dosing and can be tested at 2 hour intervals thereafter (time interval dependent on the effect) as long as
- 10 the effect of TRPA1 antagonist lasts. In some cases, more than one treatment of the compound of the present invention (TRPA1 antagonist) is given before or after the effect of the previous dose subsides to provide repetitive dosing regimens.

- [0578] All publications and patent applications cited in this specification are herein incorporated by reference as if each individual publication or patent application were
- 15 specifically and individually indicated to be incorporated by reference.

- [0579] Although the foregoing has been described in some detail by way of illustration and example for purposes of clarity of understanding, it will be readily apparent to one of ordinary skill in the art in light of the disclosed teachings that certain changes and modifications may be made thereto without departing from the spirit or scope of the
- 20 disclosure.

WHAT IS CLAIMED IS:

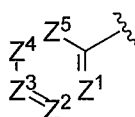
1. A compound of Formula I:



or a pharmaceutically acceptable salt thereof;

wherein:

A is a cyclic group of Formula Ia:



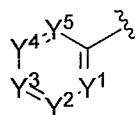
Ia

wherein Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are each a member selected from the group consisting of N, CH, and CR^a ; or, alternatively for Z^1 , the member Z^1 and X, together with atoms in the rings to which they are attached, form an additional fused, five- to eight-membered cycloalkyl or heterocyclyl ring with from 0 to 4 R^z substituents;

with the proviso that at least one member selected from the group consisting of Z^2 , Z^3 , and Z^4 is N;

each R^z is a member independently selected from the group consisting of halo, C_1 - C_3 alkyl, C_1 - C_3 haloalkyl, and C_1 - C_3 alkoxy; or, alternatively, two R^z substituents, together with the carbon atom to which they are attached, join to form an oxo, spirocycloalkyl, or spiroheterocyclyl group;

B is a cyclic group of Formula Ib:



Ib

wherein Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are each a member independently selected from the group consisting of N, CH, and CR^b ; or, alternatively, the members $-Y^2=Y^3-$ or $-Y^4=Y^5-$ are combined into a single member selected from the group consisting of NH, NR^c , O, and S;

each R^a and R^b is a member independently selected from the group consisting of cyano, carboxyl, C_1 - C_4 alkyl, C_1 - C_4 hydroxyalkyl, C_3 - C_8 cycloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, halo, C_0 - C_6 amino, C_1 - C_6 amido, C_1 - C_4 alkyloxycarbonyl, C_1 - C_6 alkylsulfonyl, and hydroxyl; or, alternatively, two adjacent R^a or R^b , together with the atoms in groups A or B to which they are attached, form an additional fused aryl, heteroaryl, cycloalkyl, or heterocyclyl ring with from 0 to 4 R^z substituents;

each R^c is a member independently selected from the group consisting of hydrogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_3 - C_6 cycloalkyl, $(C_3$ - C_6 cycloalkyl) C_1 - C_3 alkyl, and C_1 - C_7 acyl;

each u is an integer independently selected from 0 to 4;

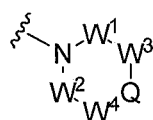
v is an integer from 0 to 5;

X is N or CR^d ; or, alternatively, X is CR^d , wherein X and the member Z^1 , together with atoms in the rings in which they are included, form the additional fused, five- to eight-membered cycloalkyl or heterocyclyl ring with from 0 to 4 R^z substituents;

each R^d is a member independently selected from the group consisting of hydrogen, halo, cyano, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkoxy, C_3 - C_6 cycloalkyl, and C_3 - C_6 cycloalkoxy;

each L^1 , L^2 , and L^3 , if present, is a member independently selected from the group consisting of $C=O$, $C=S$, $C=NH$, and $C=NR^e$;

C is a cyclic group of Formula Ic:



Ic

wherein Q is a member selected from the group consisting of $C(R^e)(D)$, $N(E)$, F , and G ; or, alternatively, the members $-W^3-Q-$ or $-W^4-Q-$ join to form a member H ; and

wherein W^1 , W^2 , W^3 , and W^4 are each an independently selected $C(R^f)_2$; or, alternatively, the members $-W^3-Q-$ or $-W^4-Q-$ join to form a member H ;

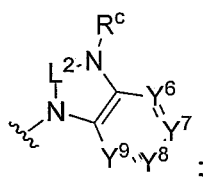
R^e is a member selected from the group consisting of hydrogen, C_1 - C_3 alkyl, and C_1 - C_3 fluoroalkyl; or, alternatively, R^e and an R^f substituent of W^1 , W^2 , W^3 , or

W^4 join to form a $-(C(R^Z)_2)_t-$ bridge or a $-(CH_2)_t-$ bridge, wherein t is an integer selected from 2 or 3;

each R^f is a member independently selected from the group consisting of hydrogen, C_1 - C_3 alkyl, C_1 - C_3 fluoroalkyl, and halo; or, alternatively, two adjacent R^f , together with the atoms in group C to which they are attached, form an additional aryl, heteroaryl, cycloalkyl, or heterocyclyl fused ring with from 0 to 4 R^Z substituents; or, alternatively, two geminal R^f , together with the atom in group C to which they are attached, form a spirocycloalkyl or spiroheterocyclyl ring with from 0 to 4 R^Z substituents; or, alternatively, two axial R^f substituents of a pair of W^n selected from the group consisting of (W^1 and W^2), (W^2 and W^3), and (W^3 and W^4) join to form a $-(C(R^Z)_2)_t-$ bridge or a $-(CH_2)_t-$; or, alternatively, R^e and an R^f substituent of W^1 , W^2 , W^3 , or W^4 join to form a $-(C(R^Z)_2)_t-$ bridge or a $-(CH_2)_t-$ bridge;

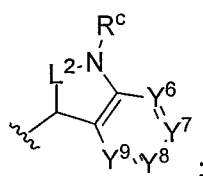
each t is an integer selected from 2 or 3;

D is a bicyclic group of Formula Id:



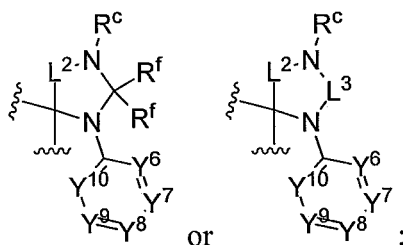
Id

E is a bicyclic group of Formula Ie:



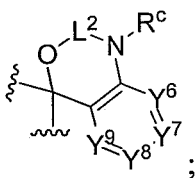
Ie

F is a spirocyclic group of Formula If:



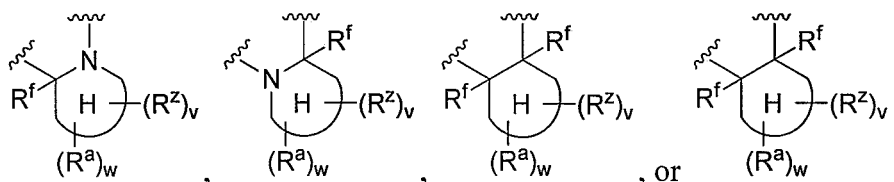
If

G is a bicyclic spirocyclic group of Formula Ig:



Ig

H is a fused group of Formula Ih:



Ih

wherein the H ring is a fused, five- to eight-membered cycloalkyl or heterocyclyl ring;

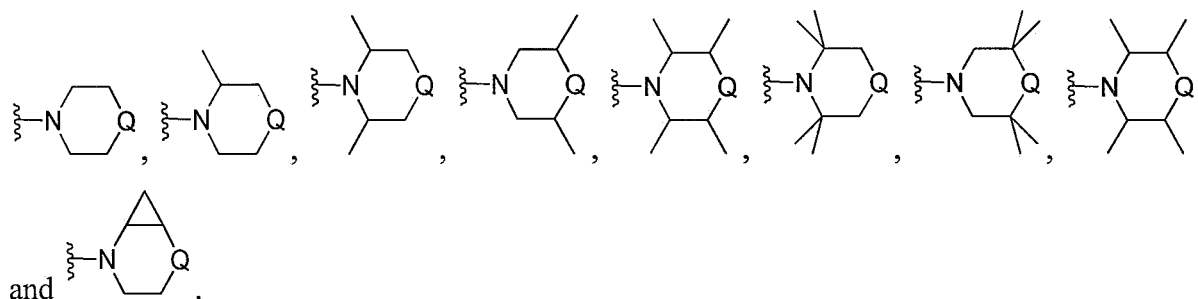
wherein v is an integer from 0 to 4; and

wherein w is an integer from 0 to 2; and

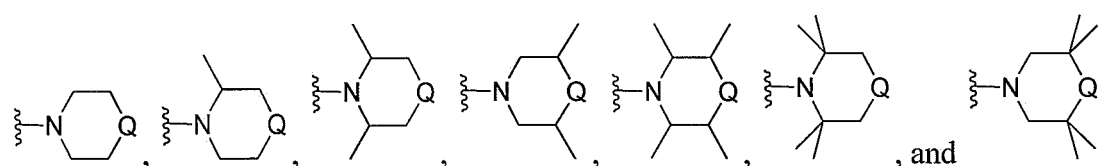
Y^6 , Y^7 , Y^8 , Y^9 , and Y^{10} , if present, are each a member independently selected from the group consisting of N, CH, and CR^b ; or, alternatively for Y^8 and Y^9 , the members $-Y^6=Y^7-$ or $-Y^8=Y^9-$ are combined into a single member selected from the group consisting of NR^c , O, and S.

2. The compound or salt of claim 2, wherein Q is $C(R^e)(D)$.
3. The compound or salt of claim 2, wherein Q is $N(E)$.
4. The compound or salt of claim 2, wherein Q is F.
5. The compound or salt of claim 2, wherein Q is G.
6. The compound or salt of claim 2, wherein the members $-W^3-Q-$ or $-W^4-Q-$ join to form a member H.
7. The compound or salt of any one of the preceding claims, wherein W^1 , W^2 , W^3 , and W^4 comprise from 1 to 4 independently selected R^f groups other than hydrogen.
8. The compound or salt of any one of the preceding claims, wherein W^1 , W^2 , W^3 , and W^4 comprise from 1 to 4 independently selected R^f alkyl groups.

9. The compound or salt of any one of the preceding claims, wherein C is a member selected from the group consisting of:

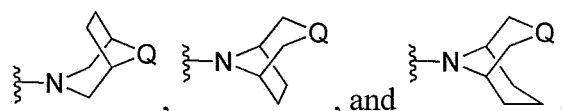


10. The compound or salt of any one of the preceding claims, wherein C is a member selected from the group consisting of:

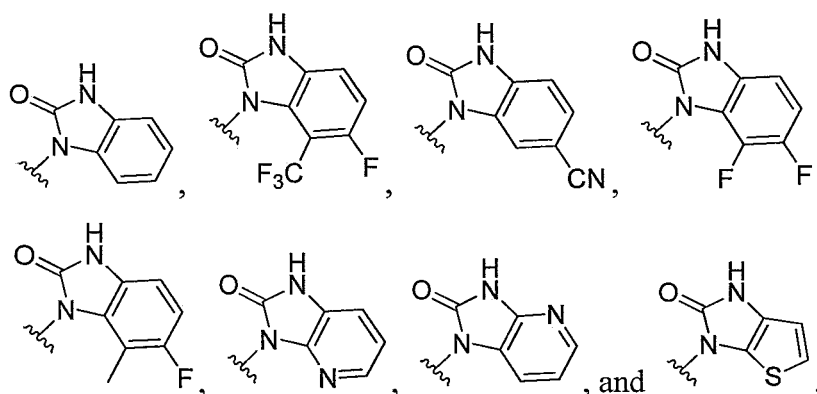


11. The compound or salt of any one of the preceding claims, wherein the pair of W^n is selected from the group consisting of (W^1 and W^2) and (W^3 and W^4).

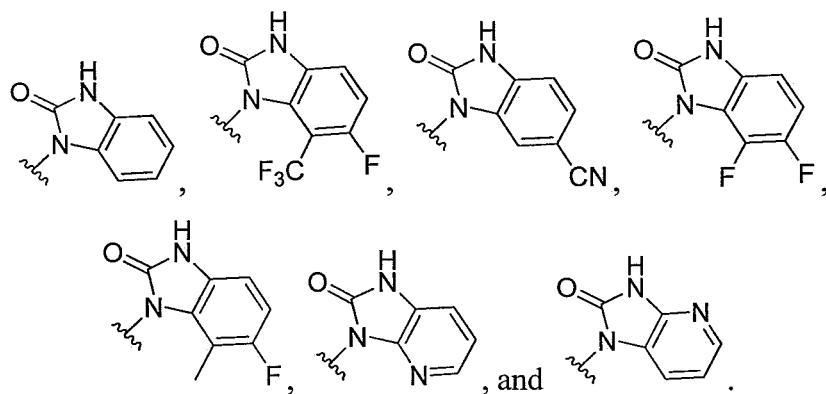
12. The compound or salt of claim 11, wherein C is a member selected from the group consisting of:



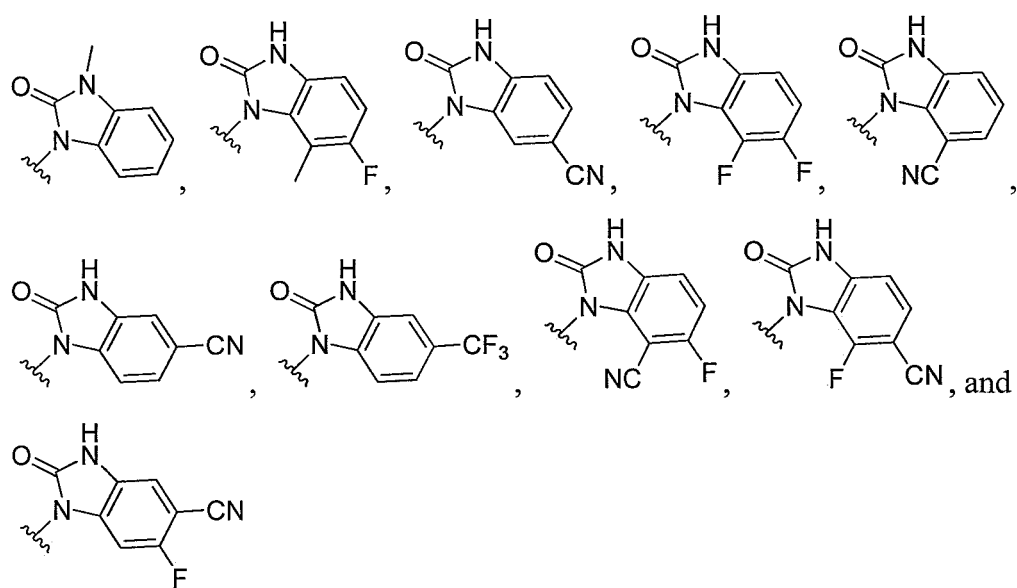
13. The compound or salt of any one of the preceding claims, wherein D is a member selected from the group consisting of:



14. The compound or salt of any one of the preceding claims, wherein D is a member selected from the group consisting of:



15. The compound or salt of any one of the preceding claims, wherein D is a member selected from the group consisting of:



16. The compound or salt of any one of the preceding claims, wherein L^2 is $C=O$.

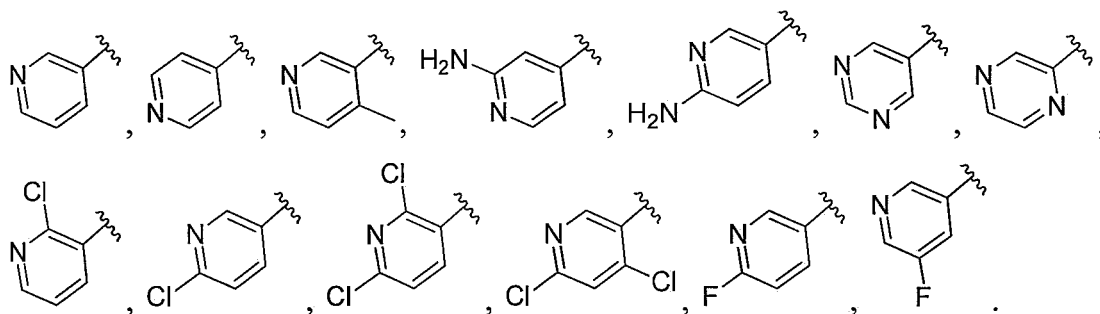
17. The compound or salt of any one of the preceding claims, wherein L^3 is $C=O$.

18. The compound or salt of any one of the preceding claims, wherein Z^1 , Z^2 , Z^3 , Z^4 , and Z^5 are each a member selected from the group consisting of N, CH, and CR^a .

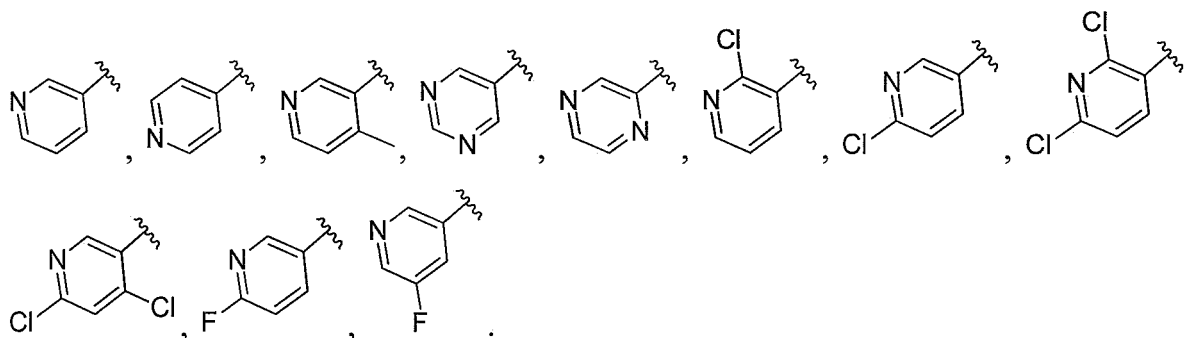
19. The compound or salt of any one of the preceding claims, wherein Z^1 and X, together with atoms in the rings to which they are attached, form an additional fused, five- to eight-membered cycloalkyl or heterocyclyl ring with from 0 to 4 R^z substituents.

20. The compound or salt of any one of the preceding claims, wherein Z^2 is N.

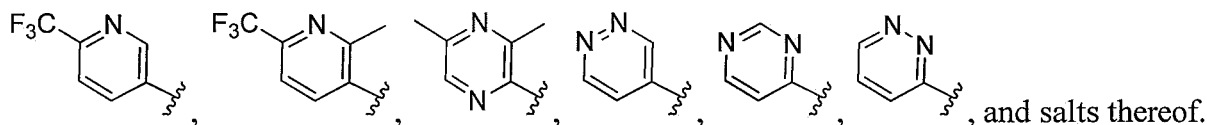
21. The compound or salt of any one of the preceding claims, wherein Z^3 is N.
22. The compound or salt of any one of the preceding claims, wherein Z^4 is N.
23. The compound or salt of any one of the preceding claims, wherein A is a member selected from the group consisting of:



24. The compound or salt of any one of the preceding claims, wherein A is a member selected from the group consisting of:



25. The compound or salt of any one of the preceding claims, wherein A is a member selected from the group consisting of:



26. The compound or salt of any one of the preceding claims, wherein Y^1 , Y^2 , Y^3 , Y^4 , and Y^5 are each a member independently selected from the group consisting of N, CH, and CR^b .
27. The compound or salt of any one of the preceding claims, wherein Y^1 is CR^b , and wherein the $Y^1 R^b$ is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, and trifluoromethoxy.
28. The compound or salt of any one of claims 1-26, wherein Y^1 is N.

29. The compound or salt of any one of the preceding claims, wherein Y^2 is CR^b , and R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, and trifluoromethoxy.

30. The compound or salt of any one of claims 1-28, wherein Y^2 is N.

31. The compound or salt of any one of the preceding claims, wherein Y^3 is CR^b , and R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, and trifluoromethoxy.

32. The compound or salt of any one of claims 1-30, wherein Y^3 is N.

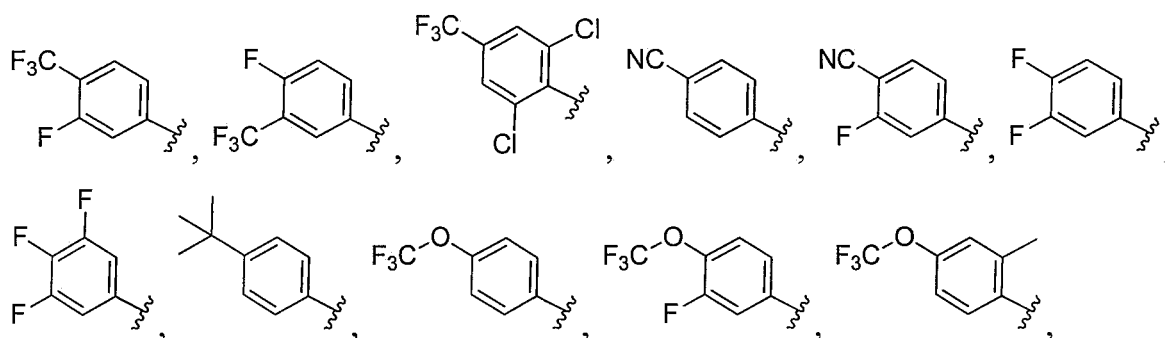
33. The compound or salt of any one of the preceding claims, wherein Y^4 is CR^b , and R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, and trifluoromethoxy.

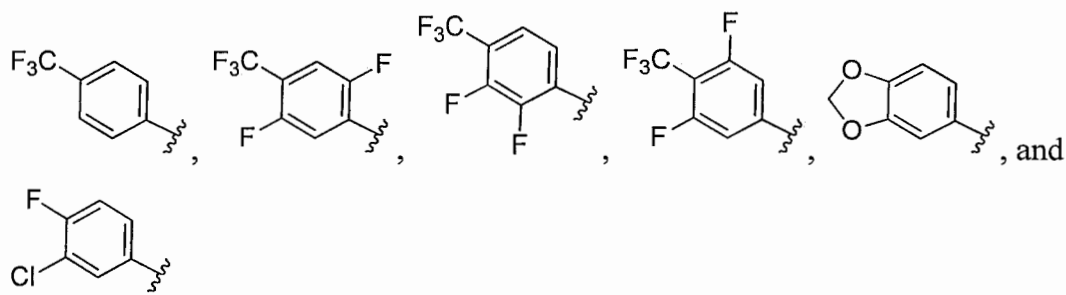
34. The compound or salt of any one of claims 1-32, wherein Y^4 is N.

35. The compound or salt of any one of the preceding claims, wherein Y^5 is CR^b , and R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, and trifluoromethoxy.

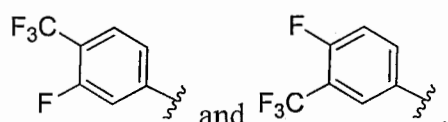
36. The compound or salt of any one of claims 1-34, wherein Y^5 is N.

37. The compound or salt of any one of the preceding claims, wherein B is a member selected from the group consisting of:

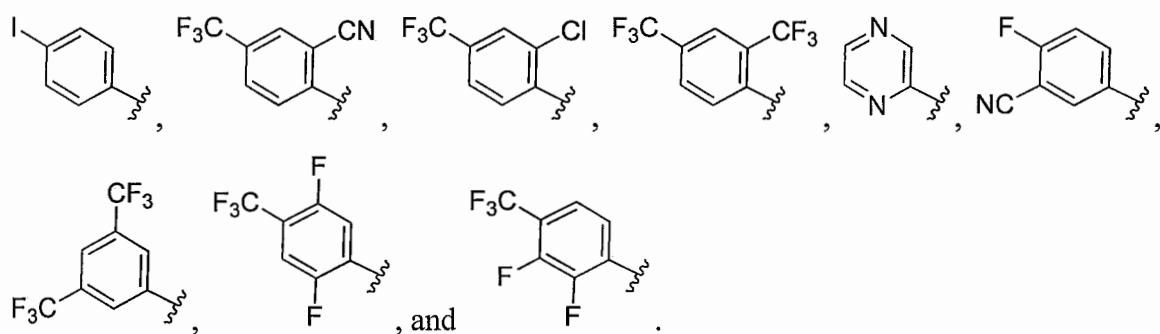




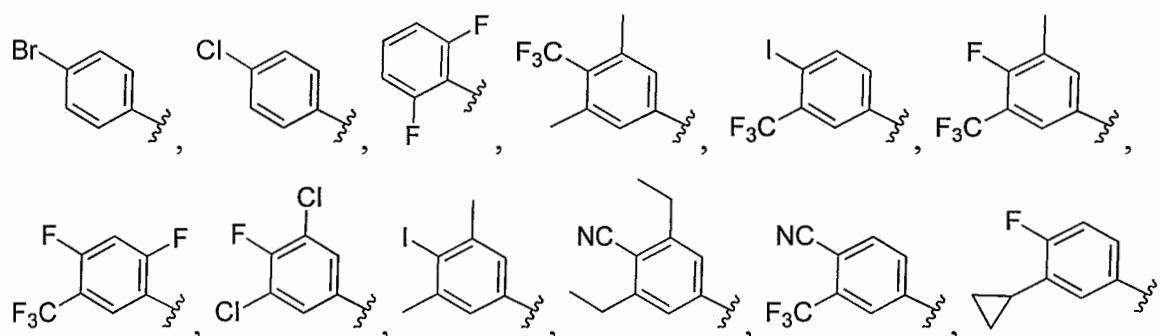
38. The compound or salt of any one of the preceding claims, wherein B is a member selected from the group consisting of:

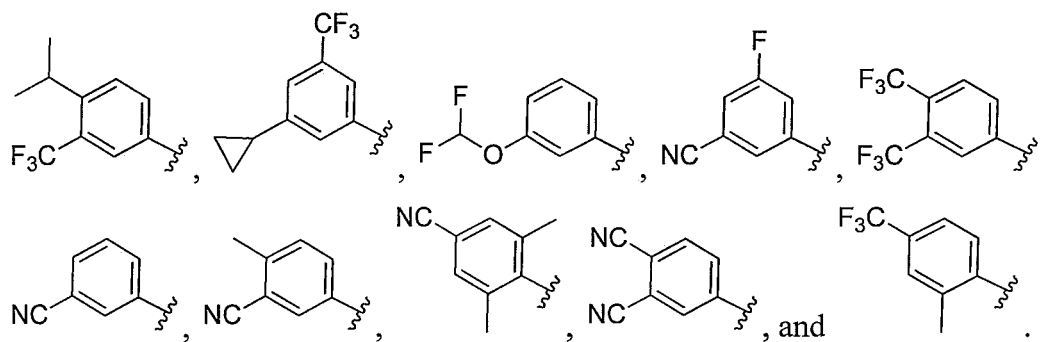


39. The compound or salt of any one of claims 1-35, wherein B is a member selected from the group consisting of:



40. The compound or salt of any one of claims 1-35, wherein B is a member selected from the group consisting of:





41. The compound or salt of any one of the preceding claims, wherein each R^a and R^b is a member independently selected from the group consisting of cyano, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, halo, C_0 - C_6 amino, C_1 - C_6 amido, and hydroxyl.
42. The compound or salt of any one of the preceding claims, wherein each R^a and R^b is a member independently selected from the group consisting of cyano, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, C_1 - C_4 haloalkyl, C_1 - C_4 haloalkoxy, and halo.
43. The compound or salt of any one of the preceding claims, wherein u is an integer independently selected from 0 to 3.
44. The compound or salt of any one of the preceding claims, wherein v is an integer independently selected from 0 to 3.
45. The compound or salt of any one of the preceding claims, wherein X is N.
46. The compound or salt of any one of the preceding claims, wherein each R^c is independently selected from the group consisting of hydrogen, cyano, C_1 - C_3 alkyl, trifluoromethyl, cycloalkyl, trifluoromethoxy, and C_1 - C_3 alkoxy.
47. The compound or salt of any one of the preceding claims, wherein each R^c is independently selected from the group consisting of hydrogen, cyano, C_1 - C_3 alkyl, trifluoromethyl, cyclopropyl, trifluoromethoxy, and C_1 - C_3 alkoxy.
48. The compound or salt of any one of the preceding claims, wherein each R^c is independently selected from the group consisting of hydrogen, methyl, bromo, chloro, trifluoromethyl, ethyl, isopropyl, isobutyl, cyclopropyl, cyclobutyl, and cyclopropylmethyl.
49. The compound or salt of any one of the preceding claims, wherein L^1 is $C=O$.

50. The compound or salt of any one of the preceding claims, wherein Y^6 , Y^7 , Y^8 , Y^9 , and Y^{10} , if present, are each a member selected from the group consisting of N, CH, and CR^b .

51. The compound or salt of any one of the preceding claims, wherein Y^6 is CR^b , and R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, trifluoromethoxy, $-C(O)N(H)Me$, $-NMe_2$, and $-SO_2Me$.

52. The compound or salt of any one of claims 1-50, wherein Y^6 is N.

53. The compound or salt of any one of the preceding claims, wherein Y^7 is CR^b , and R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, and trifluoromethoxy.

54. The compound or salt of any one of claims 1-52, wherein Y^7 is N.

55. The compound or salt of any one of the preceding claims, wherein Y^8 is CR^b , and R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, trifluoromethoxy, $-C(O)N(H)Me$, $-NMe_2$, and $-SO_2Me$.

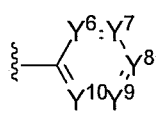
56. The compound or salt of any one of claims 1-54, wherein Y^8 is N.

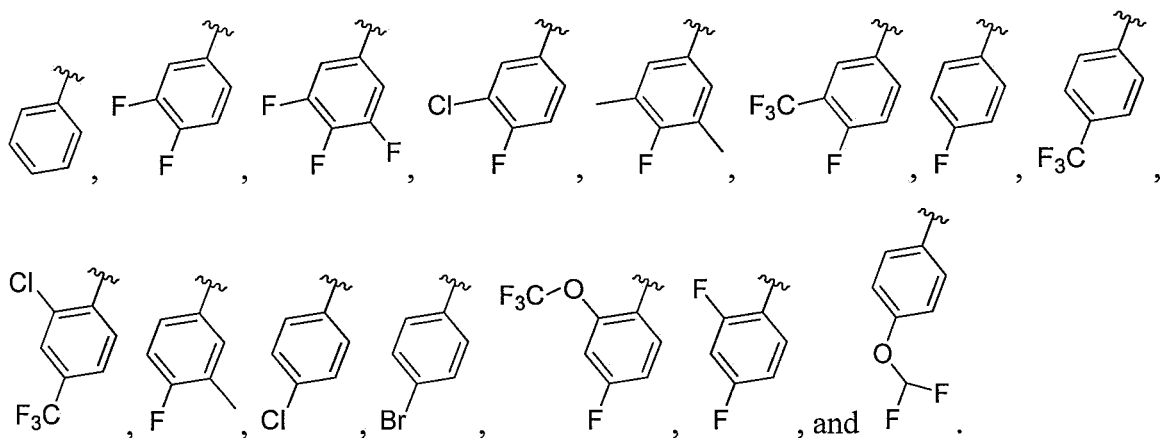
57. The compound or salt of any one of the preceding claims, wherein Y^9 is CR^b , and R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, and trifluoromethoxy.

58. The compound or salt of any one of claims 1-56, wherein Y^9 is N.

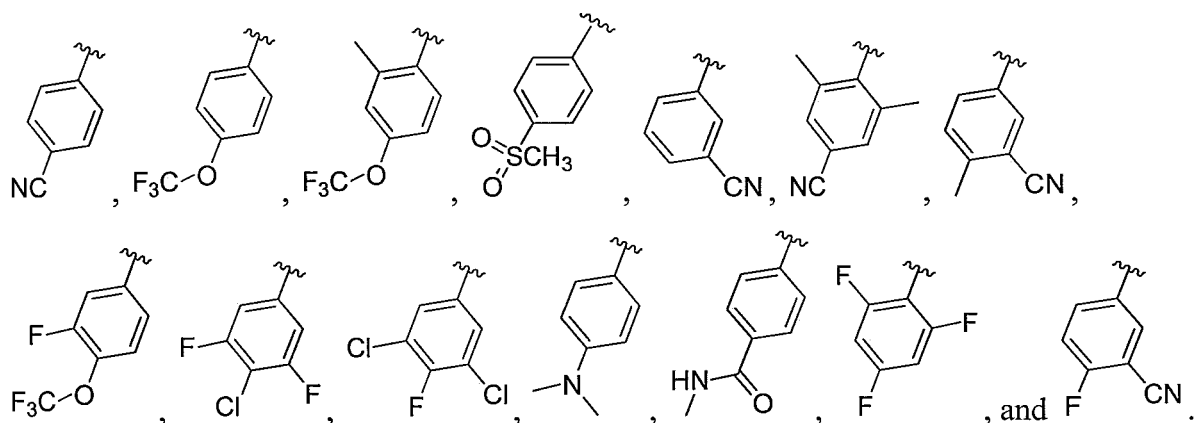
59. The compound or salt of any one of the preceding claims, wherein Y^{10} is CR^b , and R^b is a member selected from the group consisting of chloro, cyano, fluoro, methyl, trifluoromethyl, trifluoromethoxy, $-C(O)N(H)Me$, $-NMe_2$, and $-SO_2Me$.

60. The compound or salt of any one of claims 1-59, wherein Y^{10} is N.

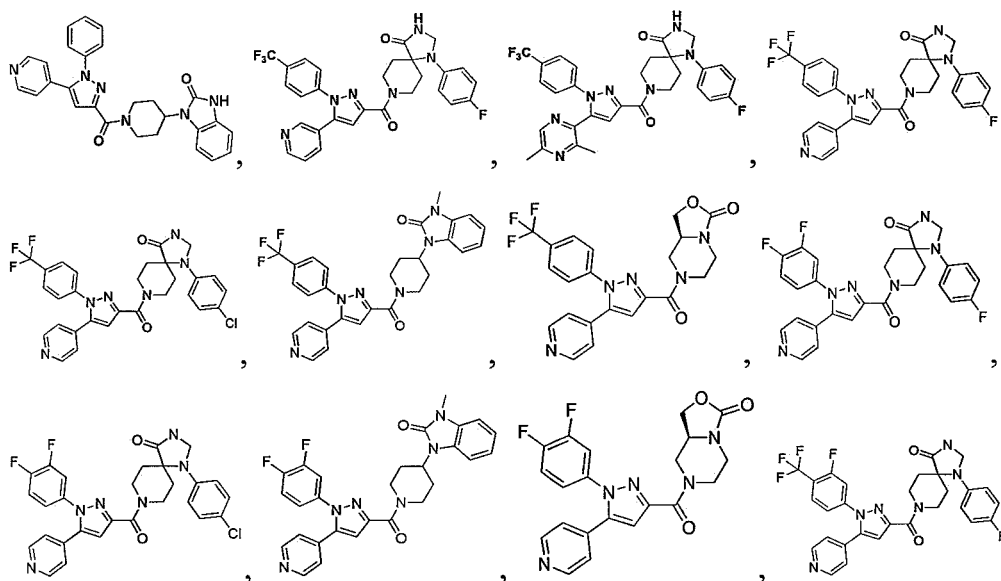
61. The compound or salt of any one of claims 1-50, wherein  is a member selected from the group consisting of:

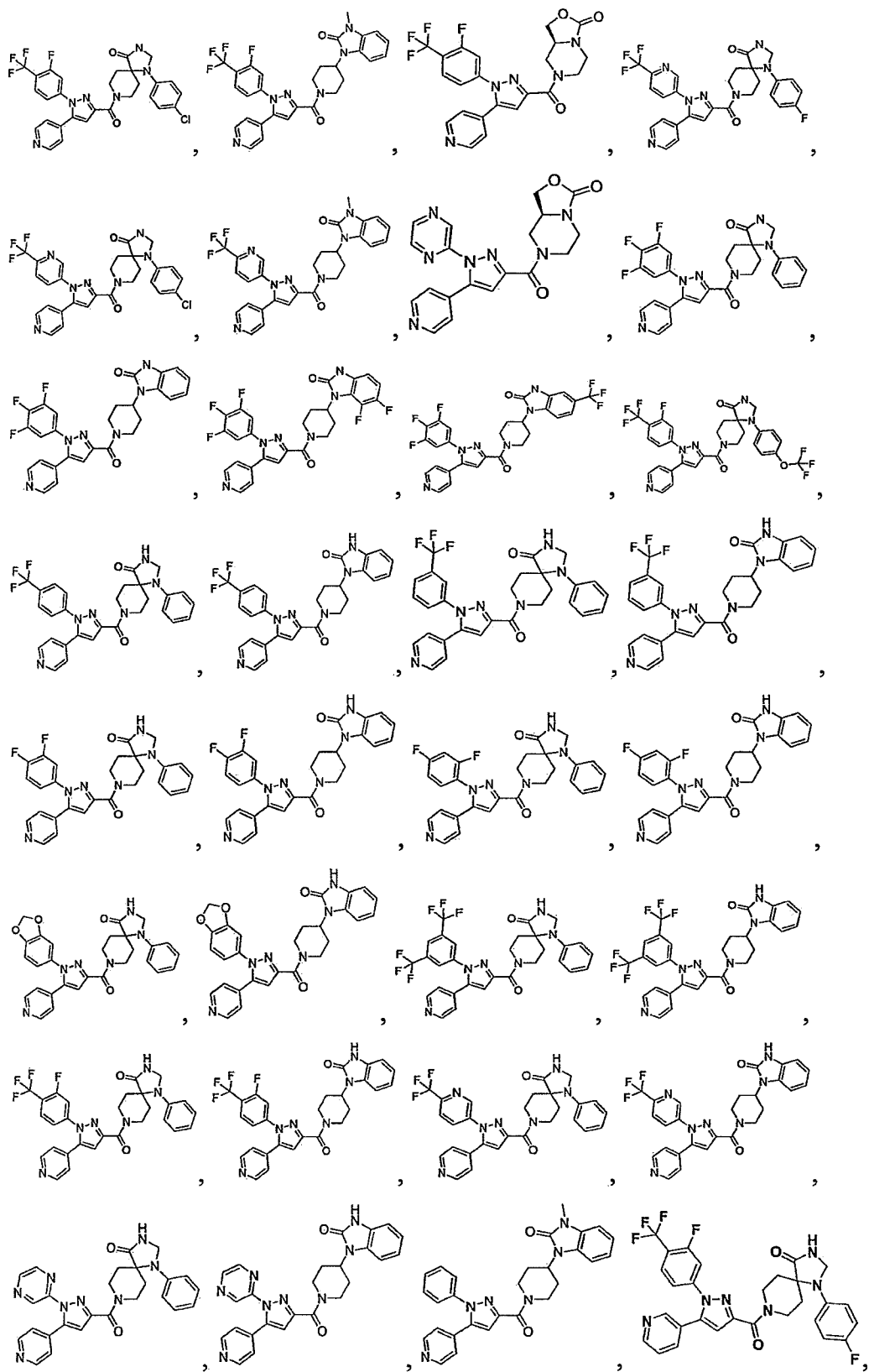


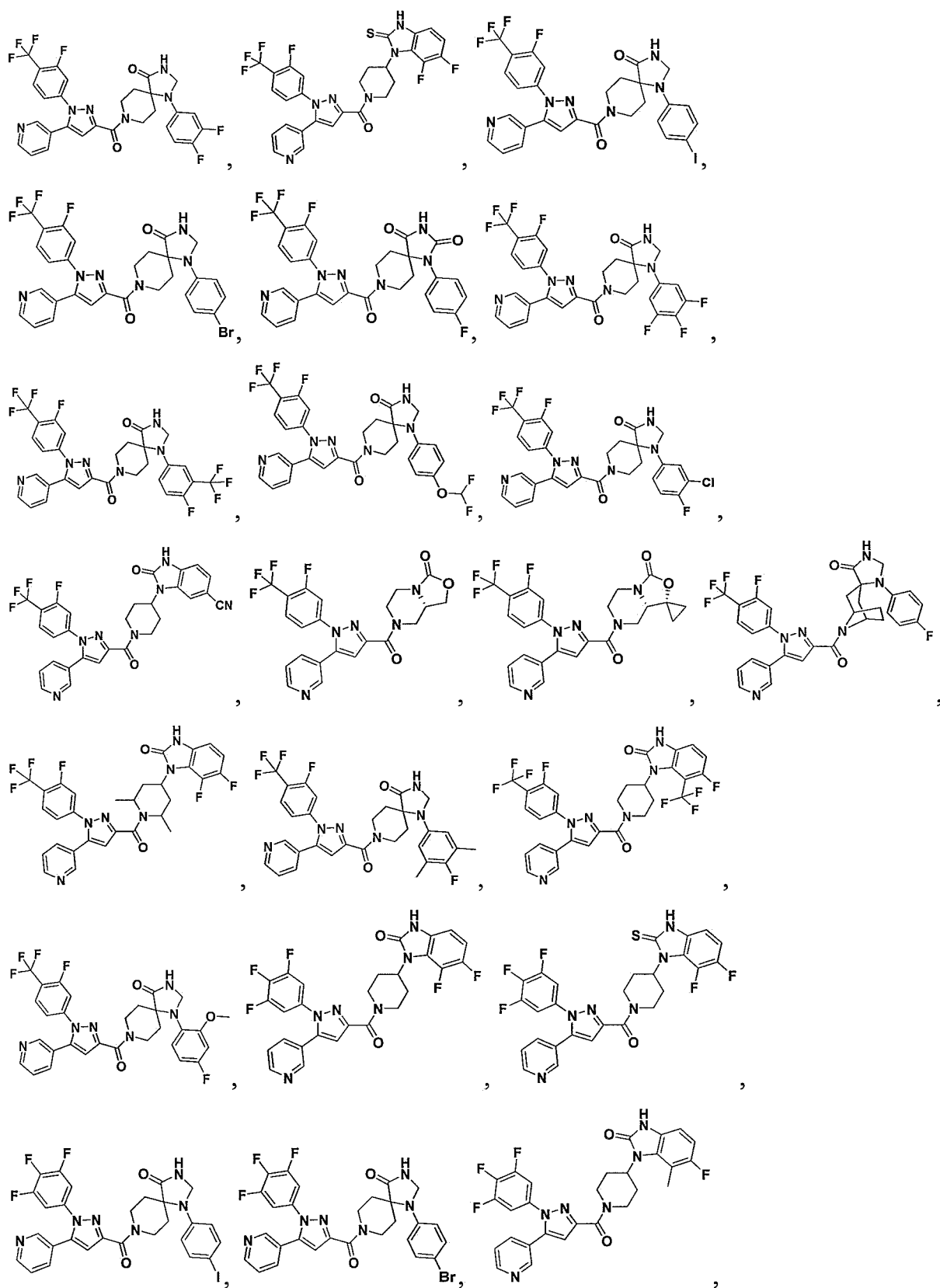
62. The compound or salt of any one of claims 1-50, wherein is a member selected from the group consisting of:

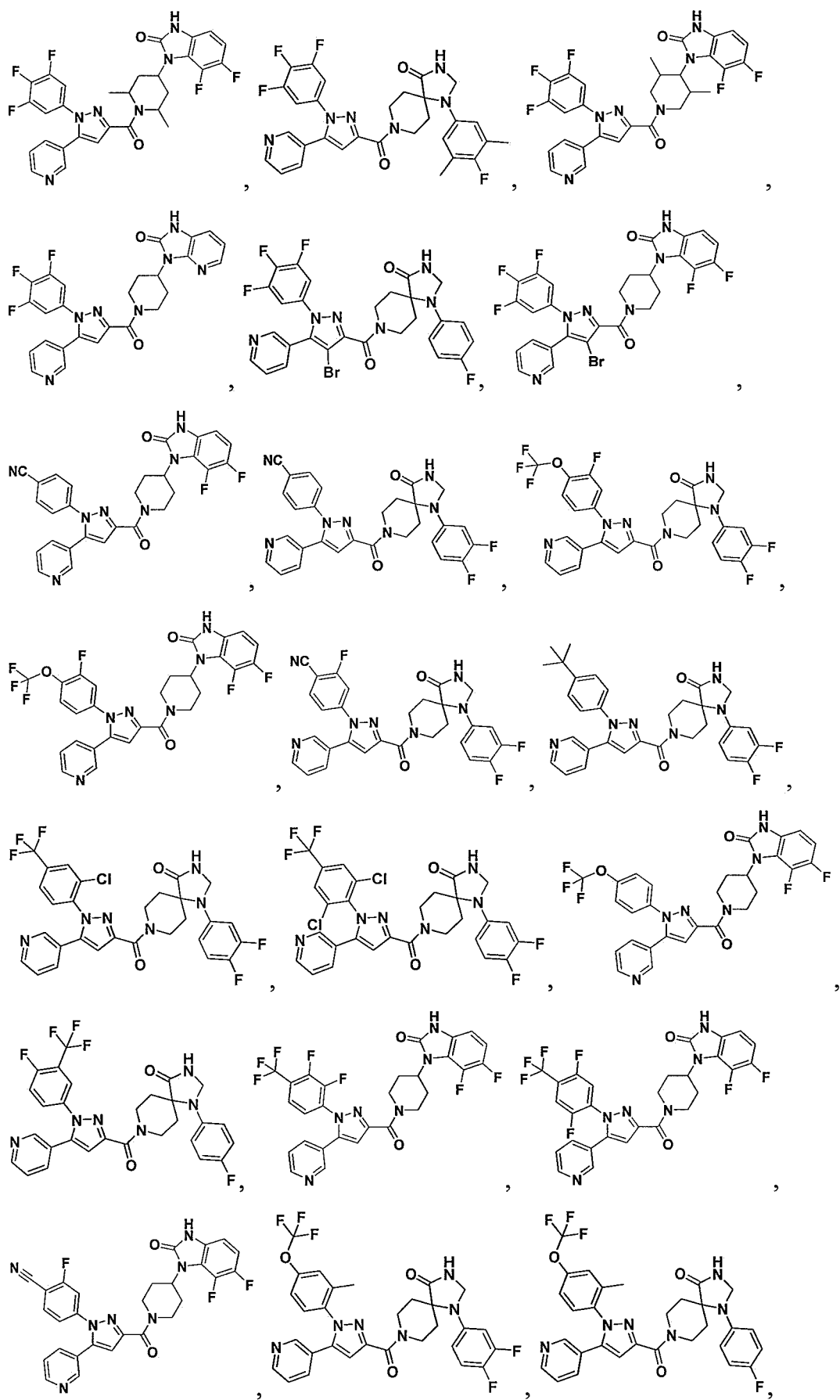


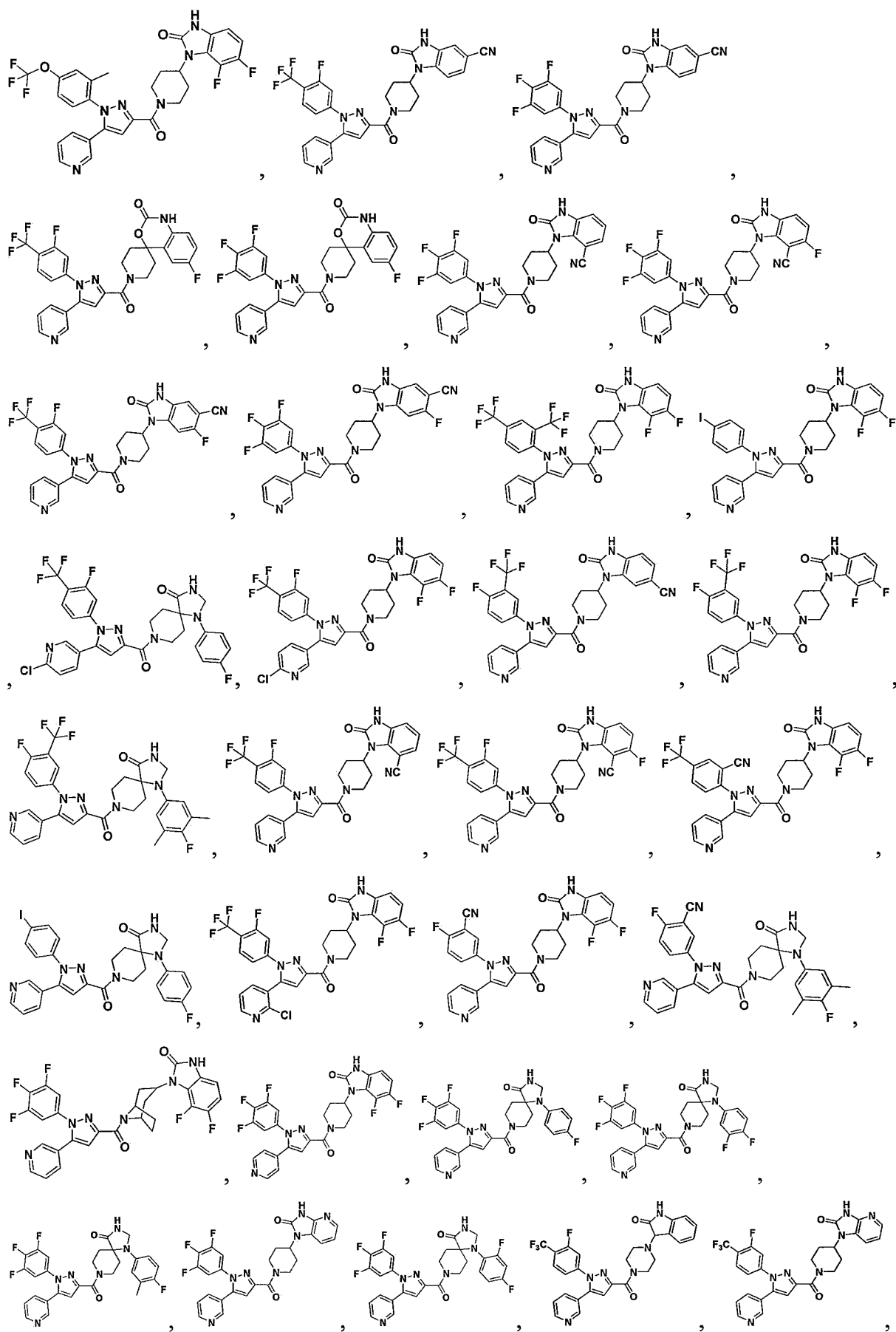
63. The compound or salt of claim 1, wherein the compound is selected from the group consisting of:

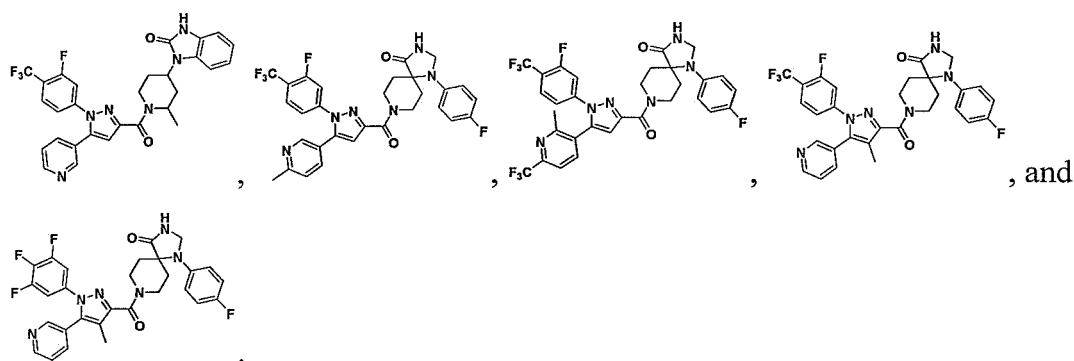












64. A pharmaceutical composition comprising a therapeutically effective amount of a compound of any one of claims 1-63, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable carrier, excipient, or diluent.

65. The pharmaceutical composition according to claim 64 further comprising a second therapeutic agent selected from the group consisting of: i) opioid receptor agonists, ii) opioid receptor antagonists, iii) calcium channel antagonists, iv) 5-HT receptor agonists, v) 5-HT receptor antagonists vi) sodium channel antagonists, vii) NMDA receptor agonists, viii) NMDA receptor antagonists, ix) COX-2 selective inhibitors, x) neurokinin receptor antagonists, including NK1 antagonists, xi) non-steroidal anti-inflammatory drugs, xii) selective serotonin reuptake inhibitors, xiii) selective serotonin and norepinephrine reuptake inhibitors, xiv) tricyclic antidepressant drugs, xv) norepinephrine modulators, xvi) 5-lipoxygenase inhibitors, xvii) cannabinoid receptor agonists, xviii) inhibitors of fatty acid amide hydrolase, ix) beta-adrenergic receptor agonists, x) prostanoid receptor antagonists, xxi) leukotriene receptor antagonists, xxii) histamine receptor antagonists, xxiii) steroids, xxiv) CGRP antagonists, xxv) peroxisome proliferator-activated receptor (PPAR) agonists, and xxvi) acetaminophen.

66. The pharmaceutical composition of claim 64 or 65, wherein the composition is formulated as a solution or a suspension.

67. The pharmaceutical composition of any one of claims 64-66, wherein the composition is formulated for intraarticular, intravesical, intramuscular, intradermal, intraperitoneal, intraocular, intravitreal, intrathecal, subcutaneous, intravenous, or intravenous infusion administration.

68. Use of a therapeutically effective amount, or a prophylactically effective amount, of a compound of any one of claims 1-63, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing pain.

69. The use of claim 68, wherein pain comprises acute pain, chronic pain, inflammatory pain, neuropathic pain, nociceptive pain, or periprocedural pain.

70. The use of claim 68 or 69, wherein said medicament is to be administered with a second therapeutic agent selected from the group consisting of: i) opioid receptor agonists, ii) opioid receptor antagonists, iii) calcium channel antagonists, iv) 5-HT receptor agonists, v) 5-HT receptor antagonists, vi) sodium channel antagonists, vii) NMDA receptor agonists, viii) NMDA receptor antagonists, ix) COX-2 selective inhibitors, x) neurokinin receptor antagonists, including NK1 antagonists, xi) non-steroidal anti-inflammatory drugs, xii) selective serotonin reuptake inhibitors, xiii) selective serotonin and norepinephrine reuptake inhibitors, xiv) tricyclic antidepressant drugs, xv) antiepileptic drugs, xvi) 5-lipoxygenase inhibitors, xvii) cannabinoid receptor agonists, xviii) inhibitors of fatty acid amide hydrolase (FAAH), ix) beta-adrenergic receptor agonists, xx) prostanoid receptor antagonists, xxi) leukotriene receptor antagonists, xxii) histamine receptor antagonists, xxiii) steroids, xxiv) CGRP antagonists, xxv) peroxisome proliferator-activated receptor (PPAR) agonists, and xxvi) acetaminophen.

71. The use of claim 70, wherein the 5-HT receptor agonist is a 5-HT_{1B} receptor agonist or a 5HT_{1D} receptor agonist.

72. The use of claim 70, wherein the 5-HT receptor agonist is a triptan.

73. The use of claim 72, wherein the triptan is sumatriptan, rizatriptan, naratriptan, zolmitriptan, eletriptan, almotriptan, or frovatriptan.

74. The use of claim 70, wherein the opioid receptor agonist is morphine, codeine, hydrocodone, oxymorphone, pentazocine, nalbuphine, fentanyl, sufentanil, tramadol, meperidine, methadone, or etorphine.

75. The use of claim 70, wherein the non-steroid anti-inflammatory drug is aspirin, ibuprofen, naproxen, ketoprofen, flurbiprofen, loxoprofen, indomethacin, etodolac, diflunisal, ketorolac, nabumetone, oxaprozin, piroxicam, meloxicam, or diclofenac.

76. The use of claim 70, wherein the COX-2 inhibitor is celecoxib, etoricoxib, lumiracoxib, parecoxib, rofecoxib, or valdecoxib.
77. The use of claim 70, wherein the second therapeutic agent is acetaminophen.
78. Use of a therapeutically effective amount, or a prophylactically effective amount, of a compound of any one of claims 1-63, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prevention of pain before, during or after surgical procedure.
79. Use of a therapeutically effective amount, or a prophylactically effective amount, of a compound of any one of claims 1-63, or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prevention of pain associated with an interventional procedure, wherein the medicament is to be periprocedurally administered.
80. The use of any one of claims 68-79, wherein the therapeutically effective amount, or the prophylactically effect amount, of the compound is to be administered by intraarticular, intravesical, intramuscular, intradermal, intraperitoneal, intraocular, intravitreal, intrathecal, subcutaneous, intravenous, or intravenous infusion administration.