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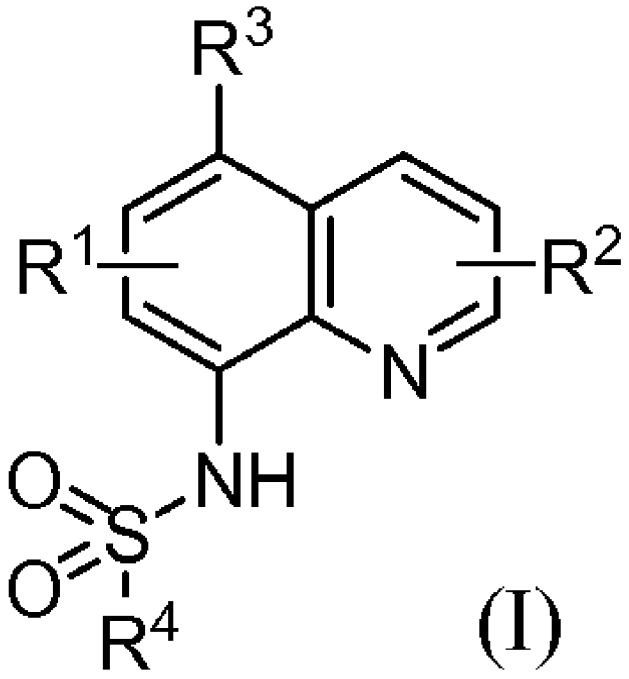

(I)

(57) Abstract: Disclosed are sulfonamidoquinoline compounds, as well as pharmaceutical compositions and methods of use. One embodiment is a compound having the structure. Formule (I) and pharmaceutically acceptable salts, prodrugs and N-oxides thereof (and solvates and hydrates thereof), wherein R^1, R^2, R^3 and R^4 are as described herein. In certain embodiments, a compound disclosed herein inhibits ubiquitination, and can be used to treat disease by blocking the degradation of tumor suppressors.

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QUINOLINE DERIVATIVES USEFUL AS UBIQUITINATION

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Patent Application No. 62/037,449, filed on August 14, 2014, which is hereby incorporated herein by reference in its entirety.

BACKGROUND

Field of Invention

[0002] This invention comprises compounds, pharmaceutical compositions and methods of use of the compounds and compositions containing them. This invention relates more particularly to certain sulfonamidoquinoline compounds and pharmaceutical compositions thereof, and to methods of inhibiting ubiquitination. Further methods comprise treating and/or preventing disease using certain sulfonamidoquinoline compounds to block the degradation of tumor suppressors.

Technical Background

[0003] Ubiquitination of a protein provides a signal for its targeted degradation and recycling via the ubiquitin-proteasome pathway. The process of ubiquitination takes place in a series of steps, beginning with the activation of ubiquitin through a ubiquitin-activating enzyme E1 and the transfer to a ubiquitin-conjugating enzyme E2. Finally the ubiquitin is linked to the lysine of the target protein in the presence of an ubiquitin-protein ligase E3 (referred to as a ubiquitin ligase). Chains of four or more ubiquitin domains activates the degradation process by the proteasome.

[0004] The E3 ubiquitin ligase acts as a substrate recognition module for the ubiquitination system in which each E3 provides specificity for only a small number of substrates. This specificity makes E3 ligases attractive targets for drug discovery (analogous to kinases), for instance by preventing degradation of pro-apoptotic proteins in cancer cells.

[0005] The development of small molecule E3 ligase inhibitors is challenging due to the requirement of the molecules to disrupt protein-protein interactions (PPI's). PPI's are an area that has not been well explored in small-molecule drug-discovery because the interaction surfaces are often large with flat or shallow grooves at the interfaces. This is in contrast to the tight, well defined pockets present in traditional enzymes or receptors.

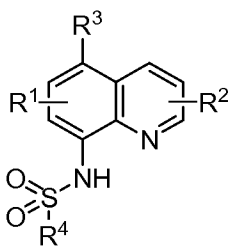
However, it has the potential to be rewarding and is beginning to be recognized, and there have been several examples of the disruption of E3 ligase binding. One of the initial investigations in this area came from work on the disruption of binding between p53 and MDM2. MDM2 serves as the E3 ligase for p53 promoting degradation. The work resulted in the identification of *cis*-imidazolines known as Nutlins, which displace p53 from its complex with MDM2 in the 100-300 nM range. These efforts have spurred an effort to develop structure-activity relationships (SAR) around these and similar structures, resulting in compounds that inhibit the p53-MDM2 interaction with single digit nanomolar potencies and below. Further, there have been several reports of small molecules being used to target E3 ligases including the von Hippel-Lindau ligase to disrupt the VHL-HIF-1α interaction as well as a non-ligase PPI between HIF1α and HIF1α.

[0006] The Skp1-Cullin 1-F-Box (SCF) family of E3 ligases are a well characterized family held together through PPI's. The complex consists of the scaffold protein Cullin-1, which binds Roc1 (recruiting the E2) and Skp1 (recruiting the F-Box protein). One particular E3 ligase complex is responsible for p27, the substrate recognition component Skp2 and an adaptor protein Cks1. p27, a CDK inhibitor, is a negative regulator of cell cycle progression. Low levels of p27 have been implicated in a number of cancers, while elevated levels of Cks1 have been associated with low levels of p27 and poor prognosis in cancer patients. There have been several groups that have targeted the SCF ligases with the goal of increasing levels of p27. Molecules have also been identified as disrupting PPI's between Skp1-Skp2 and Skp2-Cks1-p27, and as interacting with alternative E3 ligases in the SCF system including Cdc4, Met30 and βTRCP1. There have not been any reports of compounds targeted to the Cks1-Skp2 PPI.

SUMMARY

[0007] The present invention comprises compounds, pharmaceutical compositions and methods of using them to treat and/or prevent disease by inhibiting ubiquitination.

[0008] Disclosed herein are compounds having structural formula (I)



(I)

and pharmaceutically acceptable salts, prodrugs and *N*-oxides thereof (and solvates and hydrates thereof), wherein R^1, R^2, R^3 and R^4 are as described herein.

[0009] Also disclosed herein are pharmaceutical compositions. Examples of such compositions include those having at least one pharmaceutically acceptable carrier, diluent or excipient; and a compound, pharmaceutically acceptable salt, prodrug or *N*-oxide (or solvate or hydrate) as described herein.

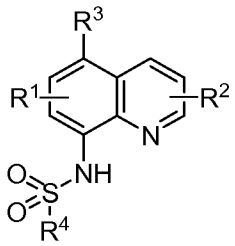
[0010] Another aspect of the present invention comprises methods for treating and/or preventing disease by blocking the degradation of tumor suppressors. Accordingly, the invention also comprises methods for treating disease using the presently disclosed compounds and pharmaceutical compositions.

[0011] The compounds of the invention inhibit Cks1-Skp2 PPI and ubiquitination, and they increase levels of p27.

DETAILED DESCRIPTION

[0012] In one aspect, the invention comprises compounds that inhibit ubiquitination.

[0013] In embodiment I_1 of this first aspect, the compounds have structural formula (I):



(I)

and pharmaceutically acceptable salts, prodrugs and *N*-oxides thereof, and solvates and hydrates thereof,

wherein

R^1 is -hydrogen, -(C_1-C_6 haloalkyl), -Y-(C_1-C_6 haloalkyl), -Y-(C_0-C_6 alkyl)-Ar, -Y-(C_0-C_6 alkyl)-Het, -Y-(C_0-C_6 alkyl)-Cak, -Y-(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN,

wherein Y is O, S, N(R^5), and R^5 is -hydrogen or -(C_1-C_6 alkyl);

R^2 is -hydrogen, -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -Y-(C_1-C_6 alkyl), -Y-(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN;

wherein Y is O, S, N(R^5), and R^5 is -hydrogen or -(C_1-C_6 alkyl);

R^3 is -hydrogen, -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN; and

R^4 is -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het or -(C_0-C_6 alkyl)-Cak,

wherein

each Ar (aryl), Het (heteroaryl), Cak (cycloalkyl), Hca (heterocycloalkyl), alkyl, and haloalkyl is optionally substituted,

provided that:

at least one of R^1 and R^3 is not hydrogen.

[0014] Embodiment I_2 comprises compounds of embodiment I_1, provided that the compound is not:

N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
N-(6-chloroquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
2,6-difluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
4-chloro-2-fluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(7-chloroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-bromoquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
2,4-dichloro-N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)pyridine-3-sulfonamide;
2-amino-N-(5-chloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;

N-(5-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide;
N-(5-bromoquinolin-8-yl)-5-(oxazol-5-yl)thiophene-2-sulfonamide; or
N-(5-bromoquinolin-8-yl)-4-(2-methylpyrimidin-4-yl)benzenesulfonamide.

[0015] In embodiment I_3, the compounds are of embodiment I_1 or I_2, wherein

R^1 is -(C_1-C_6 haloalkyl), -Y-(C_1-C_6 haloalkyl), -Y-(C_0-C_6 alkyl)-Ar, -Y-(C_0-C_6 alkyl)-Het, -Y-(C_0-C_6 alkyl)-Cak, -Y-(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN,

wherein Y is O, S, N(R^5), and R^5 is -hydrogen or -(C_1-C_6 alkyl),

provided that the compound is not:

N-(6-chloroquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
2,6-difluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
4-chloro-2-fluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(7-chloroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide; or
N-(6-bromoquinolin-8-yl)benzenesulfonamide.

[0016] In embodiment I_4, the compounds are of any embodiment I_1, I_2, or I_3, wherein

R^3 is -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN,

provided that the compound is not:

N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
2,4-dichloro-N-(5-chloroquinolin-8-yl)benzenesulfonamide;

N-(5-chloroquinolin-8-yl)pyridine-3-sulfonamide;
2-amino-N-(5-chloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(5-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide;
N-(5-bromoquinolin-8-yl)-5-(oxazol-5-yl)thiophene-2-sulfonamide; or
N-(5-bromoquinolin-8-yl)-4-(2-methylpyrimidin-4-yl)benzenesulfonamide.

[0017] In embodiment I_5, the compounds are of any embodiment I_1, I_2, I_3 or I_4 wherein

R^1 is -(C_1-C_6 haloalkyl), -Y-(C_1-C_6 haloalkyl), -Y-(C_0-C_6 alkyl)-Ar, -Y-(C_0-C_6 alkyl)-Het, -Y-(C_0-C_6 alkyl)-Cak, -Y-(C_0-C_6 alkyl)-Hca, -NO_2 or -CN,

wherein Y is O, S, N(R^5), and R^5 is -hydrogen or -(C_1-C_6 alkyl),

provided that the compound is not:

N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide; or
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide.

[0018] In embodiment I_6, the compounds are of embodiment I_1, I_2, I_3, I_4 or I_5 wherein

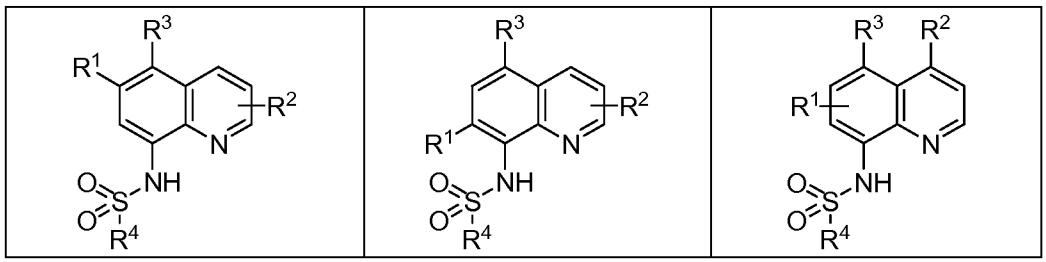
R^3 is -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -(C_0-C_6 alkyl)-Hca, -NO_2 or -CN,

provided that the compound is not:

N-(5-morpholinoquinolin-8-yl)benzenesulfonamide.

[0019] The invention further comprises subgenera of formula (I) in which structural formula (I), R^1, R^2, R^3, and R^4 are any combination of groups as defined hereinbelow (*e.g.*, structural formula (I) is formula (If), R^1 is group (1k), R^2 is group 2(b), R^3 is group (3dd) and R^4 is group (4q)):

[0020] **<u>Structural Formula (I) is one of formulae (Ia) – (Ik):</u>**



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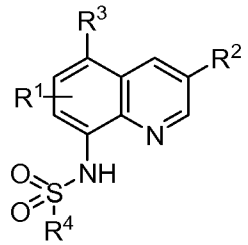	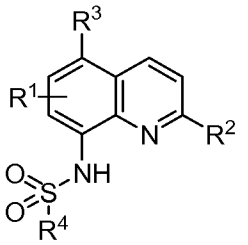	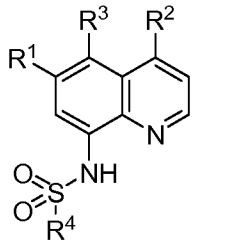
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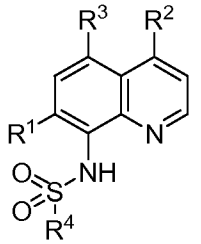	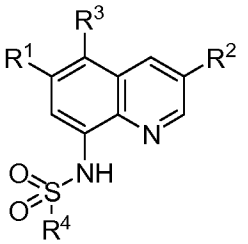	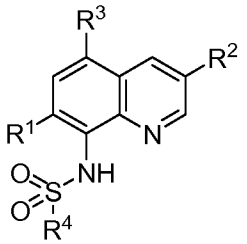
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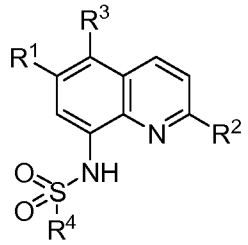
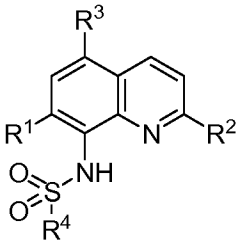
		
(Ij)	(Ik)	

[0021] **R^1 is selected from one of the following groups (1a) – (1bbb):**

(1a) -hydrogen, -(C_1-C_6 haloalkyl), -Y-(C_1-C_6 haloalkyl), -Y-(C_0-C_6 alkyl)-Ar, -Y-(C_0-C_6 alkyl)-Het, -Y-(C_0-C_6 alkyl)-Cak, -Y-(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN, wherein Y is O, S, N(R^5), and R^5 is -hydrogen or -(C_1-C_6 alkyl).

(1b) As in group **(1a)**, wherein Y is O or N(R^5).

(1c) As in group **(1a)**, wherein Y is N(R^5).

(1d) As in group **(1a)**, wherein Y is S or N(R^5).

(1e) As in any of groups **(1a)-(1d)**, wherein R^5 is NH.

(1f) As in any of groups **(1a)-(1d)**, wherein R^5 is NMe.

(1g) As in any of groups **(1a)-(1d)**, wherein R^5 is NEt.

(1h) As in group **(1a)**, wherein Y is O.

(1i) As in group **(1a)**, wherein Y is S.

(1j) -hydrogen, -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN.

(1k) -hydrogen, -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN, wherein -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak and -O-(C_0-C_6 alkyl)-Hca are each optionally substituted with one or more substituents selected from the group consisting of -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 and -CN.

(1l) -hydrogen, -(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -NO_2 or -CN.

(1m) -(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -NO_2 or -CN.

(1n) -hydrogen, -(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -NO_2 or -CN, wherein -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak and -O-(C_0-C_6 alkyl)-Hca are each optionally substituted with one or more substituents selected from the group consisting of -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 and -CN.

(1o) -(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -NO_2 or -CN, wherein -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak and -O-(C_0-C_6 alkyl)-Hca are each optionally substituted with one or more substituents selected from the group consisting of -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 and -CN.

(1p) -hydrogen, -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

(1q) -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

(1r) -hydrogen, -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN.

(1s) -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN.

(1t) -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, or -O-(C_0-C_6 alkyl)-Hca.

(1u) -hydrogen, -O-(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak or -O-(C_0-C_6 alkyl)-Hca.

(1v) -O-(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak or -O-(C_0-C_6 alkyl)-Hca.

(1w) -O-(C_1-C_6 haloalkyl).

(1x) -hydrogen.

(1y) -O-(C_1-C_6 haloalkyl).

(1z) $-OCF_3$.

(1aa) -O-(C_0-C_6 alkyl)-Ar or -O-(C_0-C_6 alkyl)-Het.

(1bb) -O-(C_0-C_6 alkyl)-Ar.

(1cc) -O-(C_0-C_6 alkyl)-Het.

(1dd) -O-(C_0-C_6 alkyl)-Cak or -O-(C_0-C_6 alkyl)-Hca.

(1ee) -O-(C_0-C_6 alkyl)-Cak.

(1ff) -O-(C_0-C_6 alkyl)-Hca.

(1gg) -hydrogen, -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -halogen, $-NO_2$ or -CN, wherein -(C_1-C_6 haloalkyl) and -O-(C_1-C_6 haloalkyl) are each optionally substituted with one or more -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, $-NO_2$ or -CN.

(1hh) -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -halogen, $-NO_2$ or -CN, wherein -(C_1-C_6 haloalkyl) and -O-(C_1-C_6 haloalkyl) are each optionally substituted with one or more -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, $-NO_2$ or -CN.

(1ii) -hydrogen, -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -halogen, $-NO_2$ or -CN, wherein -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak and -O-(C_0-C_6 alkyl)-Hca are each optionally substituted with one or more -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, $-NO_2$ or -CN.

(1jj) -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -halogen, $-NO_2$ or -CN, wherein -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak and -O-(C_0-C_6 alkyl)-Hca are each optionally substituted with one or more -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, $-NO_2$ or -CN.

(1kk) -hydrogen, -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak or -O-(C_0-C_6 alkyl)-Hca, wherein -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak and -O-(C_0-C_6 alkyl)-Hca are each optionally substituted with one or more -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, $-NO_2$ or -CN.

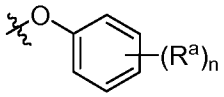
(1ll) -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak or -O-(C_0-C_6 alkyl)-Hca, wherein -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak and -O-(C_0-C_6 alkyl)-Hca are each optionally substituted with one or more -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

(1mm) -O-(C_0-C_6 alkyl)-Ar or -O-(C_0-C_6 alkyl)-Het, wherein -O-(C_0-C_6 alkyl)-Ar or -O-(C_0-C_6 alkyl)-Het are each optionally substituted with one or more -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

(1nn) -O-(C_0-C_6 alkyl)-Ar, optionally substituted with one or more -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

(1oo) -O-(C_0-C_6 alkyl)-Ar, optionally substituted with one or more -O-(C_1-C_6 alkyl), -halogen or -CN.

(1pp) -O-(C_0-C_6 alkyl)-phenyl, optionally substituted with one or more -O-(C_1-C_6 alkyl), -halogen or -CN.

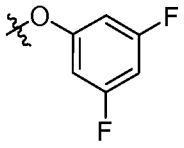
(1qq)  , wherein R^a is independently -hydrogen, -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN, and n is 1, 2, 3, 4 or 5.

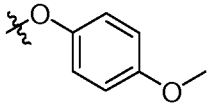
(1rr) As group **(1qq)**, wherein, R^a is independently -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen or -CN, and n is 1, 2, 3 or 4.

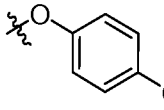
(1ss) As group **(1qq)**, wherein, R^a is independently -O-(C_1-C_6 alkyl), -halogen or -CN, and n is 1 or 2.

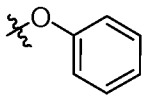
(1tt) As group **(1qq)**, wherein, R^a is independently -OMe, fluoro, chloro, bromo, iodo or -CN, and n is 1 or 2.

(1uu) As group **(1qq)**, wherein, R^a is independently -OMe, fluoro, chloro, bromo or -CN, and n is 1 or 2.

(1vv)  .

(1ww)  .

(1xx)  .

(1yy)  .

(1zz) -O-(C_0-C_6 alkyl)-Het, optionally substituted with one or more -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

(1aaa) -O-(C_0-C_6 alkyl)-pyridyl, optionally substituted with one or more -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

(1bbb) -O-(C_0-C_6 alkyl)-Ar or -O-(C_0-C_6 alkyl)-Het, wherein -O-(C_0-C_6 alkyl)-Ar or -O-(C_0-C_6 alkyl)-Het are each optionally substituted with one or more -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

[0022] **R^2 is selected from one of the following groups (2a) – (2xx):**

(2a) -hydrogen, -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -Y-(C_1-C_6 alkyl), -Y-(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN, wherein Y is O, S, N(R^5), and R^5 is -hydrogen or -(C_1-C_6 alkyl).

(2b) As in group **(2a)**, wherein Y is O or N(R^5).

(2c) As in group **(2a)**, wherein Y is N(R^5).

(2d) As in group **(2a)**, wherein Y is S or N(R^5).

(2e) As in any of groups **(2a)-(2d)**, wherein R^5 is NH.

(2f) As in any of groups **(2a)-(2d)**, wherein R^5 is NMe.

(2g) As in any of groups **(2a)-(2d)**, wherein R^5 is NEt.

(2h) As in group **(2a)**, wherein Y is O.

(2i) As in group **(2a)**, wherein Y is S.

(2j) -hydrogen, -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

(2k) -hydrogen, -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN, wherein -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl) and -O-(C_1-C_6 haloalkyl) are each optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

(2l) -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

(2m) -hydrogen, -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl) or -O-(C_1-C_6 haloalkyl).

(2n) -hydrogen, -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

(2o) -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

(2p) -hydrogen, -halogen, -NO_2 or -CN.

(2q) -hydrogen, -NO_2 or -CN.

(2r) -hydrogen, -halogen or -CN.

(2s) -hydrogen or -halogen.

(2t) -hydrogen or -CN.

(2u) -hydrogen.

(2v) -halogen.

(2w) -fluoro, -chloro, -bromo or -iodo.

(2x) -fluoro, -chloro or -bromo.

(2y) -chloro or -bromo.

(2z) -fluoro or -bromo.

(2aa) -fluoro or -chloro.

(2bb) -fluoro.

(2cc) -chloro.

(2dd) -bromo.

(2ee) -hydrogen, -(C_1-C_6 alkyl) or -(C_1-C_6 haloalkyl).

(2ff) -hydrogen, -O-(C_1-C_6 alkyl) or -O-(C_1-C_6 haloalkyl).

(2gg) -hydrogen, -(C_1-C_6 alkyl) or -O-(C_1-C_6 alkyl).

(2hh) -hydrogen or -(C_1-C_6 alkyl).

(2ii) -hydrogen or -O-(C_1-C_6 alkyl).

(2jj) -(C_1-C_6 alkyl).

(2kk) -methyl.

(2ll) -ethyl.

(2mm) -*n*-propyl.

(2nn) -*i*-propyl.

(2oo) -O-(C_1-C_6 alkyl).

(2pp) -OMe.

(2qq) -OEt.

(2rr) -O-*n*-Pr.

(2ss) -O-*i*-Pr.

(2tt) -O-(C_1-C_6 haloalkyl).

(2uu) -OCF_3.

(2vv) -(C_1-C_6 alkyl) or -(C_1-C_6 haloalkyl).

(2ww) -O-(C_1-C_6 alkyl) or -O-(C_1-C_6 haloalkyl).

(2xx) -(C_1-C_6 alkyl) or -O-(C_1-C_6 alkyl).

[0023] **R^3 is selected from one of the following groups (3a) – (3ssss):**

(3a) -hydrogen, -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN.

(3b) -hydrogen, -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN, wherein -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak and -(C_0-C_6 alkyl)-Hca are each optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(3c) -hydrogen, -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN.

(3d) -hydrogen, -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -NO_2 or CN.

(3e) -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -NO_2 or CN.

(3f) -hydrogen, -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -NO_2 or CN, wherein -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak and -(C_0-C_6 alkyl)-Hca are each optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(3g) -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -NO_2 or CN, wherein -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak and -(C_0-C_6 alkyl)-Hca are each optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(3h) -hydrogen, -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak or -(C_0-C_6 alkyl)-Hca.

(3i) -hydrogen, -halogen, -NO_2 or -CN.

(3j) -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN.

(3k) -halogen, -NO_2 or -CN.

(3l) -hydrogen or -halogen.

(3m) -hydrogen.

(3n) -halogen.

(3o) -fluoro, -chloro, -bromo or -iodo.

(3p) -fluoro, -chloro or -bromo.

(3q) -chloro or -bromo.

(3r) -fluoro or -bromo.

(3s) -fluoro or -chloro.

(3t) -fluoro.

(3u) -chloro.

(3v) -bromo.

(3w) -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak or -(C_0-C_6 alkyl)-Hca.

(3x) -(C_0-C_6 alkyl)-Ar or -(C_0-C_6 alkyl)-Het.

(3y) -(C_0-C_6 alkyl)-Cak or -(C_0-C_6 alkyl)-Hca.

(3z) -(C_0-C_6 alkyl)-Ar.

(3aa) -(C_0-C_6 alkyl)-phenyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(3bb) -Ar.

(3cc) -phenyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(3dd) -phenyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

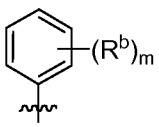
(3ee) -phenyl optionally substituted with one or more -(C_1-C_6 alkyl), -halogen, -NO_2 or -CN.

(3ff) -phenyl optionally substituted with one or more -(C_1-C_6 alkyl), -halogen, or -CN.

(3gg) -phenyl optionally substituted with one or more -(C_1-C_6 alkyl) or -halogen.

(3hh) -phenyl optionally substituted with one or more -(C_1-C_6 alkyl).

(3ii) -phenyl optionally substituted with one or more -halogen.

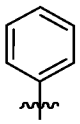
(3jj)  , wherein R^b is independently hydrogen, -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN, and m is 1, 2, 3, 4 or 5.

(3kk) As group **(3jj)**, wherein, R^b is independently -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen or -CN, and m is 1, 2, 3 or 4.

(3ll) As group **(3jj)**, wherein, R^b is independently -O-(C_1-C_6 alkyl), -halogen or -CN, and m is 1 or 2.

(3mm) As group **(3jj)**, wherein, R^b is independently -OMe, fluoro, chloro, bromo, iodo or -CN, and m is 1 or 2.

(3nn) As group **(3jj)**, wherein, R^b is independently -OMe, fluoro, chloro, bromo or -CN, and m is 1 or 2.

(3oo)  .

(3pp) -(C_0-C_6 alkyl)-Het.

(3qq) -(C_0-C_6 alkyl)-pryidyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(3rr) -(C_0-C_6 alkyl)-furanyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(3ss) -(C_0-C_6 alkyl)-thiophenyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(3tt) -(C_0-C_6 alkyl)-benzofuranyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(3uu) -(C_0-C_6 alkyl)- benzothiaphenyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(3vv) -Het.

(3ww) -pyridyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(3xx) -pyridyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

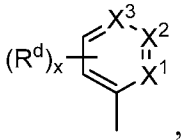
(3yy) -pyridyl optionally substituted with one or more -(C_1-C_6 alkyl), -halogen, -NO_2 or -CN.

(3zz) -pyridyl optionally substituted with one or more -(C_1-C_6 alkyl), -halogen, or -CN.

(3aaa) -pyridyl optionally substituted with one or more -(C_1-C_6 alkyl) or -halogen.

(3bbb) -pyridyl optionally substituted with one or more -(C_1-C_6 alkyl).

(3ccc) -pyridyl optionally substituted with one or more -halogen.

(3ddd)  , wherein R^d is independently -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN, x is 1, 2, 3, 4 or 5, and one of X^1, X^2 and X^3 is N.

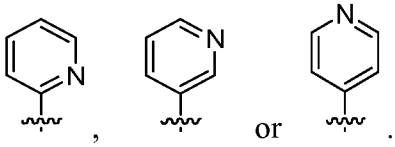
(3eee) As group **(3ddd)**, wherein, R^d is independently -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen or -CN, x is 1, 2, 3 or 4 , and one of X^1, X^2 and X^3 is N.

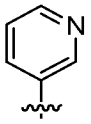
(3fff) As group **(3ddd)**, wherein, R^d is independently -O-(C_1-C_6 alkyl), -halogen or -CN, x is 1 or 2, and one of X^1, X^2 and X^3 is N.

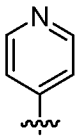
(3ggg) As group **(3ddd)**, wherein, R^d is independently -OMe, fluoro, chloro, bromo, iodo or -CN, x is 1 or 2, and X^2 or X^3 is N.

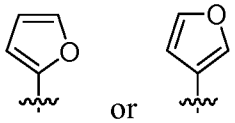
(3hhh) As group **(3ddd)**, wherein, R^d is independently -OMe, fluoro, chloro, bromo or -CN, x is 1 or 2, and one of X^2 is N.

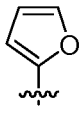
(3iii) As group **(3ddd)**, wherein, R^d is independently -OMe, fluoro, chloro, bromo or -CN, x is 1 or 2, and one of X^3 is N.

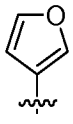
(3jjj)  .

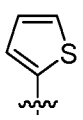
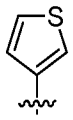
(3kkk)  .

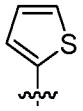
(3lll)  .

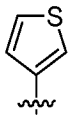
(3mmm)  .

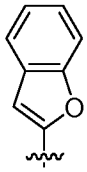
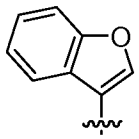
(3nnn)  .

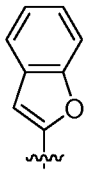
(3ooo)  .

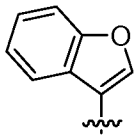
(3ppp)  or  .

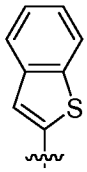
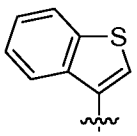
(3qqq)  .

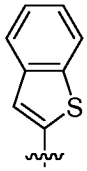
(3rrr)  .

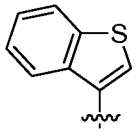
(3sss)  or  .

(3ttt)  .

(3uuu)  .

(3vvv)  or  .

(3www)  .

(3xxx)  .

(3yyy) -(C_0-C_6 alkyl)-Cak.

(3zzz) -Cak.

(3aaaa) -cyclopropyl, -cyclobutyl, -cyclopentyl or -cyclohexyl.

(3bbbb) -cyclopropyl, -cyclopentyl or -cyclohexyl.

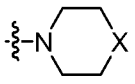
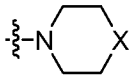
(3cccc) -cyclopentyl or -cyclohexyl.

(3dddd) -cyclopentyl.

(3eeee) -cyclohexyl.

(3ffff) -(C_0-C_6 alkyl)-Hca.

(3gggg) -Hca.

(3hhhh)  , wherein X is -O-, -S-, N(R^5) or -C(H)-CH_2-Ar; and the  group is optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(3iiii) As group **(3hhhh)**, wherein X is -O-, N(R^5) or -C(H)-CH_2-Ar.

(3jjjj) As group **(3hhhh)**, wherein X is -O- or -C(H)-CH_2-Ar.

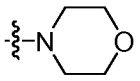
(3kkkk) As group **(3hhhh)**, wherein X is -O- or N(R^5).

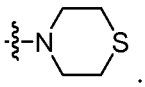
(3llll) As group **(3hhhh)**, wherein X is N(R^5) or -C(H)-CH_2-Ar.

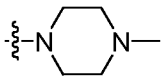
(3mmmm) As group **(3hhhh)**, wherein X is -O-.

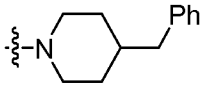
(3nnnn) As group **(3hhhh)**, wherein X is N(R^5).

(3oooo) As group **(3hhhh)**, wherein X is -C(H)-CH_2-Ar.

(3pppp)  .

(3qqqq)  .

(3rrrr)  .

(3ssss)  .

[0024] **<u>R^4 is selected from one of the following groups (4a) – (4yyy):</u>**

(4a) -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het or -(C_0-C_6 alkyl)-Cak.

(4b) -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het or -(C_0-C_6 alkyl)-Cak, wherein -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het and -(C_0-C_6 alkyl)-Cak are each optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl), N(R^5)(R^6), -halogen, -NO_2 or -CN,

wherein R^5 and R^6 are independently -hydrogen, -(C_1-C_6 alkyl) or -C(O)-(C_1-C_6 alkyl).

(4c) -(C_1-C_6 alkyl) or -(C_1-C_6 haloalkyl).

(4d) -(C_1-C_6 alkyl).

(4e) -methyl.

(4f) -ethyl.

(4g) -*n*-propyl.

(4h) -*i*-propyl.

(4i) -(C_1-C_6 haloalkyl).

(4j) $-CF_3$.

(4k) -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het or -(C_0-C_6 alkyl)-Cak.

(4l) -(C_0-C_6 alkyl)-Ar or -(C_0-C_6 alkyl)-Het.

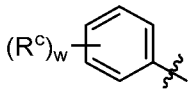
(4m) -(C_0-C_6 alkyl)-Cak or -(C_0-C_6 alkyl)-Het.

(4n) -(C_0-C_6 alkyl)-Ar, or -(C_0-C_6 alkyl)-Cak.

(4o) -(C_0-C_6 alkyl)-Ar.

(4p) -Ar.

(4q) -phenyl.

(4r)  , wherein R^c is independently -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, $-NO_2$ or -CN, and w is 1, 2, 3, 4 or 5.

(4s) As group **(4r)**, wherein, R^c is independently -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen or -CN, and w is 1, 2, 3 or 4.

(4t) As group **(4r)**, wherein, R^c is independently -O-(C_1-C_6 alkyl), -halogen or -CN, and w is 1 or 2.

(4u) As group **(4r)**, wherein, R^c is independently -OMe, fluoro, chloro, bromo, iodo or -CN, and w is 1 or 2.

(4v) As group **(4r)**, wherein, R^c is independently -OMe, fluoro, chloro, bromo or -CN, and w is 1 or 2.

(4w) As group **(4r)**, wherein, R^c is -Me, and w is 1, 2 or 3.

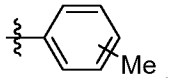
(4x) -Ar, substituted with one or more of -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl), N(R^5)(R^6), -halogen, $-NO_2$ or -CN, wherein R^5 and R^6 are independently -hydrogen, -(C_1-C_6 alkyl) or -C(O)-(C_1-C_6 alkyl).

(4y) -phenyl, substituted with one or more of -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl), N(R^5)(R^6), -halogen, -NO_2 or -CN, wherein R^5 and R^6 are independently -hydrogen, -(C_1-C_6 alkyl) or -C(O)-(C_1-C_6 alkyl).

(4z) -phenyl, substituted with one or more of -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl) or N(R^5)(R^6), wherein R^5 and R^6 are independently -hydrogen, -(C_1-C_6 alkyl) or -C(O)-(C_1-C_6 alkyl).

(4aa) -phenyl, substituted with one or more of -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl) or -O-(C_1-C_6 alkyl).

(4bb) -phenyl, substituted with one or more -(C_1-C_6 alkyl).

(4cc) 

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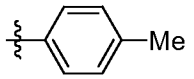
(4dd) 

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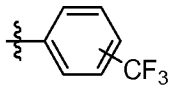
(4ee) -phenyl, substituted with one or more -(C_1-C_6 haloalkyl.

(4ff) 

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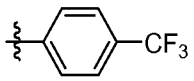
(4gg) 

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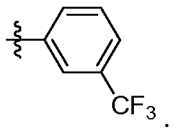
(4hh) 

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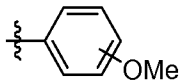
(4ii) -phenyl, substituted with one or more -O-(C_1-C_6 alkyl).

(4jj) 

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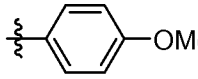
(4kk) 

.

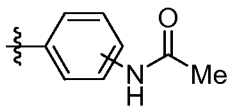
(4ll) -phenyl, substituted with one or more N(R^5)(R^6), wherein R^5 and R^6 are independently -hydrogen, -(C_1-C_6 alkyl) or -C(O)-(C_1-C_6 alkyl).

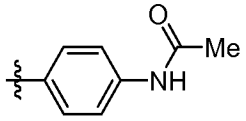
(4mm) -phenyl, substituted with one or more N(R^5)(R^6), wherein R^5 and R^6 are independently -hydrogen or -(C_1-C_6 alkyl).

(4nn) -phenyl, substituted with one or more N(R^5)(R^6), wherein R^5 and R^6 are independently -hydrogen or -C(O)-(C_1-C_6 alkyl).

(4oo) -phenyl, substituted with one $N(R^5)(R^6)$, wherein R^5 is -hydrogen and R^6 is -C(O)-(C_1-C_6 alkyl).

(4pp) -phenyl, substituted with one $N(R^5)(R^6)$, wherein R^5 is -hydrogen and R^6 is -C(O)-methyl.

(4qq)  .

(4rr)  .

(4ss) -(C_0-C_6 alkyl)-Het.

(4tt) -(C_0-C_6 alkyl)-pryidyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(4uu) -(C_0-C_6 alkyl)-furanyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(4vv) -(C_0-C_6 alkyl)-thiophenyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(4ww) -(C_0-C_6 alkyl)-benzofuranyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(4xx) -(C_0-C_6 alkyl)- benzothiaphenyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(4yy) -Het.

(4zz) -pyridyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

(4aaa) -pyridyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

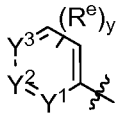
(4bbb) -pyridyl optionally substituted with one or more -(C_1-C_6 alkyl), -halogen, -NO_2 or -CN.

(4ccc) -pyridyl optionally substituted with one or more -(C_1-C_6 alkyl), -halogen, or -CN.

(4ddd) -pyridyl optionally substituted with one or more -(C_1-C_6 alkyl) or -halogen.

(4eee) -pyridyl optionally substituted with one or more -(C_1-C_6 alkyl).

(4fff) -pyridyl optionally substituted with one or more -halogen.

(4ggg)  , wherein R^e is independently -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN, y is 1, 2, 3, 4 or 5, and Y^1, Y^2, and Y^3 are idependently C or N, provided one of Y^1, Y_2, and Y^3 is N.

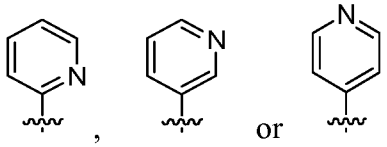
(4hhh) As group **(4ggg)**, wherein, R^e is independently -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen or -CN, y is 1, 2, 3 or 4.

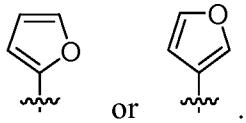
(4iii) As group **(4ggg)**, wherein, R^e is independently -O-(C_1-C_6 alkyl), -halogen or -CN, y is 1 or 2, and one of Y^1, Y^2 and Y^3 is N.

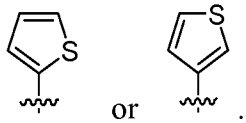
(4jjj) As group **(4ggg)**, wherein, R^e is independently -OMe, fluoro, chloro, bromo, iodo or -CN, y is 1 or 2, and Y^2 or Y^3 is N.

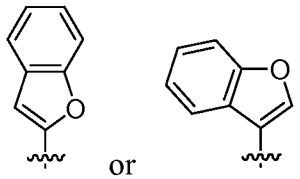
(4kkk) As group **(4ggg)**, wherein, R^e is independently -OMe, fluoro, chloro, bromo or -CN, y is 1 or 2, and Y^2 is N.

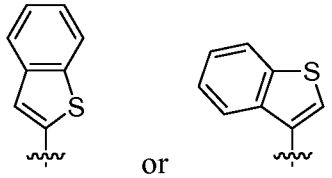
(4lll) As group **(4ggg)**, wherein, R^e is independently -OMe, fluoro, chloro, bromo or -CN, y is 1 or 2, and Y^3 is N.

(4mmm)  .

(4nnn)  .

(4ooo)  .

(4ppp)  .

(4qqq)  .

(4rrr) -(C_0-C_6 alkyl)-Cak.

(4sss) -Cak.

(4ttt) -cyclopropyl, -cyclobutyl, -cyclopentyl or -cyclohexyl.

(4uuu) -cyclopropyl, -cyclopentyl or -cyclohexyl.

(4vvv) -cyclopentyl or -cyclohexyl.

(4www) -cyclopropyl.

(4xxx) -cyclopentyl.

(4yyy) -cyclohexyl.

[0025] Particular embodiments of this aspect of the invention comprise compounds of any one of the formulae (I), and (Ia) – (Ik), each as defined in each of the following rows, wherein each entry is a group number as defined above (e.g., (1x) refers to R^1 is -hydrogen), and a dash "-" indicates that the variable is as defined in embodiment I_1 or defined according to any one of the applicable variable definitions **(1a)-(4yyy)** [*e.g.*, when R^3 is a dash, it can be either as defined in embodiment I_1 or any one of definitions (**3a**)-(**3ssss**)]:

	(I)	R^1	R^2	R^3	R^4
(1)-1	Ia	1a	2u	3a	4a
(1)-2	Ic	1h	2s	3d	4d
(1)-3	Id	1l	2u	3e	4i
(1)-4	Ie	1m	2ee	3f	4p
(1)-5	Ia	1n	2jj	3g	4q
(1)-6	Ic	1o	2oo	3m	4r
(1)-7	Id	1u	2tt	3n	4s
(1)-8	Ie	1x	2a	3w	4t
(1)-9	Ia	1bb	2s	3x	4u
(1)-10	Ia	1nn	2u	3jj	4v
(1)-11	Ic	1qq	2ee	3kk	4w
(1)-12	Id	1rr	2jj	3ll	4cc
(1)-13	Ie	1ss	2oo	3mm	4dd
(1)-14	Ia	1tt	2tt	3nn	4ff
(1)-15	Ia	1uu	2a	3oo	4ll
(1)-16	Ic	-	2u	3pp	4qq
(1)-17	Id	1ww	2u	3ddd	4rr

	(I)	R^1	R^2	R^3	R^4
(1)-18	Ie	1yy	2u	3hhh	4ggg
(1)-19	Ia	1l	2u	3a	4sss
(1)-20	Ic	1a	2s	3d	4www
(1)-21	-	1h	2u	3e	4a
(1)-22	Ie	1l	2ee	3f	4d
(1)-23	Ia	1m	2jj	3g	4i
(1)-24	Ic	1n	2oo	3m	4p
(1)-25	Ia	1o	2tt	3n	4q
(1)-26	Ic	1u	2a	3w	4r
(1)-27	Id	1x	2s	3x	4s
(1)-28	Ie	1bb	2u	3jj	4t
(1)-29	Ia	1nn	2ee	3kk	4u
(1)-30	Ic	1qq	2jj	3ll	4v
(1)-31	Id	1rr	2oo	3mm	4w
(1)-32	-	1ss	2tt	3nn	4cc
(1)-33	Ia	1tt	2a	3oo	4dd
(1)-34	Ic	-	2u	3pp	4ff

	(I)	R^1	R^2	R^3	R^4
(1)-35	Id	1vv	2u	3ddd	4ll
(1)-36	Ie	1ww	2u	3hhh	4qq
(1)-37	Ia	1yy	2u	3a	4rr
(1)-38	Ic	1nn	2s	3d	4ggg
(1)-39	-	1qq	2u	3e	4sss
(1)-40	Ie	1rr	2ee	3f	4www
(1)-41	Ia	1ss	2u	3g	4a
(1)-42	Ic	1a	2s	3m	4d
(1)-43	Id	1h	2u	3n	4i
(1)-44	Ie	1l	2ee	3w	4p
(1)-45	Ia	1m	2jj	3x	4q
(1)-46	Ic	1n	2oo	3a	4r
(1)-47	Id	1o	2u	3d	4s
(1)-48	Ie	1u	2s	3e	4t
(1)-49	Ia	1x	2u	3f	4u
(1)-50	Ic	1bb	2ee	3g	4v
(1)-51	Id	1nn	-	3m	4w
(1)-52	Ia	1qq	2oo	3n	4a
(1)-53	Ic	1rr	2tt	3w	4d
(1)-54	-	1ss	2a	3x	4i
(1)-55	Ia	1tt	2s	3jj	4p
(1)-56	Ic	1uu	2u	3kk	4q
(1)-57	Id	1a	2ee	3ll	4r
(1)-58	Ie	1h	2jj	3mm	4s
(1)-59	Ia	1l	2oo	3nn	4t
(1)-60	-	1m	2tt	3oo	4u
(1)-61	Id	1n	2a	3pp	4v

	(I)	R^1	R^2	R^3	R^4
(1)-62	Ie	1o	2u	3ddd	4w
(1)-63	Ia	1u	2u	3hhh	4cc
(1)-64	Ic	1x	2u	3a	4dd
(1)-65	Id	1bb	2u	3d	4ff
(1)-66	Ia	1nn	2s	3a	4ll
(1)-67	Ic	1qq	2u	3d	4qq
(1)-68	Id	1rr	2ee	3e	4rr
(1)-69	Ie	1ss	2jj	3f	4ggg
(1)-70	Ia	1tt	2oo	3g	4sss
(1)-71	Ic	1uu	2tt	3m	4www
(1)-72	Id	1vv	2a	3n	4a
(1)-73	Ie	1ww	2s	3w	4d
(1)-74	Ia	1yy	2u	3x	4i
(1)-75	Ic	1a	2ee	3jj	4p
(1)-76	Id	1h	2jj	3kk	4a
(1)-77	Ie	1l	2oo	3a	4d
(1)-78	Ia	1m	2tt	3d	4i
(1)-79	Ic	1n	2a	3e	4p
(1)-80	Id	1o	2u	3f	4q
(1)-81	Ie	1u	2u	3g	4a
(1)-82	Ia	1x	2u	3m	4d
(1)-83	Ic	1bb	2u	3n	4i
(1)-84	Id	1nn	2s	3a	4p
(1)-85	Ie	1qq	2u	3d	4q
(1)-86	Ia	1rr	2ee	3e	4r
(1)-87	Ic	1ss	2jj	3f	4s
(1)-88	Id	1tt	2oo	3g	4t

	(I)	R^1	R^2	R^3	R^4
(1)-89	-	1uu	2tt	3m	4u
(1)-90	Ia	1vv	2a	3n	4v
(1)-91	Ic	1ww	2s	3w	4w
(1)-92	Id	1yy	2u	3x	4cc
(1)-93	Ie	1a	2ee	3jj	4dd
(1)-94	Ia	1h	2jj	3kk	4ff
(1)-95	Ia	1l	2oo	3ll	4ll
(1)-96	Ic	1m	2tt	3mm	4qq
(1)-97	-	1a	2a	3a	4rr
(1)-98	Ie	1h	2u	3d	4ggg
(1)-99	Ia	1l	2u	3e	4sss
(1)-100	Ic	1m	2u	3f	4www
(1)-101	Id	1n	2u	3g	4a
(1)-102	Ie	1o	2s	3m	4d
(1)-103	Ia	1u	2u	3n	4i
(1)-104	Ic	1x	2ee	3w	4p
(1)-105	Id	1bb	2jj	3x	4q
(1)-106	Ie	1nn	2oo	3jj	4r
(1)-107	Ia	1qq	2tt	3kk	4s
(1)-108	Ic	1rr	2a	3ll	4t
(1)-109	Ia	1ss	2s	3mm	4a
(1)-110	Ic	1tt	2u	3nn	4d
(1)-111	Id	1uu	2ee	3oo	4i
(1)-112	Ie	1vv	2u	3pp	4p
(1)-113	Ia	1ww	2s	3ddd	4q
(1)-114	Ic	1yy	2u	3hhh	4r
(1)-115	-	1a	2s	3a	4s

	(I)	R^1	R^2	R^3	R^4
(1)-116	-	1h	2u	3d	4t
(1)-117	Id	1l	2ee	3e	4u
(1)-118	Ie	1m	2jj	3f	4v
(1)-119	Ia	1n	2oo	3g	4w
(1)-120	Ic	1o	2tt	3m	4cc
(1)-121	Id	1u	2a	3n	4dd
(1)-122	Ie	1x	2s	3w	4ff
(1)-123	Ia	1bb	2u	3x	4ll
(1)-124	Ic	-	2s	3jj	4qq
(1)-125	Id	1qq	2u	3kk	4a
(1)-126	Ie	1rr	2ee	3ll	4d
(1)-127	Ia	1ss	2jj	3mm	4i
(1)-128	Ia	1tt	2oo	3nn	4p
(1)-129	-	1uu	2tt	3oo	4q
(1)-130	Id	-	2a	3pp	4r
(1)-131	Ie	1ww	2s	3ddd	4s
(1)-132	Ia	1yy	2u	3hhh	4t
(1)-133	Ic	-	2ee	3a	4u
(1)-134	Id	1h	2jj	3d	4v
(1)-135	Ie	1l	2oo	3e	4w
(1)-136	Ia	1m	2tt	3f	4cc
(1)-137	Ic	1n	2a	3g	4dd
(1)-138	Id	1o	2u	-	4ff
(1)-139	Ie	1u	2u	3n	4ll
(1)-140	Ia	1x	2u	3w	-
(1)-141	Ic	1bb	2u	3x	4rr
(1)-142	-	1nn	2s	3jj	4ggg

	(I)	R^1	R^2	R^3	R^4
(1)-143	Ie	1qq	2u	3kk	4sss
(1)-144	Ia	1rr	2ee	3ll	4www
(1)-145	Ic	1ss	-	3mm	4a
(1)-146	Id	1tt	2oo	3nn	4d
(1)-147	Ie	1uu	2tt	3oo	4i
(1)-148	Ia	1vv	2a	3pp	4p
(1)-149	Ic	1ww	2s	3ddd	4q
(1)-150	Id	1yy	2u	3hhh	4r
(1)-151	Ie	1a	2ee	3a	4s
(1)-152	Ia	1h	2jj	3d	4t
(1)-153	Ic	1l	2oo	3e	4u
(1)-154	Id	1m	-	3f	4v
(1)-155	Ie	1n	2a	3g	4w
(1)-156	Ia	1o	2u	3m	4a
(1)-157	Ic	1u	2u	3n	4d
(1)-158	Id	1x	2u	3w	4i
(1)-159	Ie	1bb	2u	3x	4p
(1)-160	Ia	-	2s	3jj	4q
(1)-161	Ic	1qq	2u	3kk	4r
(1)-162	Id	1rr	2ee	3ll	4s
(1)-163	Ie	1ss	-	3mm	4t
(1)-164	Ia	1tt	2oo	3nn	4u
(1)-165	Ic	-	2tt	3oo	4v
(1)-166	Id	1vv	2a	3pp	4a
(1)-167	-	1ww	2s	3ddd	4d
(1)-168	Ia	1yy	2u	3hhh	4i
(1)-169	Ic	1a	2ee	3a	4p

	(I)	R^1	R^2	R^3	R^4
(1)-170	Id	1h	2jj	3d	4q
(1)-171	Ie	1l	2oo	3e	4r
(1)-172	Ia	1m	2tt	3f	4s
(1)-173	Ic	1n	2a	3g	4t
(1)-174	Id	1o	2u	3m	4u
(1)-175	Ie	1u	2u	3n	4v
(1)-176	Ia	1x	2u	3a	4w
(1)-177	Ic	1bb	2u	3d	4cc
(1)-178	Id	1nn	2s	3e	4dd
(1)-179	Ie	1qq	2u	3f	4ff
(1)-180	Ia	1rr	2ee	3g	4ll
(1)-181	Ic	1ss	-	3m	4qq
(1)-182	-	1tt	2oo	3n	4rr
(1)-183	Ie	1uu	2tt	3w	4ggg
(1)-184	Ia	1vv	2a	3x	4sss
(1)-185	Ic	1ww	2s	3jj	4www
(1)-186	-	1yy	2u	3kk	4a
(1)-187	Ie	1a	2ee	3ll	4d
(1)-188	Ia	1h	2jj	3mm	4i
(1)-189	Ic	1l	2oo	3nn	4p
(1)-190	Id	1a	2u	3oo	4q
(1)-191	-	1h	2s	3pp	4r
(1)-192	Ia	1l	2u	3ddd	4s
(1)-193	Ic	1m	2ee	-	4t
(1)-194	Id	1n	2jj	3a	4u
(1)-195	Ie	1o	2oo	3d	4v
(1)-196	Ia	1u	2tt	3e	-

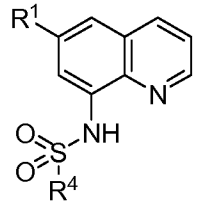
	(I)	R^1	R^2	R^3	R^4
(1)-197	Ic	1x	2a	3f	4a
(1)-198	Id	1bb	2s	3g	4d
(1)-199	Ie	1l	2u	-	4i
(1)-200	Ia	1m	2ee	3n	4p
(1)-201	Ic	1n	2u	3w	4q
(1)-202	Id	1o	2s	3x	4r
(1)-203	Ie	1u	2u	3jj	4s
(1)-204	Ia	1x	2s	3kk	4t
(1)-205	Ic	1bb	2u	3a	4u
(1)-206	Id	1nn	2ee	3d	4v
(1)-207	Ie	1qq	2jj	3e	4w
(1)-208	Ia	1rr	2oo	3f	4cc
(1)-209	Ic	1ss	2tt	3g	4dd
(1)-210	Id	1tt	2a	3m	4ff
(1)-211	Ie	1a	2s	3n	4ll
(1)-212	Ia	1h	2u	3w	4qq
(1)-213	Ic	1l	2ee	3a	4a
(1)-214	-	1m	2jj	3d	4d
(1)-215	Ie	1n	2oo	3e	4i
(1)-216	Ia	1o	2tt	3f	4p
(1)-217	Ic	-	2a	3g	4q
(1)-218	Id	1x	2u	3m	4r
(1)-219	Ie	1bb	2u	3n	4s
(1)-220	Ia	1nn	2u	3w	4t
(1)-221	Ic	1a	2u	3x	4u
(1)-222	-	1h	2s	3jj	4v
(1)-223	Ie	1l	2u	3kk	4w

	(I)	R^1	R^2	R^3	R^4
(1)-224	Ia	1m	2ee	3ll	4cc
(1)-225	Ic	1n	2jj	3mm	4dd
(1)-226	Id	1o	2oo	3nn	4ff
(1)-227	Ie	1u	2tt	3oo	4ll
(1)-228	Ia	1x	2a	3pp	-
(1)-229	Ic	1bb	2s	3ddd	4rr
(1)-230	Id	1nn	2u	3hhh	4ggg
(1)-231	Ie	1qq	2ee	3a	4sss
(1)-232	Ia	1rr	2jj	3d	4www
(1)-233	Ic	1ss	-	3e	4a
(1)-234	-	1tt	2tt	3f	4d
(1)-235	Ie	1uu	2u	3g	4i
(1)-236	Ia	1vv	2s	3m	4p
(1)-237	Ic	-	2u	3n	4q
(1)-238	Id	1a	2ee	3w	4r
(1)-239	Ie	1h	2jj	3x	4s
(1)-240	Ia	1l	2oo	3jj	4t
(1)-241	Ic	1m	2tt	3kk	4u
(1)-242	Id	1n	2a	3ll	4v
(1)-243	Ie	1o	2s	3mm	4w
(1)-244	Ia	1u	2oo	3nn	4cc
(1)-245	Ic	1x	2tt	3oo	4dd
(1)-246	Id	1bb	2a	3pp	4a
(1)-247	-	1nn	2s	3ddd	4d
(1)-248	Ia	1qq	2u	3hhh	4i
(1)-249	Ic	1rr	2ee	3a	4p
(1)-250	-	1ss	2jj	3d	4q

	(I)	R^1	R^2	R^3	R^4
(1)-251	Ie	1tt	2oo	3e	4r
(1)-252	Ia	1uu	2tt	3f	4s
(1)-253	Ic	-	2a	3g	4t
(1)-254	Id	1ww	2u	-	4u
(1)-255	Ie	1yy	2u	3n	4v
(1)-256	Ia	1a	2u	3w	4w
(1)-257	Ic	1h	2u	3x	4cc
(1)-258	Id	1l	-	3jj	4dd
(1)-259	Ie	1m	2u	3kk	-
(1)-260	Ia	1n	2ee	3ll	4ll
(1)-261	Ic	1o	2jj	3mm	4qq
(1)-262	Id	-	2oo	3nn	4rr

	(I)	R^1	R^2	R^3	R^4
(1)-263	Ie	1x	2tt	3oo	4ggg
(1)-264	Ia	1bb	2a	3pp	4sss
(1)-265	Ic	1nn	2s	3ddd	4www
(1)-266	Id	1qq	2u	3hhh	4a
(1)-267	-	1rr	2ee	3a	4d
(1)-268	Ia	1ss	2jj	3d	-
(1)-269	Ic	1tt	2oo	3e	4p
(1)-270	-	1uu	2tt	3f	4q
(1)-271	Ie	1vv	2a	3g	4r
(1)-272	Ia	1ww	2u	3m	4s
(1)-273	Ic	-	2u	3n	4t
(1)-274	Id	1a	2u	3w	4u

[0026] In embodiment II_1 of this aspect, the invention comprises compounds according to formula (II),



(II)

wherein

R^1 is as described above in groups **(1a) - (1bbb)**,

provided that R^1 is not hydrogen; and

R^4 is as described above in groups **(4a) - (4yyy)**.

[0027] In embodiment II_2, the compounds are of embodiment II_1, provided that the compound is not:

N-(6-chloroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
2,6-difluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;

4-chloro-2-fluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-bromoquinolin-8-yl)benzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide; or
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide.

[0028] In embodiment II_3, the compound is of embodiment II_1 or II_2, wherein

R^1 is -(C_1-C_6 haloalkyl), -Y-(C_1-C_6 haloalkyl), -Y-(C_0-C_6 alkyl)-Ar, -Y-(C_0-C_6 alkyl)-Het, -Y-(C_0-C_6 alkyl)-Cak, -Y-(C_0-C_6 alkyl)-Hca, -NO_2 or -CN,

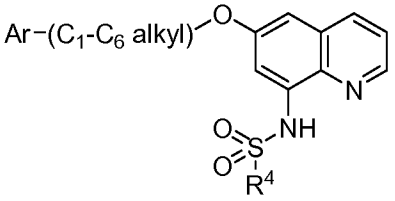
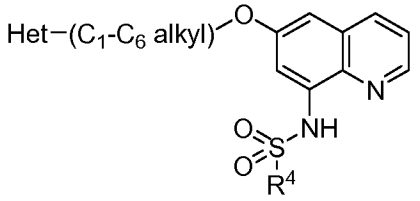
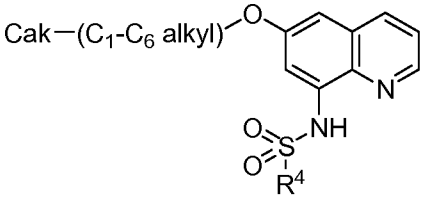
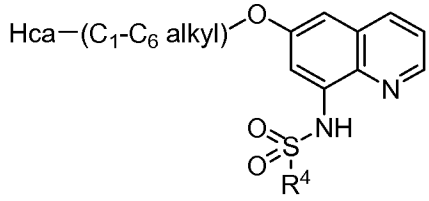
wherein Y is O, S, N(R^5), and R^5 is -hydrogen or -(C_1-C_6 alkyl),

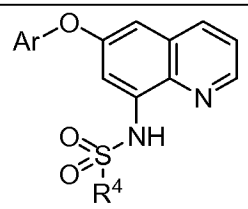
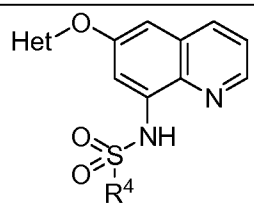
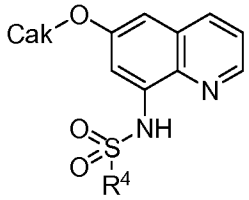
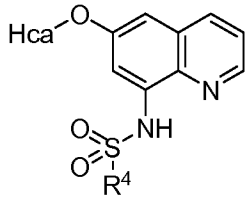
provided that the compound is not:

N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide; or
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide.

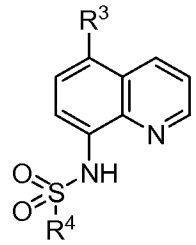
[0029] In embodiment II_4, the compounds of the invention are one of formulae (IIa) – (IIh), wherein R^4 is as defined in any embodiment hereinabove:

[0030] **Structural Formula (II) is one of formulae (IIa) – (IIh):**

	
(IIa)	(IIb)
	
(IIc)	(IId)

	
(IIe)	(IIf)
	
(IIg)	(IIh)

[0031] In embodiment III_1, the invention comprises compounds according to formula (III),



(III)

wherein

R^3 is as described above in groups **(3a) - (3ssss)**,

provided that R^3 is not hydrogen; and

R^4 is as described above in groups **(4a) - (4yyy)**.

[0032] In embodiment III_2, the compounds are of embodiment III_1, provided that the compound is not:

N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
2,4-dichloro-N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)pyridine-3-sulfonamide;
2-amino-N-(5-chloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(5-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;

N-(5-bromoquinolin-8-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide;
N-(5-bromoquinolin-8-yl)-5-(oxazol-5-yl)thiophene-2-sulfonamide; or
N-(5-bromoquinolin-8-yl)-4-(2-methylpyrimidin-4-yl)benzenesulfonamide.

[0033] In embodiment III_3, the compounds are of embodiment III_1 or III_2, wherein

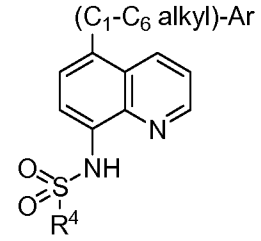
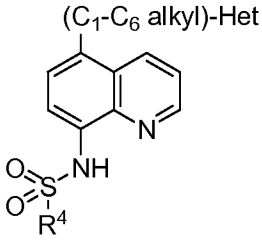
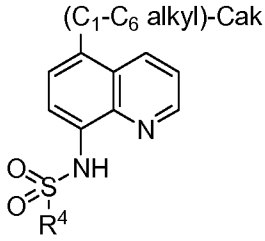
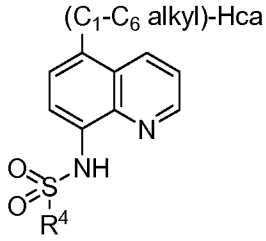
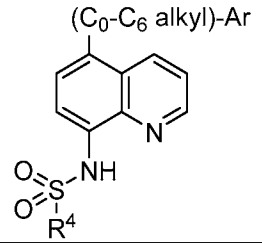
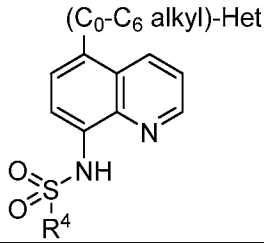
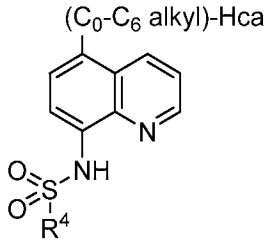
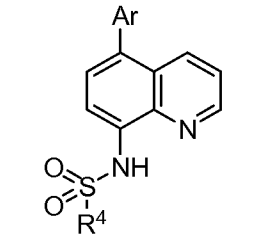
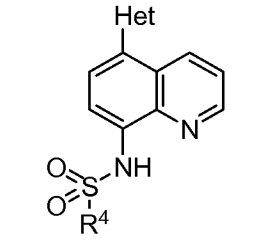
R^3 is -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -(C_0-C_6 alkyl)-Hca, -NO_2 or -CN,

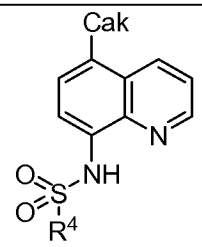
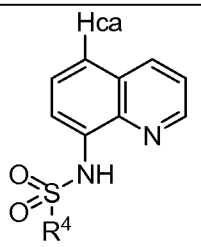
provided that the compound is not:

N-(5-morpholinoquinolin-8-yl)benzenesulfonamide.

[0034] The invention further comprises subgenera of embodiments III_1, III_2, or III_3, in which structural formula (III), R^3 and R^4 are any combination of groups as defined hereinabove, including without limitation, the following (*e.g.*, structural formula (III) is formula (IIIe), R^3 is group (3jj), and R^4 is group (4q)):

[0035] **Structural Formula (III) is one of formulae (IIIa) – (IIIk):**

 (C_1-C_6 alkyl)-Ar	 (C_1-C_6 alkyl)-Het	 (C_1-C_6 alkyl)-Cak
(IIIa)	(IIIb)	(IIIc)
 (C_1-C_6 alkyl)-Hca	 (C_0-C_6 alkyl)-Ar	 (C_0-C_6 alkyl)-Het
(IIId)	(IIIe)	(IIIf)
 (C_0-C_6 alkyl)-Hca	 Ar	 Het
(IIIg)	(IIIh)	(IIIi)

	
(IIIj)	(IIIk)

[0036] In some embodiments, where the compound has a structure according to formula (I), (III), (IIIg) or (IIIk), when R^3 is Hca, Hca is not -morpholinyl. In other embodiments, where the compound has a structure according to formula (I), (III), (IIIg) or (IIIk), the compound is not N-(5-morpholinoquinolin-8-yl)benzenesulfonamide.

[0037] Particular embodiments of this aspect of the invention comprise compounds of any one of the formulae (III), and (IIIa) – (IIIk), each as defined in each of the following rows, wherein each entry is a group number as defined above (e.g., **(3v)** refers to R^3 is -bromo), and a dash "-" indicates that the variable is as defined in embodiment I_1 or defined according to any one of the applicable variable definitions **(3a)-(3ssss)** and **(4a)-(4yyy)** [*e.g.*, when R^4 is a dash, it can be either as defined in embodiment I_1 or any one of definitions (**4a**)-(**4yyy**)]:

	(III)	**R^3**	**R^4**
(3)-1	IIIe	3aa	4a
(3)-2	IIIe	3bb	4d
(3)-3	IIIe	3cc	4i
(3)-4	IIIe	3dd	4p
(3)-5	IIIe	3ee	4q
(3)-6	IIIe	3ff	4r
(3)-7	IIIe	3gg	4s
(3)-8	IIIe	3hh	4t
(3)-9	IIIe	3ii	4u
(3)-10	IIIe	3jj	4v
(3)-11	IIIe	3kk	4w
(3)-12	IIIe	3ll	4cc

	(III)	**R^3**	**R^4**
(3)-13	IIIe	3mm	4dd
(3)-14	IIIe	3nn	4ff
(3)-15	IIIe	3oo	4ll
(3)-16	IIIh	3aa	4qq
(3)-17	IIIh	3bb	4rr
(3)-18	IIIh	3cc	4ggg
(3)-19	IIIh	3dd	4sss
(3)-20	IIIh	3ee	4www
(3)-21	IIIh	3ff	4a
(3)-22	IIIh	3gg	4d
(3)-23	IIIh	3hh	4i
(3)-24	IIIh	3ii	4p

	(III)	R^3	R^4
(3)-25	IIIh	3jj	4q
(3)-26	IIIh	3kk	4r
(3)-27	IIIh	3ll	4s
(3)-28	IIIh	3mm	4t
(3)-29	IIIh	3nn	4u
(3)-30	IIIh	3oo	4v
(3)-31	IIIe	3jj	4a
(3)-32	IIIe	3jj	4d
(3)-33	IIIe	3jj	4i
(3)-34	IIIe	3jj	4p
(3)-35	IIIe	3jj	4q
(3)-36	IIIe	3jj	4r
(3)-37	IIIe	3jj	4s
(3)-38	IIIe	3jj	4t
(3)-39	IIIe	3jj	4u
(3)-40	IIIe	3jj	4v
(3)-41	IIIe	3jj	4w
(3)-42	IIIe	3jj	4cc
(3)-43	IIIe	3jj	4dd
(3)-44	IIIe	3jj	4ff
(3)-45	IIIe	3jj	4ll
(3)-46	IIIe	3jj	4qq
(3)-47	IIIe	3jj	4rr
(3)-48	IIIe	3jj	4ggg
(3)-49	IIIe	3jj	4sss
(3)-50	IIIe	3jj	4www

	(III)	R^3	R^4
(3)-51	IIIf	3qq	4a
(3)-52	IIIf	3rr	4d
(3)-53	IIIf	3ss	4i
(3)-54	IIIf	3tt	4p
(3)-55	IIIf	3uu	4q
(3)-56	IIIf	3ww	4r
(3)-57	IIIf	3xx	4s
(3)-58	IIIf	3yy	4t
(3)-59	IIIf	3zz	4u
(3)-60	IIIf	3aaa	4v
(3)-61	IIIf	3bbb	4w
(3)-62	IIIf	3ccc	4cc
(3)-63	IIIf	3ddd	4dd
(3)-64	IIIf	3eee	4ff
(3)-65	IIIf	3fff	4ll
(3)-66	IIIf	3ggg	4qq
(3)-67	IIIf	3hhh	4rr
(3)-68	IIIf	3iii	4ggg
(3)-69	IIIf	3jjj	4sss
(3)-70	IIIf	3mmm	4www
(3)-71	IIIf	3ppp	4w
(3)-72	IIIf	3sss	4cc
(3)-73	IIIf	3vvv	4dd
(3)-74	IIIi	3qq	4a
(3)-75	IIIi	3rr	4d
(3)-76	IIIi	3ss	4i

	(III)	R^3	R^4
(3)-77	IIIi	3tt	4p
(3)-78	IIIi	3uu	4q
(3)-79	IIIi	3ww	4r
(3)-80	IIIi	3xx	4s
(3)-81	IIIi	3yy	4t
(3)-82	IIIi	3zz	4u
(3)-83	IIIi	3aaa	4v
(3)-84	IIIi	3bbb	4w
(3)-85	IIIi	3ccc	4cc
(3)-86	IIIi	3ddd	4dd
(3)-87	IIIi	3eee	4ff
(3)-88	IIIi	3fff	4ll
(3)-89	IIIi	3ggg	4qq
(3)-90	IIIi	3hhh	4rr
(3)-91	IIIi	3iii	4ggg
(3)-92	IIIi	3jjj	4sss
(3)-93	IIIi	3mmm	4www
(3)-94	IIIi	3ppp	4ff
(3)-95	IIIi	3sss	4ll
(3)-96	IIIi	3vvv	4qq
(3)-97	IIIf	3ddd	4a
(3)-98	IIIf	3ddd	4d
(3)-99	IIIf	3ddd	4i
(3)-100	IIIf	3ddd	4p
(3)-101	IIIf	3ddd	4q
(3)-102	IIIf	3ddd	4r

	(III)	R^3	R^4
(3)-103	IIIf	3ddd	4s
(3)-104	IIIf	3ddd	4t
(3)-105	IIIf	3ddd	4u
(3)-106	IIIf	3ddd	4v
(3)-107	IIIf	3ddd	4w
(3)-108	IIIf	3ddd	4cc
(3)-109	IIIf	3ddd	4dd
(3)-110	IIIf	3ddd	4ff
(3)-111	IIIf	3ddd	4ll
(3)-112	IIIf	3ddd	4qq
(3)-113	IIIf	3ddd	4rr
(3)-114	IIIf	3ddd	4ggg
(3)-115	IIIf	3ddd	4sss
(3)-116	IIIf	3ddd	4www
(3)-117	IIIj	3aaaa	4a
(3)-118	IIIj	3bbbb	4d
(3)-119	IIIj	3cccc	4i
(3)-120	IIIj	3dddd	4p
(3)-121	IIIj	3eeee	4q
(3)-122	IIIj	3aaaa	4r
(3)-123	IIIj	3bbbb	4s
(3)-124	IIIj	3cccc	4t
(3)-125	IIIj	3dddd	4u
(3)-126	IIIj	3eeee	4v
(3)-127	IIIj	3aaaa	4w
(3)-128	IIIj	3bbbb	4cc

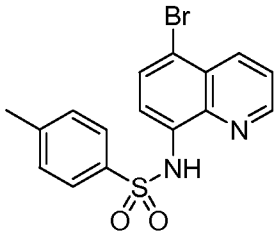
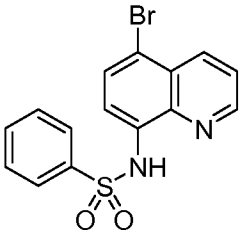
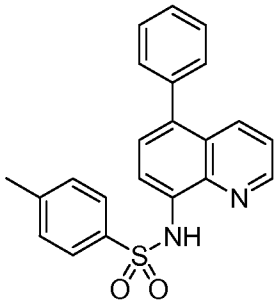
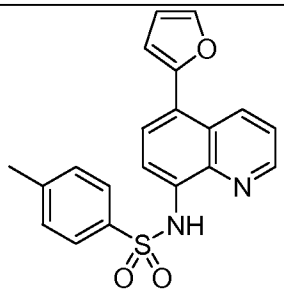
	(III)	R^3	R^4
(3)-129	IIIj	3cccc	4dd
(3)-130	IIIj	3dddd	4ff
(3)-131	IIIj	3eeee	4ll
(3)-132	IIIj	3aaaa	4qq
(3)-133	IIIj	3bbbb	4rr
(3)-134	IIIj	3cccc	4ggg
(3)-135	IIIj	3dddd	4sss
(3)-136	IIIj	3eeee	4www
(3)-137	IIIg	3hhhh	4a
(3)-138	IIIg	3iiii	4d
(3)-139	IIIg	3jjjj	4i
(3)-140	IIIg	3kkkk	4p
(3)-141	IIIg	3llll	4q
(3)-142	IIIg	3nnnn	4r
(3)-143	IIIg	3oooo	4s
(3)-144	IIIg	3pppp	4t
(3)-145	IIIg	3ssss	4u
(3)-146	IIIg	3hhhh	4v
(3)-147	IIIg	3iiii	4w
(3)-148	IIIg	3jjjj	4cc
(3)-149	IIIg	3kkkk	4dd
(3)-150	IIIg	3llll	4ff
(3)-151	IIIg	3nnnn	4ll
(3)-152	IIIg	3oooo	4qq
(3)-153	IIIg	3pppp	4rr
(3)-154	IIIg	3ssss	4ggg

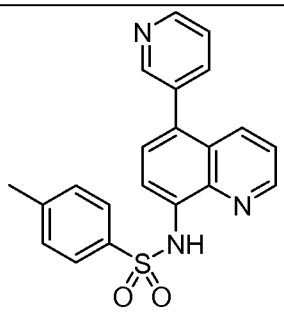
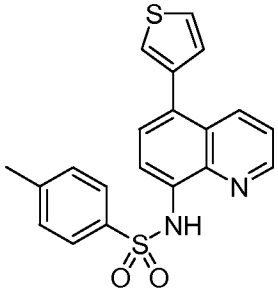
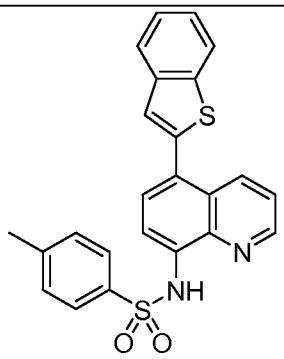
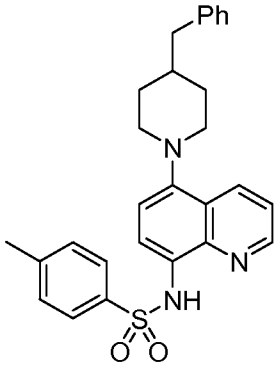
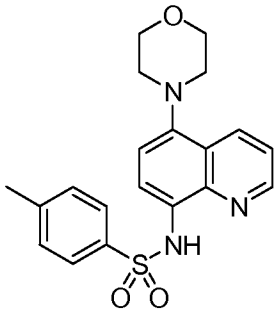
	(III)	R^3	R^4
(3)-155	IIIk	3hhhh	4a
(3)-156	IIIk	3iiii	4d
(3)-157	IIIk	3jjjj	4i
(3)-158	IIIk	3kkkk	4p
(3)-159	IIIk	3llll	4q
(3)-160	IIIk	3nnnn	4r
(3)-161	IIIk	3oooo	4s
(3)-162	IIIk	3pppp	4t
(3)-163	IIIk	3ssss	4u
(3)-164	IIIk	3hhhh	4v
(3)-165	IIIk	3iiii	4w
(3)-166	IIIk	3jjjj	4cc
(3)-167	IIIk	3kkkk	4dd
(3)-168	IIIk	3llll	4ff
(3)-169	IIIk	3nnnn	4ll
(3)-170	IIIk	3oooo	4qq
(3)-171	IIIk	3pppp	4rr
(3)-172	IIIk	3ssss	4ggg
(3)-173	IIIg	3hhhh	4a
(3)-174	IIIg	3hhhh	4d
(3)-175	IIIg	3hhhh	4i
(3)-176	IIIg	3hhhh	4p
(3)-177	IIIg	3hhhh	4q
(3)-178	IIIg	3hhhh	4r
(3)-179	IIIg	3hhhh	4s
(3)-180	IIIg	3hhhh	4t

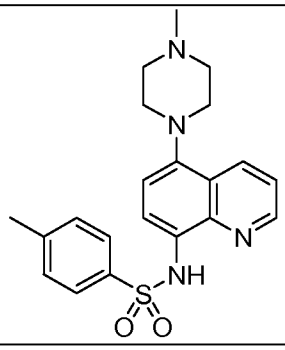
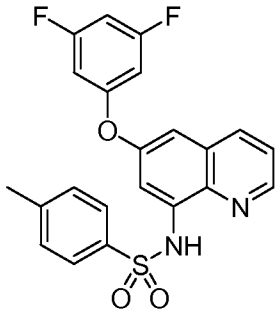
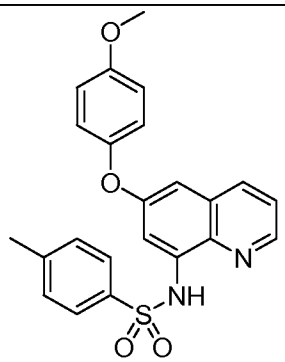
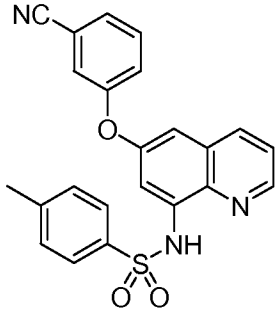
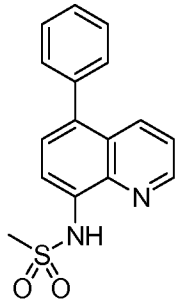
	(III)	R^3	R^4
(3)-181	IIIg	3hhhh	4u
(3)-182	IIIg	3hhhh	4v
(3)-183	IIIg	3hhhh	4w
(3)-184	IIIg	3hhhh	4cc
(3)-185	IIIg	3hhhh	4dd
(3)-186	IIIg	3hhhh	4ff

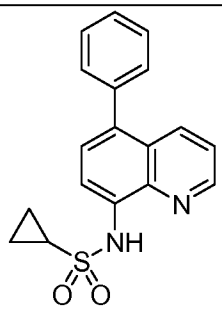
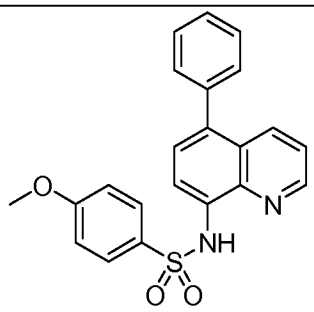
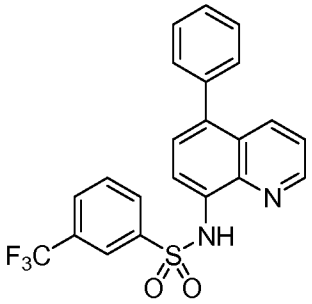
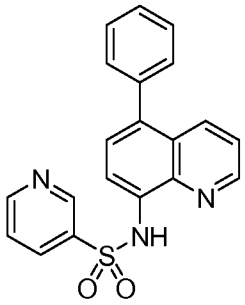
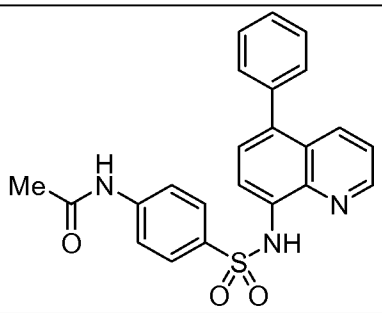
	(III)	R^3	R^4
(3)-187	IIIg	3hhhh	4ll
(3)-188	IIIg	3hhhh	4qq
(3)-189	IIIg	3hhhh	4rr
(3)-190	IIIg	3hhhh	4ggg
(3)-191	IIIg	3hhhh	4sss
(3)-192	IIIg	3hhhh	4www

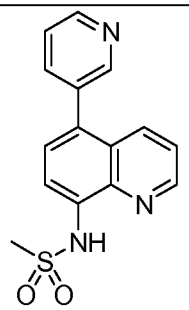
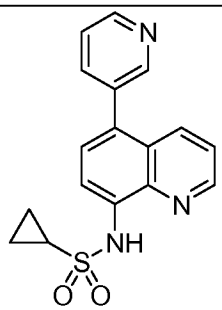
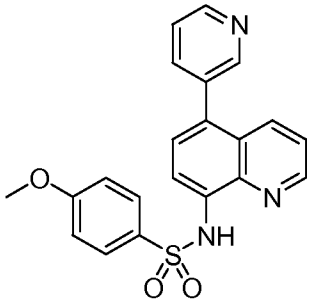
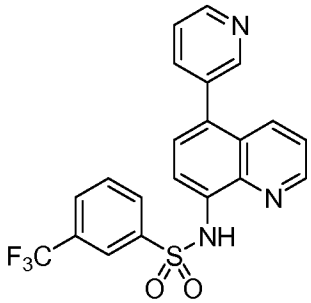
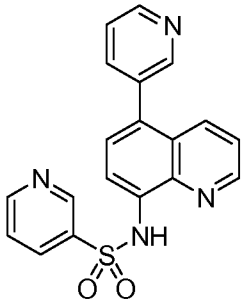
[0038] In some embodiments, the compound of formulae (I), (Ia-k), (II), (IIa-h), (III) or (IIIa-k) is:

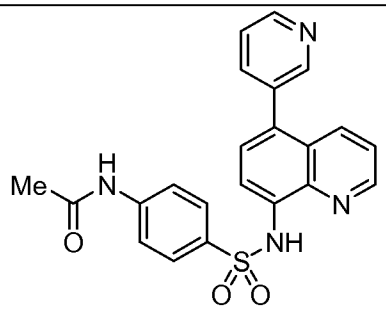
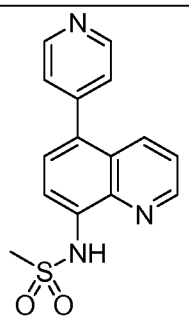
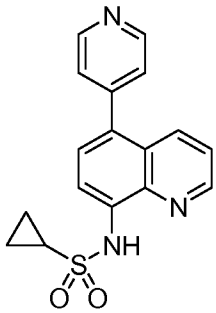
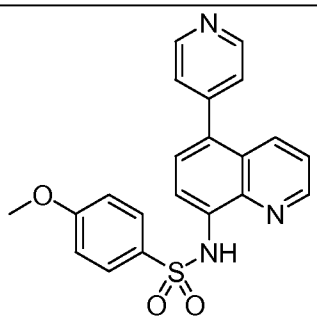
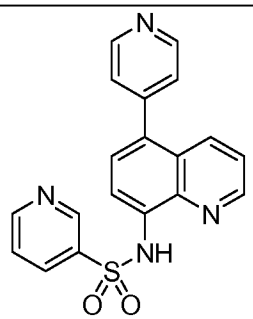
No.	Structure	Name
1		N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
2		N-(5-bromoquinolin-8-yl)benzenesulfonamide
4		4-methyl-N-(5-phenylquinolin-8-yl)benzenesulfonamide
5		N-(5-(furan-2-yl)quinolin-8-yl)-4-methylbenzenesulfonamide

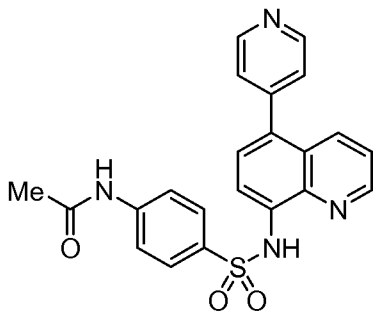
No.	Structure	Name
6		4-methyl-N-(5-(pyridin-3-yl)quinolin-8-yl)benzenesulfonamide
7		4-methyl-N-(5-(thiophen-3-yl)quinolin-8-yl)benzenesulfonamide
8		N-(5-(benzo[b]thiophen-2-yl)quinolin-8-yl)-4-methylbenzenesulfonamide
9		N-(5-(4-benzylpiperidin-1-yl)quinolin-8-yl)-4-methylbenzenesulfonamide
10		4-methyl-N-(5-morpholinoquinolin-8-yl)benzenesulfonamide

No.	Structure	Name
11		4-methyl-N-(5-(4-methylpiperazin-1-yl)quinolin-8-yl)benzenesulfonamide
12		N-(6-(3,5-difluorophenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide
13		N-(6-(4-methoxyphenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide
14		N-(6-(3-cyanophenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide
15		N-(5-phenylquinolin-8-yl)methanesulfonamide

No.	Structure	Name
16		N-(5-phenylquinolin-8-yl)cyclopropanesulfonamide
17		4-methoxy-N-(5-phenylquinolin-8-yl)benzenesulfonamide
18		N-(5-phenylquinolin-8-yl)-3-(trifluoromethyl)benzenesulfonamide
19		N-(5-phenylquinolin-8-yl)pyridine-3-sulfonamide
20		N-(4-(N-(5-phenylquinolin-8-yl)sulfamoyl)phenyl)acetamide

No.	Structure	Name
21		N-(5-(pyridin-3-yl)quinolin-8-yl)methanesulfonamide
22		N-(5-(pyridin-3-yl)quinolin-8-yl)cyclopropanesulfonamide
23		4-methoxy-N-(5-(pyridin-4-yl)quinolin-8-yl)benzenesulfonamide
24		N-(5-(pyridin-3-yl)quinolin-8-yl)-3-(trifluoromethyl)benzenesulfonamide
25		N-(5-(pyridin-3-yl)quinolin-8-yl)pyridine-3-sulfonamide

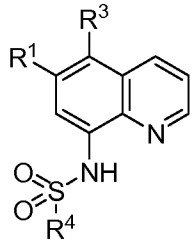
No.	Structure	Name
26		N-(4-(N-(5-(pyridin-3-yl)quinolin-8-yl)sulfamoyl)phenyl)acetamide
27		N-(5-(pyridin-4-yl)quinolin-8-yl)methanesulfonamide
28		N-(5-(pyridin-4-yl)quinolin-8-yl)cyclopropanesulfonamide
29		4-methoxy-N-(5-(pyridin-3-yl)quinolin-8-yl)benzenesulfonamide
30		N-(5-(pyridin-4-yl)quinolin-8-yl)pyridine-3-sulfonamide

No.	Structure	Name
31		N-(4-(N-(5-(pyridin-4-yl)quinolin-8-yl)sulfamoyl)phenyl)acetamide

[0039] In some embodiments, the compound of formulae (I), (Ia-k), (II), (IIa-h), (III) and (IIIa-h) is:

4-methyl-N-(5-phenylquinolin-8-yl)benzenesulfonamide;
N-(5-(furan-2-yl)quinolin-8-yl)-4-methylbenzenesulfonamide;
4-methyl-N-(5-(pyridin-3-yl)quinolin-8-yl)benzenesulfonamide;
4-methyl-N-(5-(thiophen-3-yl)quinolin-8-yl)benzenesulfonamide;
N-(5-(benzo[b]thiophen-2-yl)quinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-(4-benzylpiperidin-1-yl)quinolin-8-yl)-4-methylbenzenesulfonamide;
4-methyl-N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
4-methyl-N-(5-(4-methylpiperazin-1-yl)quinolin-8-yl)benzenesulfonamide;
N-(6-(3,5-difluorophenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide;
N-(6-(4-methoxyphenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide;
N-(6-(3-cyanophenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-phenylquinolin-8-yl)methanesulfonamide;
N-(5-phenylquinolin-8-yl)cyclopropanesulfonamide;
4-methoxy-N-(5-phenylquinolin-8-yl)benzenesulfonamide;
N-(5-phenylquinolin-8-yl)-3-(trifluoromethyl)benzenesulfonamide;
N-(5-phenylquinolin-8-yl)pyridine-3-sulfonamide;
N-(4-(N-(5-phenylquinolin-8-yl)sulfamoyl)phenyl)acetamide;
N-(5-(pyridin-3-yl)quinolin-8-yl)methanesulfonamide;
N-(5-(pyridin-3-yl)quinolin-8-yl)cyclopropanesulfonamide;
4-methoxy-N-(5-(pyridin-4-yl)quinolin-8-yl)benzenesulfonamide;
N-(5-(pyridin-3-yl)quinolin-8-yl)-3-(trifluoromethyl)benzenesulfonamide;
N-(5-(pyridin-3-yl)quinolin-8-yl)pyridine-3-sulfonamide;
N-(4-(N-(5-(pyridin-3-yl)quinolin-8-yl)sulfamoyl)phenyl)acetamide;
N-(5-(pyridin-4-yl)quinolin-8-yl)methanesulfonamide;
N-(5-(pyridin-4-yl)quinolin-8-yl)cyclopropanesulfonamide;
4-methoxy-N-(5-(pyridin-3-yl)quinolin-8-yl)benzenesulfonamide;
N-(5-(pyridin-4-yl)quinolin-8-yl)pyridine-3-sulfonamide; or
N-(4-(N-(5-(pyridin-4-yl)quinolin-8-yl)sulfamoyl)phenyl)acetamide.

[0040] In embodiment IV_1, the invention comprises compounds having structural formula (IV):



(IV)

and pharmaceutically acceptable salts, prodrugs and *N*-oxides thereof, and solvates and hydrates thereof,

wherein

R^1 is -hydrogen or -O-(C_0-C_6 alkyl)-Ar,

R^3 is -hydrogen, -(C_0-C_6 alkyl)-Ar or -(C_0-C_6 alkyl)-Het; and

R^4 is -(C_0-C_6 alkyl)-Ar or -(C_0-C_6 alkyl)-Het;

wherein

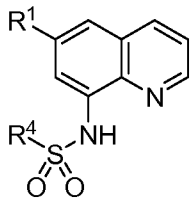
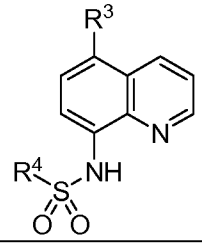
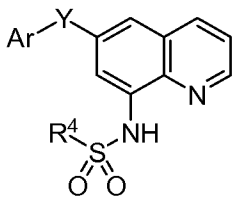
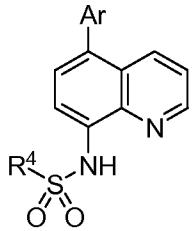
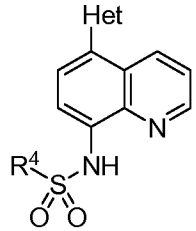
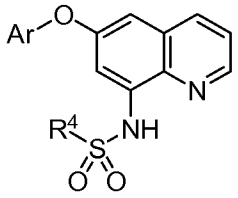
each Ar (aryl) and Het (heteroaryl) is optionally substituted.

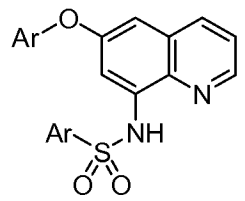
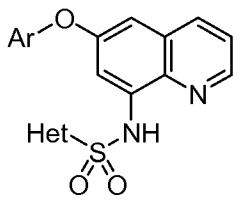
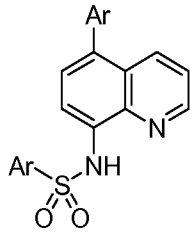
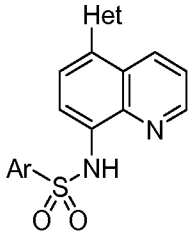
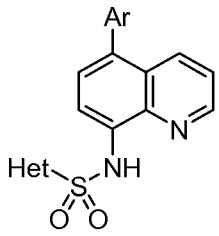
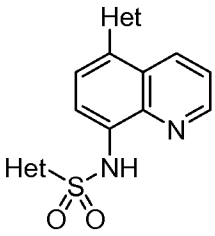
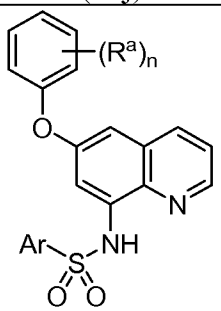
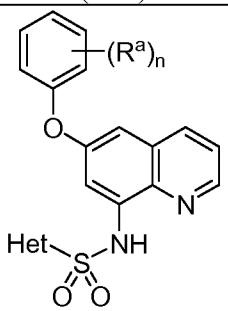
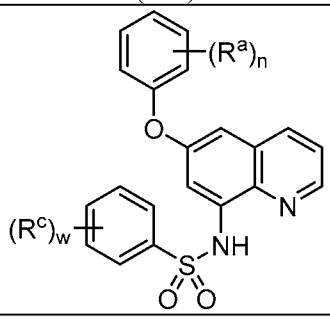
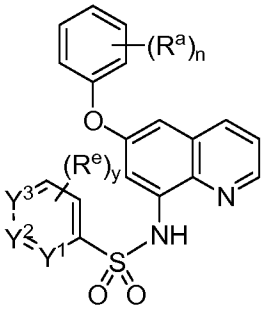
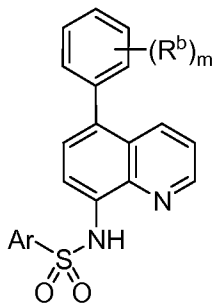
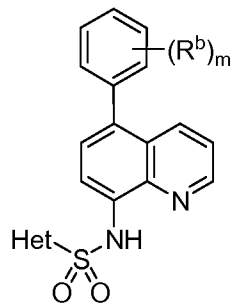
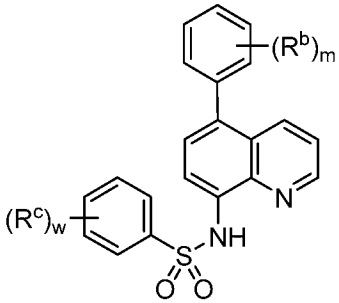
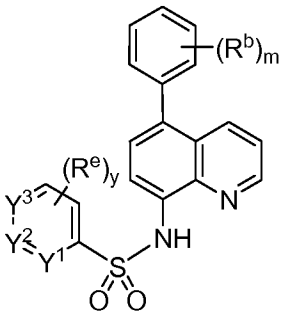
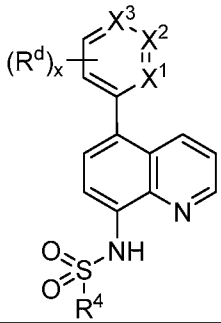
[0041] In embodiment IV_2, the compounds are of embodiment IV_1, provided that:

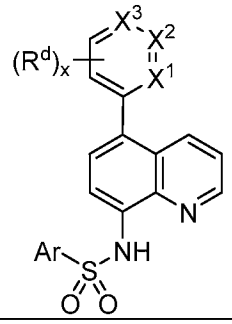
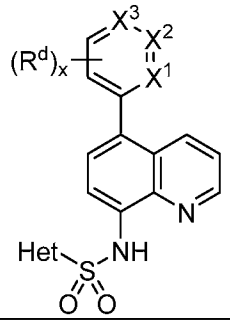
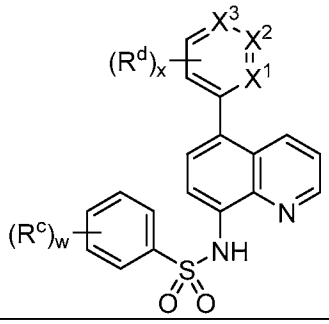
(1) at least one of R^1 and R^3 is not hydrogen; or

(2) neither R^1 nor R^3 is hydrogen.

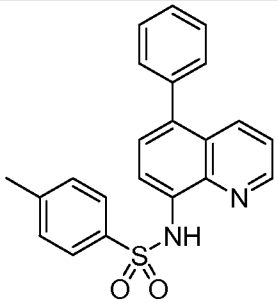
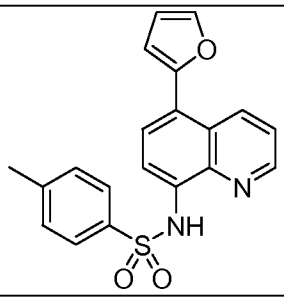
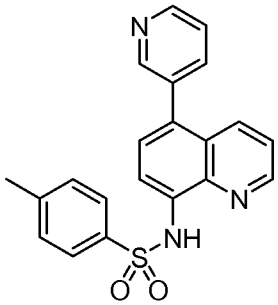
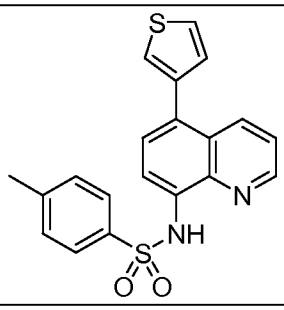
[0042] In embodiment IV_3, the compounds of the invention are of one of formulae (IVa) – (IVx), wherein R^1, R^3, and R^4 are as defined in embodiment IV_1 or IV_2, and R^a, R^b, R^c, R^e n, m, y and w are as defined in any embodiment hereinabove:

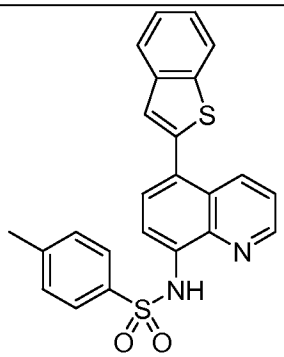
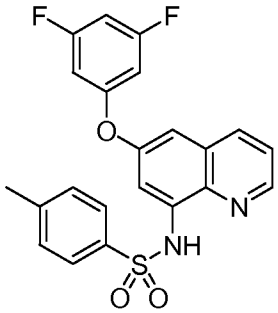
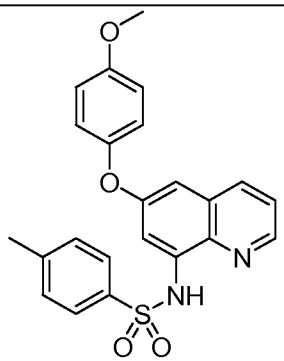
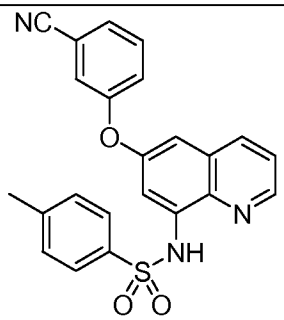
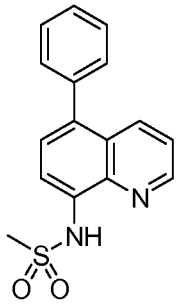
		
(IVa)	(IVb)	(IVc)
		
(IVd)	(IVe)	(IVf)

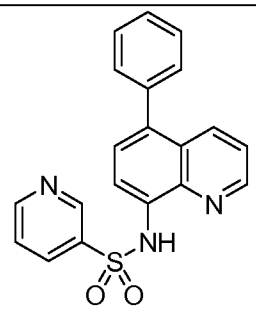
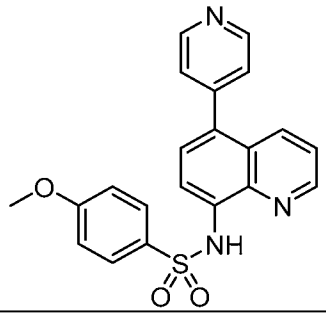
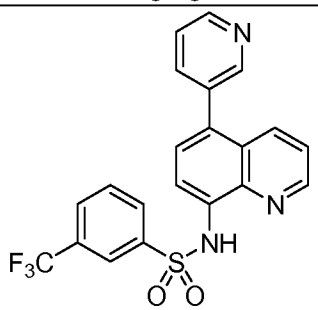
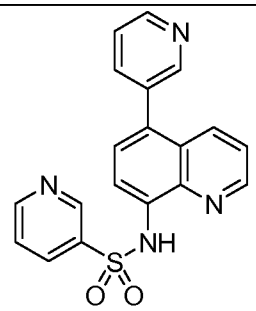
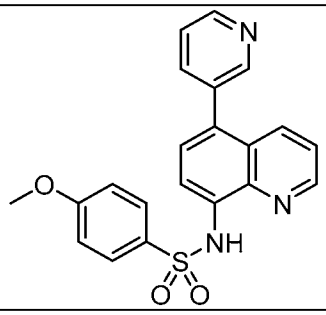
		
(IVg)	(IVh)	(IVi)
		
(IVj)	(IVk)	(IVl)
		
(IVm)	(IVn)	(IVo)
		
(IVp)	(IVq)	(IVr)
		
(IVs)	(IVt)	(IVu)

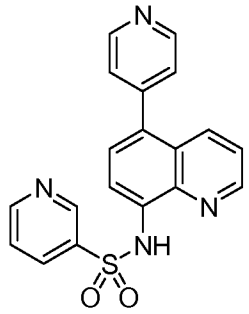
		
(IVv)	(IVw)	(IVx)

[0043] In some embodiments, the compound of formula (IV) is:

No.	Structure	Name
4		4-methyl-N-(5-phenylquinolin-8-yl)benzenesulfonamide
5		N-(5-(furan-2-yl)quinolin-8-yl)-4-methylbenzenesulfonamide
6		4-methyl-N-(5-(pyridin-3-yl)quinolin-8-yl)benzenesulfonamide
7		4-methyl-N-(5-(thiophen-3-yl)quinolin-8-yl)benzenesulfonamide

No.	Structure	Name
8		N-(5-(benzo[b]thiophen-2-yl)quinolin-8-yl)-4-methylbenzenesulfonamide
12		N-(6-(3,5-difluorophenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide
13		N-(6-(4-methoxyphenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide
14		N-(6-(3-cyanophenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide
15		N-(5-phenylquinolin-8-yl)methanesulfonamide

No.	Structure	Name
19		N-(5-phenylquinolin-8-yl)pyridine-3-sulfonamide
23		4-methoxy-N-(5-(pyridin-4-yl)quinolin-8-yl)benzenesulfonamide
24		N-(5-(pyridin-3-yl)quinolin-8-yl)-3-(trifluoromethyl)benzenesulfonamide
25		N-(5-(pyridin-3-yl)quinolin-8-yl)pyridine-3-sulfonamide
29		4-methoxy-N-(5-(pyridin-3-yl)quinolin-8-yl)benzenesulfonamide

No.	Structure	Name
30		N-(5-(pyridin-4-yl)quinolin-8-yl)pyridine-3-sulfonamide

[0044] In another aspect, the present invention comprises pharmaceutical compositions comprising a compound according to any one of the preceding aspects of the invention or any embodiment thereof, together with a pharmaceutically acceptable excipient, diluent, or carrier.

[0045] In another aspect, the invention comprises the use of a compound described by any one of the preceding aspects of the invention or any embodiment thereof, for the preparation of a medicament for the treatment of medical diseases or conditions that benefit from the inhibition of Cks1-Skp2 PPI. Medical conditions contemplated in this aspect include all diseases and conditions described herein.

[0046] In another aspect, the invention comprises methods for treating a disease or condition mediated by or involving Cks1-Skp2 PPI in a subject in need thereof, comprising administering to the subject an effective Cks1-Skp2 PPI inhibiting amount of a compound or a pharmaceutical composition according to any of the preceding aspects of the invention or any embodiment thereof. In some embodiments, the subject is an animal, particularly, a mammal. In some embodiments, the subject is a human.

[0047] In another aspect, the invention comprises methods of inhibiting Cks1-Skp2 PPI in a cell, the method comprising contacting the cell with an effective Cks1-Skp2 PPI inhibiting amount of a compound or a pharmaceutical composition according to any of the preceding aspects of the invention or any embodiment thereof. In some embodiments the cell is an animal cell, such as a mammalian cell. In some embodiments, the cells are human cells.

[0048] In another aspect, the invention comprises methods for inhibiting protein ubiquitination in subjects in need thereof, the method comprising administering an effective ubiquitination-inhibiting amount of a compound preceding aspects of the invention or any

embodiment thereof to the subject. In some embodiments, the subject is an animal, particularly, a mammal. In some embodiments, the subject is a human.

[0049] In another aspect, the invention comprises methods for treating a disease or condition mediated by or involving protein ubiquitination in a subject in need thereof, comprising administering an effective ubiquitination-inhibiting amount of a compound or a pharmaceutical composition according to any of the preceding aspects of the invention or any embodiment thereof.

[0050] In another aspect, the invention comprises methods of inhibiting protein ubiquitination in a cell, comprising contacting the cell in which inhibition of ubiquitination is desired with an effective ubiquitination-inhibiting amount of a compound or a pharmaceutical composition according to any of the preceding aspects of the invention or any embodiment thereof. In some embodiments the cell is an animal cell, such as a mammalian cell. In some embodiments, the cells are human cells.

[0051] In another aspect, the invention comprises methods for treating a disease or condition mediated by increasing p27 levels in a subject in need thereof, comprising administering an effective p27-increasing amount of a compound or a pharmaceutical composition according to any of the preceding aspects of the invention or any embodiment thereof. In some embodiments, the subject is an animal, particularly, a mammal. In some embodiments, the subject is a human.

[0052] In another aspect, the invention comprises methods of increasing p27 levels in a cell, comprising contacting the cell in which increased levels of p27 is desired with an effective p27-increasing amount of a compound or a pharmaceutical composition according to any of the preceding aspects of the invention or any embodiment thereof. In some embodiments the cell is an animal cell, such as a mammalian cell. In some embodiments, the cells are human cells.

[0053] In an embodiment of any of the above aspects, the condition or disease involves a process selected from the group consisting of inflammation, adaptive immunity, innate immunity, bone metabolism, LPS-induced angiogenesis, osteoporosis, osteopinneal diseases, lymph node development, mammary gland development, skin development, and central nervous system development.

[0054] In an embodiment of any of the above aspects, the disease or medical condition is cancer.

[0055] In some embodiments, the cancer is colon, pancreas, breast, prostate, lung, brain, ovary, cervix, testes, renal, head, or neck cancer, or lymphoma, leukemia, or melanoma.

Definitions

[0056] Terms used herein may be preceded and/or followed by a single dash, "-", or a double dash, "=", to indicate the bond order of the bond between the named substituent and its parent moiety; a single dash indicates a single bond and a double dash indicates a double bond or a pair of single bonds in the case of a spiro-substituent. In the absence of a single or double dash it is understood that a single bond is formed between the substituent and its parent moiety; further, substituents are intended to be read "left to right" unless a dash indicates otherwise. For example, arylalkyl, arylalkyl-, and –alkylaryl indicate the same functionality.

[0057] For simplicity, chemical moieties are defined and referred to throughout primarily as univalent chemical moieties (*e.g.*, alkyl, aryl, etc.). Nevertheless, such terms are also used to convey corresponding multivalent moieties under the appropriate structural circumstances clear to those skilled in the art. For example, while an "alkyl" moiety can refer to a monovalent radical (*e.g.* CH_3-CH_2-), in some circumstances a bivalent linking moiety can be "alkyl," in which case those skilled in the art will understand the alkyl to be a divalent radical (*e.g.*, -CH_2-CH_2-), which is equivalent to the term "alkylene." (Similarly, in circumstances in which a divalent moiety is required and is stated as being "aryl," those skilled in the art will understand that the term "aryl" refers to the corresponding divalent moiety, arylene). All atoms are understood to have their normal number of valences for bond formation (*i.e.*, 4 for carbon, 3 for N, 2 for O, and 2, 4, or 6 for S, depending on the oxidation state of the S). Nitrogens in the presently disclosed compounds can be hypervalent, e.g., an N-oxide or tetrasubstituted ammonium salt. On occasion a moiety may be defined, for example, as $(A)_a$-B-, wherein a is 0 or 1. In such instances, when a is 0 the moiety is B- and when a is 1 the moiety is A-B-.

[0058] As used herein, the term "alkyl" includes alkyl, alkenyl and alkynyl groups of a designed number of carbon atoms, such as 1 to 12 carbons (i.e., inclusive of 1 and 12), 1 to 6 carbons, 1 to 3 carbons, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12. The term "C_m-C_n alkyl" means an alkyl group having from m to n carbon atoms (i.e., inclusive of m and n). The term "C_m-C_n alkyl" means an alkyl group having from m to n carbon atoms. For example, "C_1-C_6 alkyl" is an alkyl group having from one to six carbon atoms. Alkyl and alkyl

groups may be straight or branched and depending on context, may be a monovalent radical or a divalent radical (i.e., an alkylene group). In the case of an alkyl or alkyl group having zero carbon atoms (i.e., "C_0 alkyl"), the group is simply a single covalent bond if it is a divalent radical or is a hydrogen atom if it is a monovalent radical. For example, the moiety "-(C_0-C_6 alkyl)-Ar" signifies connection of an optionally substituted aryl through a single bond or an alkylene bridge having from 1 to 6 carbons. Examples of "alkyl" include, for example, methyl, ethyl, propyl, isopropyl, butyl, iso-, sec- and tert-butyl, pentyl, hexyl, heptyl, 3-ethylbutyl, 3-hexenyl and propargyl. If the number of carbon atoms is not specified, the subject "alkyl" or "alkyl" moiety has from 1 to 12 carbons.

[0059] The term "haloalkyl" is an alkyl group substituted with one or more halogen atoms, e.g. F, Cl, Br and I. A more specific term, e.g., "fluoroalkyl" is an alkyl group substituted with one or more fluorine atoms. Examples of "fluoroalkyl" include fluoromethyl, difluoromethyl, trifluoromethyl, pentafluoroethyl, hexafluoroisopropyl and the like. In certain embodiments of the compounds disclosed herein, each haloalkyl is a fluoroalkyl.

[0060] The term "aryl" represents an aromatic ring system having a single ring (e.g., phenyl) which is optionally fused to other aromatic hydrocarbon rings or non-aromatic hydrocarbon rings. "Aryl" includes ring systems having multiple condensed rings and in which at least one is carbocyclic and aromatic, (e.g., 1,2,3,4-tetrahydronaphthyl, naphthyl). Examples of aryl groups include phenyl, 1-naphthyl, 2-naphthyl, indanyl, indenyl, dihydronaphthyl, fluorenyl, tetralinyl, and 6,7,8,9-tetrahydro-5*H*-benzo[a]cycloheptenyl. In certain examples, aryl groups include those having a first carbocyclic, aromatic ring fused to an aromatic or aliphatic heterocycle, for example, 2,3-dihydrobenzofuranyl.. The aryl groups herein are unsubstituted or, when specified as "optionally substituted", can unless stated otherwise be substituted in one or more substitutable positions with various groups, as described below.

[0061] The term "heteroaryl" refers to an aromatic ring system containing at least one heteroatom selected from nitrogen, oxygen and sulfur in an aromatic ring. The heteroaryl may be fused to one or more cycloalkyl or heterocycloalkyl rings. Examples of heteroaryl groups include, for example, pyridyl, pyrimidinyl, quinolinyl, benzothienyl, indolyl, indolinyl, pyridazinyl, pyrazinyl, isoindolyl, isoquinolyl, quinazolinyl, quinoxalinyl, phthalazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, indolizinyl, indazolyl, benzothiazolyl, benzimidazolyl, benzofuranyl, furanyl, thienyl, pyrrolyl, oxadiazolyl,

thiadiazolyl, benzo[1,4]oxazinyl, triazolyl, tetrazolyl, isothiazolyl, naphthyridinyl, isochromanyl, chromanyl, tetrahydroisoquinolinyl, isoindolinyl, isobenzotetrahydrofuranyl, isobenzotetrahydrothienyl, isobenzothienyl, benzoxazolyl, pyridopyridinyl, benzotetrahydrofuranyl, benzotetrahydrothienyl, purinyl, benzodioxolyl, triazinyl, pteridinyl, benzothiazolyl, imidazopyridinyl, imidazothiazolyl, dihydrobenzisoxazinyl, benzisoxazinyl, benzoxazinyl, dihydrobenzisothiazinyl, benzopyranyl, benzothiopyranyl, chromonyl, chromanonyl, pyridinyl-*N*-oxide, tetrahydroquinolinyl, dihydroquinolinyl, dihydroquinolinonyl, dihydroisoquinolinonyl, dihydrocoumarinyl, dihydroisocoumarinyl, isoindolinonyl, benzodioxanyl, benzoxazolinonyl, pyrrolyl *N*-oxide, pyrimidinyl *N*-oxide, pyridazinyl *N*-oxide, pyrazinyl *N*-oxide, quinolinyl *N*-oxide, indolyl *N*-oxide, indolinyl *N*-oxide, isoquinolyl *N*-oxide, quinazolinyl *N*-oxide, quinoxalinyl *N*-oxide, phthalazinyl *N*-oxide, imidazolyl *N*-oxide, isoxazolyl *N*-oxide, oxazolyl *N*-oxide, thiazolyl *N*-oxide, indolizinyl *N*-oxide, indazolyl *N*-oxide, benzothiazolyl *N*-oxide, benzimidazolyl *N*-oxide, pyrrolyl *N*-oxide, oxadiazolyl *N*-oxide, thiadiazolyl *N*-oxide, triazolyl *N*-oxide, tetrazolyl *N*-oxide, benzothiopyranyl S-oxide, benzothiopyranyl S,S-dioxide. Preferred heteroaryl groups include pyridyl, pyrimidyl, quinolinyl, indolyl, pyrrolyl, furanyl, thienyl and imidazolyl, pyrazolyl, indazolyl, thiazolyl and benzothiazolyl. In certain embodiments, each heteroaryl is selected from pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, imidazolyl, isoxazolyl, pyrazolyl, oxazolyl, thiazolyl, furanyl, thienyl, pyrrolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, isothiazolyl, pyridinyl-*N*-oxide, pyrrolyl *N*-oxide, pyrimidinyl *N*-oxide, pyridazinyl *N*-oxide, pyrazinyl *N*-oxide, imidazolyl *N*-oxide, isoxazolyl *N*-oxide, oxazolyl *N*-oxide, thiazolyl *N*-oxide, pyrrolyl *N*-oxide, oxadiazolyl *N*-oxide, thiadiazolyl *N*-oxide, triazolyl *N*-oxide, and tetrazolyl *N*-oxide. Preferred heteroaryl groups include pyridyl, pyrimidyl, quinolinyl, indolyl, pyrrolyl, furanyl, thienyl, imidazolyl, pyrazolyl, indazolyl, thiazolyl and benzothiazolyl. The heteroaryl groups herein are unsubstituted or, when specified as "optionally substituted", can unless stated otherwise be substituted in one or more substitutable positions with various groups, as described below.

[0062] The term "heterocycloalkyl" refers to a non-aromatic ring or ring system containing at least one heteroatom that is preferably selected from nitrogen, oxygen and sulfur, wherein said heteroatom is in a non-aromatic ring. The heterocycloalkyl may be saturated (i.e., a heterocycloalkyl) or partially unsaturated (i.e., a heterocycloalkenyl). Heterocycloalkyl includes monocyclic groups as well as bicyclic and polycyclic ring systems, including bridged and fused systems. The heterocycloalkyl ring is optionally fused

to other heterocycloalkyl rings and/or non-aromatic hydrocarbon rings and/or phenyl rings. In certain embodiments, the heterocycloalkyl groups have from 3 to 7 members in a single ring. In other embodiments, heterocycloalkyl groups have 5 or 6 members in a single ring. In some embodiments, the heterocycloalkyl groups have 3, 4, 5, 6 or 7 members in a single ring. Examples of heterocycloalkyl groups include, for example, azabicyclo[2.2.2]octyl (in each case also "quinuclidinyl" or a quinuclidine derivative), azabicyclo[3.2.1]octyl, 2,5-diazabicyclo[2.2.1]heptyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S,S-dioxide, 2-oxazolidonyl, piperazinyl, homopiperazinyl, piperazinonyl, pyrrolidinyl, azepanyl, azetidinyl, pyrrolinyl, tetrahydropyranyl, piperidinyl, tetrahydrofuranyl, tetrahydrothienyl, 3,4-dihydroisoquinolin-2(1*H*)-yl, isoindolindionyl, homopiperidinyl, homomorpholinyl, homothiomorpholinyl, homothiomorpholinyl S,S-dioxide, oxazolidinonyl, dihydropyrazolyl, dihydropyrrolyl, dihydropyrazinyl, dihydropyridinyl, dihydropyrimidinyl, dihydrofuryl, dihydropyranyl, imidazolidonyl, tetrahydrothienyl S-oxide, tetrahydrothienyl S,S-dioxide and homothiomorpholinyl S-oxide. Especially desirable heterocycloalkyl groups include morpholinyl, 3,4-dihydroisoquinolin-2(1*H*)-yl, tetrahydropyranyl, piperidinyl, aza-bicyclo[2.2.2]octyl, γ-butyrolactonyl (i.e., an oxo-substituted tetrahydrofuranyl), γ-butryolactamyl (i.e., an oxo-substituted pyrrolidine), pyrrolidinyl, piperazinyl, azepanyl, azetidinyl, thiomorpholinyl, thiomorpholinyl S,S-dioxide, 2-oxazolidonyl, imidazolidonyl, isoindolindionyl, piperazinonyl. The heterocycloalkyl groups herein are unsubstituted or, when specified as "optionally substituted", can unless stated otherwise be substituted in one or more substitutable positions with various groups, as described below.

[0063] The term "cycloalkyl" refers to a non-aromatic carbocyclic ring or ring system, which may be saturated (i.e., a cycloalkyl) or partially unsaturated (i.e., a cycloalkenyl). The cycloalkyl ring optionally fused to or otherwise attached (e.g., bridged systems) to other cycloalkyl rings. Certain examples of cycloalkyl groups present in the disclosed compounds have from 3 to 7 members in a single ring, such as having 5 or 6 members in a single ring. In some embodiments, the cycloalkyl groups have 3, 4, 5, 6 or 7 members in a single ring. Examples of cycloalkyl groups include, for example, cyclohexyl, cyclopentyl, cyclobutyl, cyclopropyl, tetrahydronaphthyl and bicyclo[2.2.1]heptane. The cycloalkyl groups herein are unsubstituted or, when specified as "optionally substituted", may be substituted in one or more substitutable positions with various groups.

[0064] The term “ring system” encompasses monocycles, as well as fused and/or bridged polycycles.

[0065] The term "oxa" means a divalent oxygen radical in a chain, sometimes designated as -O-.

[0066] The term "oxo" means a doubly bonded oxygen, sometimes designated as =O or for example in describing a carbonyl "C(O)" may be used to show an oxo substituted carbon.

[0067] The term “electron withdrawing group” means a group that withdraws electron density from the structure to which it is attached than would a similarly-attached hydrogen atom. For example, electron withdrawing groups can be selected from the group consisting of halo (*e.g.*, fluoro, chloro, bromo, and iodo), cyano, -(C_1-C_4 fluoroalkyl), -O-(C_1-C_4 fluoroalkyl), -C(O)-(C_0-C_4 alkyl), -C(O)O-(C_0-C_4 alkyl), -C(O)N(C_0-C_4 alkyl)(C_0-C_4 alkyl), -$S(O)_2$O-(C_0-C_4 alkyl), NO_2 and -C(O)-Hca in which the Hca includes a nitrogen atom to which the -C(O)- is bound, in which no alkyl, fluoroalkyl or heterocycloalkyl is substituted with an aryl, heteroaryl, cycloalkyl or heterocycloalkyl-containing group.

[0068] The term “substituted,” when used to modify a specified group or radical, means that one or more hydrogen atoms of the specified group or radical are each, independently of one another, replaced with the same or different substituent groups as defined below, unless specified otherwise.

[0069] Substituent groups for substituting for hydrogens on saturated carbon atoms in the specified group or radical are, unless otherwise specified, -R^{60}, halo, -O^-M^+, =O, -OR^{70}, -SR^{70}, -S^-M^+, =S, -$NR^{80}R^{80}$, =NR^{70}, =N-OR^{70}, trihalomethyl, -CF_3, -CN, -OCN, -SCN, -NO, -NO_2, =N_2, -N_3, -SO_2R^{70}, -$SO_2O^-M^+$, -SO_2OR^{70}, -OSO_2R^{70}, -$OSO_2O^-M^+$, -OSO_2OR^{70}, -$P(O)(O^-)_2(M^+)_2$, -$P(O)(OR^{70})O^-M^+$, -$P(O)(OR^{70})_2$, -$C(O)R^{70}$, -$C(S)R^{70}$, -$C(NR^{70})R^{70}$, -$C(O)O^-M^+$, -$C(O)OR^{70}$, -$C(S)OR^{70}$, -$C(O)NR^{80}R^{80}$, -$C(NR^{70})NR^{80}R^{80}$, -$OC(O)R^{70}$, -$OC(S)R^{70}$, -$OC(O)O^-M^+$, -$OC(O)OR^{70}$, -$OC(S)OR^{70}$, -$NR^{70}C(O)R^{70}$, -$NR^{70}C(S)R^{70}$, -$NR^{70}CO_2^-M^+$, -$NR^{70}CO_2R^{70}$, -$NR^{70}C(S)OR^{70}$, -$NR^{70}C(O)NR^{80}R^{80}$, -$NR^{70}C(NR^{70})R^{70}$ and -$NR^{70}C(NR^{70})NR^{80}R^{80}$. Each R^{60} is independently selected from the group consisting of alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl, each of which is optionally substituted with 1, 2, 3, 4 or 5 groups selected from the group consisting of halo, -O^-M^+, =O, -OR^{71}, -SR^{71}, -S^-M^+, =S, -$NR^{81}R^{81}$, =NR^{71}, =N-OR^{71},

trihalomethyl, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-SO_2R^{71}$, $-SO_2O^-M^+$, $-SO_2OR^{71}$, $-OSO_2R^{71}$, $-OSO_2O^-M^+$, $-OSO_2OR^{71}$, $-P(O)(O^-)_2(M^+)_2$, $-P(O)(OR^{71})O^-M^+$, $-P(O)(OR^{71})_2$, $-C(O)R^{71}$, $-C(S)R^{71}$, $-C(NR^{71})R^{71}$, $-C(O)O^-M^+$, $-C(O)OR^{71}$, $-C(S)OR^{71}$, $-C(O)NR^{81}R^{81}$, $-C(NR^{71})NR^{81}R^{81}$, $-OC(O)R^{71}$, $-OC(S)R^{71}$, $-OC(O)O^-M^+$, $-OC(O)OR^{71}$, $-OC(S)OR^{71}$, $-NR^{71}C(O)R^{71}$, $-NR^{71}C(S)R^{71}$, $-NR^{71}CO_2^-M^+$, $-NR^{71}CO_2R^{71}$, $-NR^{71}C(S)OR^{71}$, $-NR^{71}C(O)NR^{81}R^{81}$, $-NR^{71}C(NR^{71})R^{71}$ and $-NR^{71}C(NR^{71})NR^{81}R^{81}$. Each R^{70} is independently hydrogen or R^{60}; each R^{80} is independently R^{70} or alternatively, two $R^{80'}$s, taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered heterocycloalkyl which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S, of which N may have -H or C_1-C_3 alkyl substitution; and each M^+ is a counter ion with a net single positive charge. Each R^{71} is independently hydrogen or R^{61}, in which R^{61} is alkyl, heteroalkyl, cycloalkyl, heterocycloalkyl, heterocycloalkylalkyl, cycloalkylalkyl, aryl, arylalkyl, heteroaryl and heteroarylalkyl, each of which is optionally substituted with 1, 2, 3, 4 or 5 groups selected from the group consisting of halo, $-O^-M^+$, =O, $-OR^{72}$, $-SR^{72}$, $-S^-M^+$, =S, $-NR^{82}R^{82}$, $=NR^{72}$, $=N-OR^{72}$, trihalomethyl, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $=N_2$, $-N_3$, $-SO_2R^{71}$, $-SO_2O^-M^+$, $-SO_2OR^{72}$, $-OSO_2R^{72}$, $-OSO_2O^-M^+$, $-OSO_2OR^{72}$, $-P(O)(O^-)_2(M^+)_2$, $-P(O)(OR^{72})O^-M^+$, $-P(O)(OR^{72})_2$, $-C(O)R^{72}$, $-C(S)R^{72}$, $-C(NR^{72})R^{72}$, $-C(O)O^-M^+$, $-C(O)OR^{72}$, $-C(S)OR^{72}$, $-C(O)NR^{82}R^{82}$, $-C(NR^{72})NR^{82}R^{82}$, $-OC(O)R^{72}$, $-OC(S)R^{72}$, $-OC(O)O^-M^+$, $-OC(O)OR^{72}$, $-OC(S)OR^{72}$, $-NR^{72}C(O)R^{72}$, $-NR^{72}C(S)R^{72}$, $-NR^{72}CO_2^-M^+$, $-NR^{72}CO_2R^{72}$, $-NR^{72}C(S)OR^{72}$, $-NR^{72}C(O)NR^{82}R^{82}$, $-NR^{72}C(NR^{72})R^{72}$ and $-NR^{72}C(NR^{72})NR^{82}R^{82}$; and each R^{81} is independently R^{71} or alternatively, two R^{81}s, taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered heterocycloalkyl which may optionally include from 1 to 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S, of which N may have -H or C_1-C_3 alkyl substitution. Each R^{72} is independently hydrogen, (C_1-C_6 alkyl) or (C_1-C_6 fluoroalkyl); each R^{82} is independently R^{72} or alternatively, two R^{82}s, taken together with the nitrogen atom to which they are bonded, form a 5-, 6- or 7-membered heterocycloalkyl which may optionally include 1, 2, 3 or 4 of the same or different additional heteroatoms selected from the group consisting of O, N and S, of which N may have -H or C_1-C_3 alkyl substitution. Each M^+ may independently be, for example, an alkali ion, such as K^+, Na^+, Li^+; an ammonium ion, such as $^+N(R^{60})_4$; or an alkaline earth ion, such

as $[Ca^{2+}]_{0.5}$, $[Mg^{2+}]_{0.5}$, or $[Ba^{2+}]_{0.5}$ ("subscript 0.5 means e.g. that one of the counter ions for such divalent alkali earth ions can be an ionized form of a presently disclosed compound and the other a typical counter ion such as chloride, or two ionized presently disclosed molecules can serve as counter ions for such divalent alkali earth ions, or a doubly ionized compound can serve as the counter ion for such divalent alkali earth ions). As specific examples, $-NR^{80}R^{80}$ is meant to include $-NH_2$, -NH-alkyl, *N*-pyrrolidinyl, *N*-piperazinyl, 4-methyl-piperazin-1-yl and *N*-morpholinyl.

[0070] Substituent groups for hydrogens on unsaturated carbon atoms in "substituted" alkene, alkyne, aryl and heteroaryl groups are, unless otherwise specified, $-R^{60}$, halo, $-O^-M^+$, $-OR^{70}$, $-SR^{70}$, $-S^-M^+$, $-NR^{80}R^{80}$, trihalomethyl, $-CF_3$, -CN, -OCN, -SCN, -NO, $-NO_2$, $-N_3$, $-SO_2R^{70}$, $-SO_3^-M^+$, $-SO_3R^{70}$, $-OSO_2R^{70}$, $-OSO_3^-M^+$, $-OSO_3R^{70}$, $-PO_3^{-2}(M^+)_2$, $-P(O)(OR^{70})O^-M^+$, $-P(O)(OR^{70})_2$, $-C(O)R^{70}$, $-C(S)R^{70}$, $-C(NR^{70})R^{70}$, $-CO_2^-M^+$, $-CO_2R^{70}$, $-C(S)OR^{70}$, $-C(O)NR^{80}R^{80}$, $-C(NR^{70})NR^{80}R^{80}$, $-OC(O)R^{70}$, $-OC(S)R^{70}$, $-OCO_2^-M^+$, $-OCO_2R^{70}$, $-OC(S)OR^{70}$, $-NR^{70}C(O)R^{70}$, $-NR^{70}C(S)R^{70}$, $-NR^{70}CO_2^-M^+$, $-NR^{70}CO_2R^{70}$, $-NR^{70}C(S)OR^{70}$, $-NR^{70}C(O)NR^{80}R^{80}$, $-NR^{70}C(NR^{70})R^{70}$ and $-NR^{70}C(NR^{70})NR^{80}R^{80}$, where R^{60}, R^{70}, R^{80} and M^+ are as previously defined.

[0071] Substituent groups for hydrogens on nitrogen atoms in "substituted" heteroalkyl and heterocycloalkyl groups are, unless otherwise specified, $-R^{60}$, $-O^-M^+$, $-OR^{70}$, $-SR^{70}$, $-S^-M^+$, $-NR^{80}R^{80}$, trihalomethyl, $-CF_3$, -CN, -NO, $-NO_2$, $-S(O)_2R^{70}$, $-S(O)_2O^-M^+$, $-S(O)_2OR^{70}$, $-OS(O)_2R^{70}$, $-OS(O)_2O^-M^+$, $-OS(O)_2OR^{70}$, $-P(O)(O^-)_2(M^+)_2$, $-P(O)(OR^{70})O^-M^+$, $-P(O)(OR^{70})(OR^{70})$, $-C(O)R^{70}$, $-C(S)R^{70}$, $-C(NR^{70})R^{70}$, $-C(O)OR^{70}$, $-C(S)OR^{70}$, $-C(O)NR^{80}R^{80}$, $-C(NR^{70})NR^{80}R^{80}$, $-OC(O)R^{70}$, $-OC(S)R^{70}$, $-OC(O)OR^{70}$, $-OC(S)OR^{70}$, $-NR^{70}C(O)R^{70}$, $-NR^{70}C(S)R^{70}$, $-NR^{70}C(O)OR^{70}$, $-NR^{70}C(S)OR^{70}$, $-NR^{70}C(O)NR^{80}R^{80}$, $-NR^{70}C(NR^{70})R^{70}$ and $-NR^{70}C(NR^{70})NR^{80}R^{80}$, where R^{60}, R^{70}, R^{80} and M^+ are as previously defined.

[0072] In certain embodiments of the compounds disclosed herein, a group that is substituted has 1, 2, 3, or 4 substituents, 1, 2, or 3 substituents, 1 or 2 substituents, or 1 substituent.

[0073] In certain preferred embodiments, substituent groups on "substituted" alkyl, cycloalkyl, heterocycloalkyl, aryl and heteroaryl groups are -halo, -OH, -O-(C_1-C_4 alkyl), -O-(C_1-C_4 haloalkyl), -N(C_0-C_4 alkyl)(C_0-C_4 alkyl), -SH, -S(O)$_{0\text{-}2}$-(C_1-C_4

alkyl), -(C_1-C_4 alkyl), -(C_1-C_4 haloalkyl), -C(O)-(C_0-C_4 alkyl), -C(O)N(C_0-C_4 alkyl)(C_0-C_4 alkyl), -N(C_0-C_4 alkyl)C(O)(C_0-C_4 alkyl)(C_0-C_4 alkyl), -C(O)O-(C_0-C_4 alkyl), -OC(O)-(C_0-C_4 alkyl), $S(O)_2$-O(C_0-C_4 alkyl), and -NO_2, in which no alkyl is further substituted.

[0074] The compounds disclosed herein can also be provided as pharmaceutically acceptable salts. The term "pharmaceutically acceptable salts" or "a pharmaceutically acceptable salt thereof" refer to salts prepared from pharmaceutically acceptable non-toxic acids or bases including inorganic acids and bases and organic acids and bases. If the compound is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids. Such salts may be, for example, acid addition salts of at least one of the following acids: benzenesulfonic acid, citric acid, α-glucoheptonic acid, D-gluconic acid, glycolic acid, lactic acid, malic acid, malonic acid, mandelic acid, phosphoric acid, propanoic acid, succinic acid, sulfuric acid, tartaric acid (d, l, or dl), tosic acid (toluenesulfonic acid), valeric acid, palmitic acid, pamoic acid, sebacic acid, stearic acid, lauric acid, acetic acid, adipic acid, carbonic acid, 4-chlorobenzenesulfonic acid, ethanedisulfonic acid, ethylsuccinic acid, fumaric acid, galactaric acid (mucic acid), D-glucuronic acid, 2-oxo-glutaric acid, glycerophosphoric acid, hippuric acid, isethionic acid (ethanolsulfonic acid), lactobionic acid, maleic acid, 1,5-naphthalene-disulfonic acid, 2-naphthalene-sulfonic acid, pivalic acid, terephthalic acid, thiocyanic acid, cholic acid, n-dodecyl sulfate, 3-hydroxy-2-naphthoic acid, 1-hydroxy-2-naphthoic acid, oleic acid, undecylenic acid, ascorbic acid, (+)-camphoric acid, d-camphorsulfonic acid, dichloroacetic acid, ethanesulfonic acid, formic acid, hydriodic acid, hydrobromic acid, hydrochloric acid, methanesulfonic acid, nicotinic acid, nitric acid, orotic acid, oxalic acid, picric acid, L-pyroglutamic acid, saccharine, salicylic acid, gentisic acid, and/or 4-acetamidobenzoic acid.

[0075] The compounds described herein can also be provided in prodrug form. “Prodrug” refers to a derivative of an active compound (drug) that undergoes a transformation under the conditions of use, such as within the body, to release the active drug. Prodrugs are frequently, but not necessarily, pharmacologically inactive until converted into the active drug. Prodrugs are typically obtained by masking a functional group in the drug believed to be in part required for activity with a progroup (defined below) to form a promoiety which undergoes a transformation, such as cleavage, under the specified conditions of use to release the functional group, and hence the active drug. The cleavage of the promoiety can proceed spontaneously, such as by way of a hydrolysis

reaction, or it can be catalyzed or induced by another agent, such as by an enzyme, by light, by acid, or by a change of or exposure to a physical or environmental parameter, such as a change of temperature. The agent can be endogenous to the conditions of use, such as an enzyme present in the cells to which the prodrug is administered or the acidic conditions of the stomach, or it can be supplied exogenously. A wide variety of progroups, as well as the resultant promoieties, suitable for masking functional groups in the active drugs to yield prodrugs are well-known in the art. For example, a hydroxyl functional group can be masked as a sulfonate, ester or carbonate promoiety, which can be hydrolyzed *in vivo* to provide the hydroxyl group. An amino functional group can be masked as an amide, carbamate, imine, urea, phosphenyl, phosphoryl or sulfenyl promoiety, which can be hydrolyzed *in vivo* to provide the amino group. A carboxyl group can be masked as an ester (including silyl esters and thioesters), amide or hydrazide promoiety, which can be hydrolyzed *in vivo* to provide the carboxyl group. Specific examples of suitable progroups and their respective promoieties will be apparent to those of skill in the art.

[0076] The compounds disclosed herein can also be provided as *N*-oxides.

[0077] The presently disclosed compounds, salts, prodrugs and *N*-oxides can be provided, for example, in solvate or hydrate form.

[0078] One of ordinary skill in the art of medicinal chemistry also will appreciate that the disclosed structures are intended to include isotopically enriched forms of the present compounds. As used herein "isotopes" includes those atoms having the same atomic number but different mass numbers. As is known to those of skill in the art, certain atoms, such as hydrogen occur in different isotopic forms. For example, hydrogen includes three isotopic forms, protium, deuterium and tritium. As will be apparent to those of skill in the art upon consideration of the present compounds, certain compounds can be enriched at a given position with a particular isotope of the atom at that position. For example, compounds having a fluorine atom, may be synthesized in a form enriched in the radioactive fluorine isotope ^{18}F. Similarly, compounds may be enriched in the heavy isotopes of hydrogen: deuterium and tritium; and similarly can be enriched in a radioactive isotope of carbon, such as ^{13}C. Such isotopic variant compounds undergo different metabolic pathways and can be useful, for example, in studying the ubiquitination pathway and its role in disease.

[0079] As used herein, the term "cell" is meant to refer to a cell that is *in vitro*, ex vivo or *in vivo*. In some embodiments, an ex vivo cell can be part of a tissue sample excised from

an organism such as a mammal. In some embodiments, an *in vitro* cell can be a cell in a cell culture. In some embodiments, an *in vivo* cell is a cell living in an organism such as a mammal.

[0080] As used herein, the term "contacting" refers to the bringing together of indicated moieties in an *in vitro* system or an *in vivo* system. For example, "contacting" an enzyme with a compound includes the administration of a compound described herein to an individual or patient, such as a human, as well as, for example, introducing a compound into a sample containing a cellular or purified preparation containing the enzyme.

[0081] As used herein, the terms "individual," "patient," or "subject" are used interchangeably, refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, swine, cattle, sheep, horses, or primates, and most preferably humans.

[0082] As used herein, the phrase "therapeutically effective amount" refers to the amount of active compound or pharmaceutical agent that elicits the biological or medicinal response that is being sought in a tissue, system, animal, individual or human by a researcher, veterinarian, medical doctor or other clinician.

[0083] In certain embodiments, a therapeutically effective amount can be an amount suitable for

(1) preventing the disease; for example, preventing a disease, condition or disorder in an individual who may be predisposed to the disease, condition or disorder but does not yet experience or display the pathology or symptomatology of the disease;

(2) inhibiting the disease; for example, inhibiting a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder; or

(3) ameliorating the disease; for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing the pathology and/or symptomatology) such as decreasing the severity of disease.

[0084] As used here, the terms "treatment" and "treating" means (i) ameliorating the referenced disease state, condition, for disorder, such as, for example, ameliorating a disease, condition or disorder in an individual who is experiencing or displaying the pathology or symptomatology of the disease, condition or disorder (*i.e.*, reversing or improving the pathology and/or symptomatology) such as decreasing the severity of

disease; or (ii) eliciting the referenced biological effect (*e.g.,* modulation or inhibition of Cks1-Skp2 PPI, inhibition of ubiqutination, or increase in p27 levels).

[0085] Manifestation of amelioration of a disease condition by inhibiting ubiquitination and/or Cks1-Skp2 PPI may require the concomitant or sequential administration of additional therapeutic agents, such as antineoplastic agents in the case of cancer, or antiretroviral agents in the case of viral diseases. For example, administration of ubiquitination and/or Cks1-Skp2 PPI inhibitors for the treatment of cancer does not always produce a direct antitumor effect when used as a single agent. However, when combined with chemotherapeutic drugs (antineoplastic) the antitumor effect observed is higher than the sum of effects of each agent alone.

[0086] As used herein, the terms "catalytic pocket", "catalytic site", "active site" collectively and indistinctly refer to a region of the enzyme that contains amino acid residues responsible for the substrate binding (charge, hydrophobicity, steric hindrance) and catalytic amino acid residues which act as proton donors or acceptors or are responsible for binding a cofactor and participate in the catalysis of a chemical reaction.

[0087] As used herein, the phrase "pharmaceutically acceptable salt" refers to both pharmaceutically acceptable acid and base addition salts and solvates. Such pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alkanoic such as acetic, HOOC-$(CH_2)_n$-COOH where n is 0-4, and the like. Non-toxic pharmaceutical base addition salts include salts of bases such as sodium, potassium, calcium, ammonium, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

Methods of Use

[0088] The compounds and pharmaceutical compositions described herein can modulate activity of the Cks1-Skp2 PPI. The term "modulate" is meant to refer to an ability to decrease activity of an enzyme or receptor, or disrupt binding. Accordingly, compounds described herein can be used in methods of modulating Cks1-Skp2 PPI by contacting the proteins with any one or more of the compounds or compositions described herein. In some embodiments, the compounds described herein can act as inhibitors of ubiquitination. In further embodiments, the compounds described herein can be used to modulate activity of

the Cks1-Skp2 PPI in a cell or in an individual in need of modulation of the interaction by administering a modulating (*e.g.*, inhibiting) amount of a compound described herein.

[0089] Further provided are methods of inhibiting the degradation of tumor suppressors. In some embodiments methods of altering (*e.g.*, decreasing) the degradation of tumor suppressors comprise administering an effective amount of a compound or pharmaceutical composition provided herein. In some embodiments, an effective amount of a compound or pharmaceutical composition provided herein and a tumor suppressor are administered simultaneously. In other embodiments, an effective amount of a compound or pharmaceutical composition provided herein and a tumor suppressor are administered sequentially. In other embodiments, the tumor suppressor is p27.

[0090] For example, a subject undergoing or having completed a course of chemotherapy and/or radiation therapy for the treatment of a disease state, such as a cancer, can benefit from administering to the patient a therapeutically effective amount of a compound or composition recited herein for inhibiting degradation of a tumor suppressor.

Pharmaceutical Formulations and Dosage Forms

[0091] The compounds of structural formulae (I) – (IV) can be administered, for example, orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing one or more pharmaceutically acceptable carriers, diluents or excipients. The term parenteral as used herein includes percutaneous, subcutaneous, intravascular (e.g., intravenous), intramuscular, or intrathecal injection or infusion techniques and the like.

[0092] Pharmaceutical compositions can be made using the presently disclosed compounds. For example, in one embodiment, a pharmaceutical composition includes a pharmaceutically acceptable carrier, diluent or excipient, and compound as described above with reference to structural formulae (I) – (IV).

[0093] In the pharmaceutical compositions disclosed herein, one or more compounds of structural formulae (I) – (IV) may be present in association with one or more pharmaceutically acceptable carriers, diluents or excipients, and, if desired, other active ingredients. The pharmaceutical compositions containing compounds of structural formulae (I) – (IV) may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

[0094] Compositions intended for oral use can be prepared according to any suitable method for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preservative agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients that are suitable for the manufacture of tablets. These excipients can be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets can be uncoated or they can be coated by known techniques. In some cases such coatings can be prepared by suitable techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate can be employed.

[0095] Formulations for oral use can also be presented as hard gelatin capsules, wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

[0096] Formulations for oral use can also be presented as lozenges.

[0097] Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients can be suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents such as a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives,

for example ethyl, or n-propyl p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

[0098] Oily suspensions can be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

[0099] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents or suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, can also be present.

[0100] Pharmaceutical compositions can also be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil or a mineral oil or mixtures of these. Suitable emulsifying agents can be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions can also contain sweetening and flavoring agents.

[0101] In some embodiments, the pharmaceutically acceptable carrier, diluent, or excipient is not water. In other embodiments, the water comprises less than 50% of the composition. In some embodiments, composiitons comprising less than 50% water have at least 1%, 2%, 3%, 4% or 5% water. In other embodiments, the water content is present in the composition in a trace amount.

[0102] In some embodiments, the pharmaceutically acceptable carrier, diluent, or excipient is not alcohol. In other embodiments, the alcohol comprises less than 50% of the composition. In some embodiments, composiitons comprising less than 50% alcohol have at least 1%, 2%, 3%, 4% or 5% alcohol. In other embodiments, the alcohol content is present in the composition in a trace amount.

[0103] Syrups and elixirs can be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol, glucose or sucrose. Such formulations can also contain a demulcent, a preservative, flavoring, and coloring agents. The pharmaceutical compositions can be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents that have been mentioned above. The sterile injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils can be employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

[0104] Compounds of structural formulae (I) – (IV) can also be administered in the form of suppositories, e.g., for rectal administration of the drug. These compositions can be prepared by mixing the compound with a suitable non-irritating excipient that is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols.

[0105] Compounds of structural formula (I) – (IV) can also be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

[0106] The compositions can be formulated in a unit dosage form, each dosage containing from about 5 to about 100 mg, more usually about 10 to about 30 mg, of the active ingredient. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient.

[0107] The active compound can be effective over a wide dosage range and is generally administered in a pharmaceutically effective amount. It will be understood, however, that the amount of the compound actually administered will usually be determined by a physician, according to the relevant circumstances, including the condition to be treated, the

chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

[0108] For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical excipient to form a solid preformulation composition containing a homogeneous mixture of a compound described herein. When referring to these preformulation compositions as homogeneous, the active ingredient is typically dispersed evenly throughout the composition so that the composition can be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation is then subdivided into unit dosage forms of the type described above containing from, for example, 0.1 to about 500 mg of the active ingredient of a compound described herein.

[0109] The tablets or pills can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permit the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol, and cellulose acetate.

[0110] The amount of compound or composition administered to a patient will vary depending upon what is being administered, the purpose of the administration, such as prophylaxis or therapy, the state of the patient, the manner of administration, and the like. In therapeutic applications, compositions can be administered to a patient already suffering from a disease in an amount sufficient to cure or at least partially arrest the symptoms of the disease and its complications. Effective doses will depend on the disease condition being treated as well as by the judgment of the attending clinician depending upon factors such as the severity of the disease, the age, weight and general condition of the patient, and the like.

[0111] The compositions administered to a patient can be in the form of pharmaceutical compositions described above. These compositions can be sterilized by conventional sterilization techniques, or may be sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation being combined with a sterile aqueous carrier prior to administration. The pH of the compound preparations typically will be

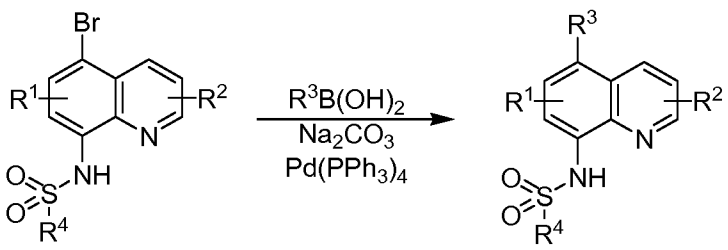
between 3 and 11, more preferably from 5 to 9 and most preferably from 7 to 8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of pharmaceutical salts.

[0112] The therapeutic dosage of the compounds can vary according to, for example, the particular use for which the treatment is made, the manner of administration of the compound, the health and condition of the patient, and the judgment of the prescribing physician. The proportion or concentration of a compound described herein in a pharmaceutical composition can vary depending upon a number of factors including dosage, chemical characteristics (*e.g.*, hydrophobicity), and the route of administration. For example, the compounds described herein can be provided in an aqueous physiological buffer solution containing about 0.1 to about 10% w/v of the compound for parenteral administration. Some typical dose ranges are from about 1 μg/kg to about 1 g/kg of body weight per day. In some embodiments, the dose range is from about 0.01 mg/kg to about 100 mg/kg of body weight per day. The dosage is likely to depend on such variables as the type and extent of progression of the disease or disorder, the overall health status of the particular patient, the relative biological efficacy of the compound selected, formulation of the excipient, and its route of administration. Effective doses can be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

[0113] The compounds described herein can also be formulated in combination with one or more additional active ingredients which can include any pharmaceutical agent such as anti-viral agents, vaccines, antibodies, immune enhancers, immune suppressants, anti-inflammatory agents and the like.

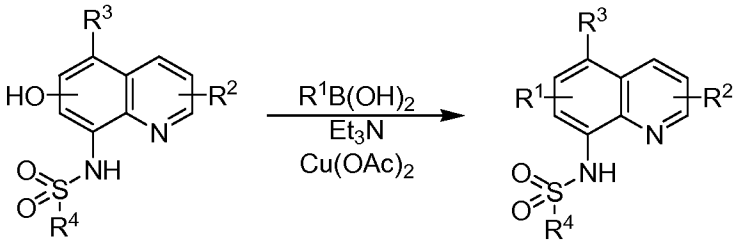
Examples

[0114] The compounds disclosed herein can be made using procedures familiar to the person of ordinary skill in the art and as described herein. For example, compounds of structural formulae (I) – (IV) can be prepared according to Schemes 1 or 2, below, or analogous synthetic schemes:



Scheme 1

[0115] Referring to Scheme 1, to a mixture of the bromoisoquinoline and R^3-boronic acid (1.5 eq) in dioxane was added aqueous sodium carbonate (3.0 eq). The reaction mixture was degassed by bubbling argon through. Tetrakis(triphenylphosphine)palladium (0.1 eq) was added and the reaction further degassed before sealing and heating to 150°C in the microwave for 1 hour. The reaction was cooled and partitioned between EtOAc and $NaHCO_3$. The organics were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. MPLC yielded the Suzuki coupled compound.



Scheme 2

[0116] Referring to Scheme 2, to a solution of the 6-hydroxyquinoline (1.0 eq) and the R^1-boronic acid (2.0 eq) in dichloromethane was added freshly crushed 4Å molecular sieves. Copper acetate (1.0 eq) was added followed by triethylamine (5.0 eq) and the reactions stirred at room temperature for 24 hours. The solution was diluted with CH_2Cl_2, washed with $NaHCO_3$, dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography yielded the aryl ethers.

[0117] One of skill in the art can adapt the reaction sequences of Schemes 1 and 2 to fit the desired target molecule. Of course, in certain situations one of skill in the art will use different reagents to affect one or more of the individual steps or to use protected versions of certain of the substituents. Additionally, one skilled in the art would recognize that compounds of structural formulae (I) – (IV) can be synthesized using different routes altogether.

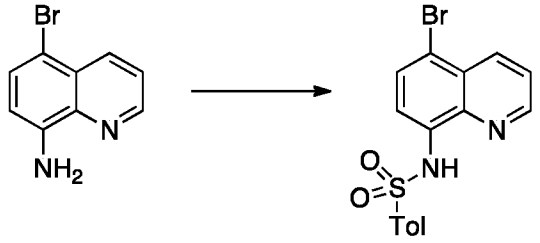
[0118] Compounds suitable for use in the presently disclosed pharmaceutical compositions include compounds of Table 1, above. These compounds can be made according to the general schemes described above, for example using a procedure similar to that described below in the Examples.

[0119] The following examples are intended to further illustrate certain embodiments and are not intended to limit the scope of the presently disclosed compounds.

EXAMPLES

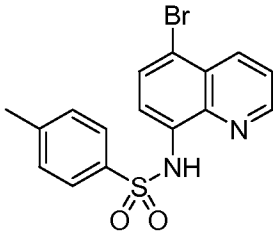
Example 1: Synthesis and Characterization

General Procedure for Sulfonamide Formation



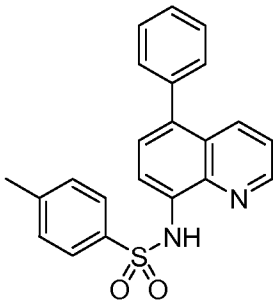
[0120] To a solution of 5-bromo-8-aminoquinoline (0.507 g, 2.27 mmol, 1.0 eq) in dichloromethane (15 mL) at 0°C was added toluenesulfonyl chloride (0.477 g, 2.50 mmol, 1.1 eq) followed by triethylamine (0.47 mL, 3.41 mmol, 1.5 eq). The reaction was allowed to warm to room temperature and stirred for 20 hours. The reaction was partitioned between CH_2Cl_2 (50 mL) and $NaHCO_3$ (50 mL). The organics were washed with water (50 mL) and brine (50 mL) before drying (Na_2SO_4) and concentrating under reduced pressure. Column chromatography (silica, 20→70% EtOAc-hexane) yielded the sulfonamide.

Compound **1**: N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide



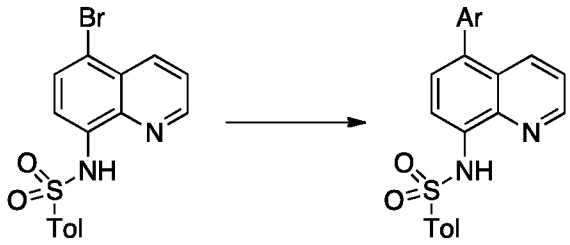
[0121] ^{1}H NMR ($CDCl_3$) δ 9.19 (1H, s, SO_2NH), 8.76 (1H, dd, J 4.0, 1.5 Hz, quinolineH-2), 8.42 (1H, dd, J 8.5, 1.5 Hz, quinolineH-4), 7.78 (2H, d, J 8.5 Hz, 2H of $SO_2C_6H_4Me$), 7.78, 7.67 (2H, 2d, J 8.5 Hz, quinolineH-6 and H-7), 7.50 (1H, dd, J 9.0, 4.0 Hz, quinolineH-3), 7.15 (2H, d, J 8.0 Hz, 2H of $SO_2C_6H_4Me$), 2.29 (3H, s, $C_6H_4C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 148.2, 144.0, 139.1, 136.2, 135.9, 133.8, 130.3, 129.6, 127.5, 127.2, 123.0, 115.2, 114.9, 21.5; *m/z*: 377, 379 $[M+H]^+$ (found $[M+H]^+$, 376.9989, $C_{16}H_{13}BrN_2O_2S$ requires $[M+H]^+$ 376.9954)

Compound **4**: 4-methyl-N-(5-phenylquinolin-8-yl)benzenesulfonamide



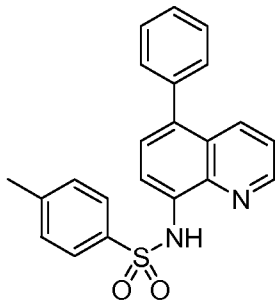
[0122] To a solution of 5-chloroquinoline-8-sulfonyl chloride hydrochloric acid salt (0.030 g, 0.101 mmol, 1.0 eq) in dichloromethane (1 mL) was added p-toluidine (0.012 g, 0.111 mmol, 1.1 eq) followed by triethylamine (0.029 mL, 0.211 mmol, 2.1 eq) and dimethylaminopyridine (0.001 g, 0.010 mmol, 0.1 eq). The reaction was stirred at room temperature for 20 hours, before diluting with EtOAc-CH_2Cl_2 (35:5, 40 mL). The solution was washed with $NaHCO_3$ (40 mL), water (40 mL) and brine (40 mL). The organics were dried (Na_2SO_4) and concentrated under reduced pressure. MPLC (20→60% EtOAc-hexane) yielded the sulfonamide as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 9.20 (1H, dd, J 4.5, 1.5 Hz, quinolineH-2), 8.71 (1H, dd, J 8.5, 1.5 Hz, quinolineH-4), 8.24 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 8.17 (1H, s, SO_2NH), 7.72 (1H, dd, J 8.4, 4.5 Hz, quinolineH-3), 7.64 (1H, d, J 8.0 Hz, 1H of quinolineH-6 or H-7), 6.91 (2H, d, J 8.5 Hz, 2H of C_6H_4Me), 6.84 (2H, d, J 8.5 Hz, 2H of C_6H_4Me), 2.18 (3H, s, $C_6H_4C\underline{H}_3$); *m/z*: 333, 335 $[M+H]^+$. To a mixture of phenylboronic acid (0.010 g, 0.082 mmol, 1.3 eq) and the chloroquinoline (0.021 g, 0.063 mmol, 1.0 eq) in dioxane (1 mL) was added sodium carbonate (0.063 mL of a 2M aqueous solution, 0.127 mmol, 2.0 eq). The mixture was degassed by bubbling argon through before adding tetrakis(triphenylphosphine)palladium (0.014 g, 0.013 mmol, 0.2 eq). The reaction was further degassed before sealing and heating in a microwave to 150°C for 1 hour. After cooling the reaction was diluted with EtOAc (40 mL) and washed with $NaHCO_3$ (2 x 20 mL) and brine (20 mL). The organics were dried (Na_2SO_4) and concentrated under reduced pressure. Column chromatography (silica, 15→40% EtOAc-hexane) yielded the coupled compound as a colorless oil; ^{1}H NMR ($CDCl_3$) δ 9.14 (1H, m, quinolineH-2), 8.42 (1H, s, SO_2NH), 8.34 (2H, m, quinolineH-4, 1H of quinolineH-6 or H-7), 7.56-7.48 (5H, m, quinolineH-3, quinolineH-6 or H-7, 3H of C_6H_5), 7.39 (2H, m, 2H of C_6H_5), 6.93 (4H, s, C_6H_4Me), 2.20 (3H, s, $C_6H_4C\underline{H}_3$); *m/z*: 375 $[M+H]^+$.

General Procedure of the Suzuki Couplings



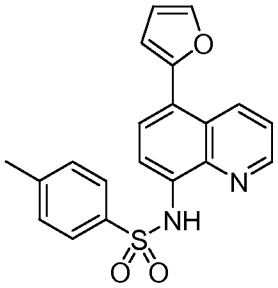
[0123] To a mixture of the bromoisoquinoline (0.085 mmol, 1.0 eq) and arylboronic acid (0.127 mmol, 1.5 eq) in dioxane (1.0 mL) was added aqueous sodium carbonate (0.127 mL of a 2M solution, 0.255 mmol, 3.0 eq). The reaction mixture was degassed by bubbling argon through. Tetrakis(triphenylphosphine)palladium (0.010 g, 0.008 mmol, 0.1 eq) was added and the reaction further degassed before sealing and heating to 150°C in the microwave for 1 hour. The reaction was cooled and partitioned between EtOAc (30 mL) and $NaHCO_3$ (30 mL). The organics were washed with brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. MPLC (0→10% MeOH-CH_2Cl_2) yielded the Suzuki coupled compound.

Compound **4**: 4-methyl-N-(5-phenylquinolin-8-yl)benzenesulfonamide



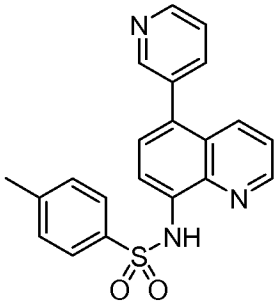
[0124] ^1H NMR ($CDCl_3$) δ 9.33 (1H, br s, SO_2NH), 8.77 (1H, dd, J 4.5, 1.5 Hz, quinolineH-2), 8.20 (1H, dd, J 9.0, 2.0 Hz, quinolineH-4), 7.85 (3H, d, J 8.0 Hz, quinolineH-6 or H-7, 2H of $SO_2C_6H_4Me$), 7.47-7.35 (7H, m, quinolineH-6 or H-7, quinolineH-3, C_6H_5), 7.19 (2H, d, J 8.0 Hz, 2H of $SO_2C_6H_4Me$), 6.97 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 2.32 (3H, s, $C_6H_4C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 148.4, 143.7, 138.8, 138.5, 136.6, 134.7 (2C), 133.2, 130.0, 129.6, 128.5, 127.6, 127.3 (2C), 126.6, 121.8, 114.1, 21.5; *m/z*: 375 $[M+H]^+$ (found $[M+H]^+$, 375.1127, $C_{22}H_{18}N_2O_2S$ requires $[M+H]^+$ 375.1162).

Compound **5**: N-(5-(furan-2-yl)quinolin-8-yl)-4-methylbenzenesulfonamide



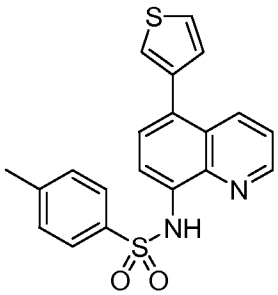
[0125] ^{1}H NMR ($CDCl_3$) δ 9.36 (1H, br s, SO_2NH), 8.78 (1H, dd, J 4.0, 1.5 Hz, quinolineH-2), 8.72 (1H, dd, J 9.0, 1.5 Hz, quinolineH-4), 7.82 (3H, m, quinolineH-6 or H-7, 2H of $SO_2C_6H_4Me$), 7.66 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.58 (1H, d, J 2.0 Hz, furanH-H-3 or H-5), 7.46 (1H, dd, J 9.0, 4.5 Hz, quinolineH-3), 7.17 (2H, d, J 8.5 Hz, 2H of $SO_2C_6H_4Me$), 6.62 (1H, d, J 3.0 Hz, furanH-3 or H-5), 6.55 (1H, dd, J 3.0, 2.0 Hz, furanH-4), 2.30 (3H, s, $C_6H_4C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 148.5, 143.8, 142.7, 138.4, 136.4, 134.7, 133.8, 129.6, 127.2, 126.4, 125.5, 123.1, 122.2, 114.2, 111.5, 108.6, 21.5; *m/z*: 365 $[M+H]^+$ (found $[M+H]^+$, 365.0937, $C_{20}H_{16}N_2O_3S$ requires $[M+H]^+$ 365.0955).

Compound **6**: 4-methyl-N-(5-(pyridin-3-yl)quinolin-8-yl)benzenesulfonamide



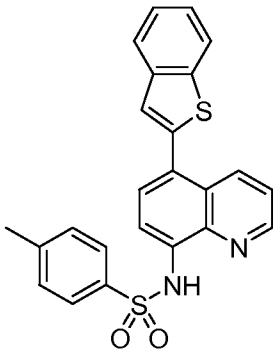
[0126] ^{1}H NMR ($CDCl_3$) δ 9.35 (1H, br s, SO_2NH), 8.80 (1H, br d, J 2.5 Hz, quinolineH-2), 8.66 (2H, m, quinolineH-4, pyH-2), 8.11 (1H, d, J 9.0 Hz, 1H of pyH-4, H-5 or H-6), 7.85 (3H, m, 2H of $SO_2C_6H_4Me$, 1H of pyH-4, H-5 or H-6), 7.71 (1H, br d, J 8.0 Hz, 1H of quinolineH-6 or H-7 or pyH-4, H-5 or H-6), 7.49-7.38 (3H, m, quinolineH-3, 2H of quinolineH-6 or H-7 or pyH-H-4, H-5 or H-6), 7.20 (2H, d, J 8.0 Hz, 2H of $SO_2C_6H_4Me$), 2.33 (3H, s, $C_6H_4C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 148.7, 143.9, 140.3, 140.1, 138.3, 136.5, 134.5, 134.2, 129.7, 128.9, 127.3, 126.7, 124.5, 124.1, 123.6, 122.3, 122.1, 113.6, 21.5; *m/z*: 381 $[M+H]^+$ (found $[M+H]^+$, 376.1114, $C_{21}H_{17}N_3O_2S$ requires $[M+H]^+$ 376.1114).

Compound **7**: 4-methyl-N-(5-(thiophen-3-yl)quinolin-8-yl)benzenesulfonamide



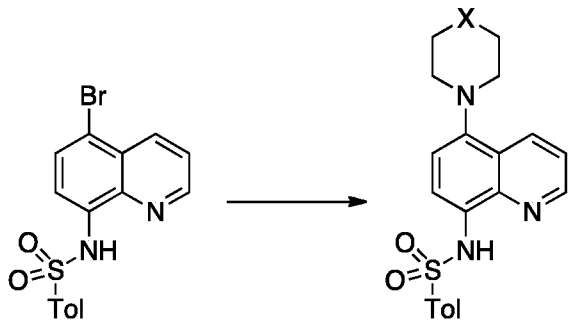
[0127] ^{1}H NMR ($CDCl_3$) δ 9.32 (1H, br s, SO_2NH), 8.77 (1H, dd, J 4.5, 1.5 Hz, quinolineH-2), 8.32 (1H, dd, J 8.5, 2.0 Hz, quinolineH-4), 7.84 (2H, d, J 8.5 Hz, 2H of $SO_2C_6H_4Me$), 7.83 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.46-7.43 (2H, m, quinolineH-6 or H-7, 1H of thiophene), 7.40 (1H, dd, J 8.5, 4.5 Hz, quinolineH-3), 7.30 (1H, dd, J 2.5, 1.5 Hz, 1H of thiophene), 7.19 (2H, d, J 8.5 Hz, 2H of $SO_2C_6H_4Me$), 7.18 (1H, m, 1H of thiophene), 2.31 (3H, s, $C_6H_4C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 148.4, 143.7, 139.3, 138.5, 136.6, 134.6, 133.2, 129.6, 129.4, 129.1, 127.3, 126.8, 125.9, 123.7, 121.9, 114.2, 21.5; *m/z*: 381 $[M+H]^+$ (found $[M+H]^+$, 381.0710, $C_{20}H_{16}N_2O_2S_2$ requires $[M+H]^+$ 381.0726).

Compound **8**: N-(5-(benzo[b]thiophen-2-yl)quinolin-8-yl)-4-methylbenzenesulfonamide



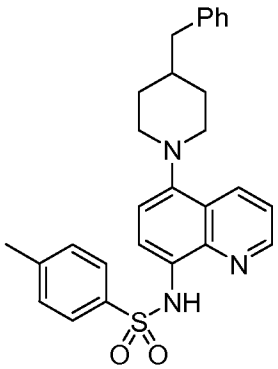
[0128] ^{1}H NMR ($CDCl_3$) δ 9.32 (1H, br s, SO_2NH), 8.73 (1H, dd, J 4.0, 1.5 Hz, quinolineH-2), 8.51 (1H, dd, J 9.0, 1.5 Hz, quinolineH-4), 7.79 (2H, d, J 8.5 Hz, 2H of $SO_2C_6H_4Me$), 7.79-7.74 (3H, 3 x ArH), 7.54 (1H, d, J 8.5 Hz, 1 x ArH), 7.41-7.27 (4H, m, 4 x ArH), 7.19 (2H, d, J 8.5 Hz, 2H of $SO_2C_6H_4Me$), 2.27 (3H, s, $C_6H_4C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 148.7, 143.9, 140.3, 140.2, 140.1, 138.3, 136.5, 134.5, 134.2, 129.7, 128.9, 127.3, 126.9, 126.7, 124.7, 124.5, 124.1, 123.6, 122.3, 122.1, 113.6, 21.5; *m/z*: 431 $[M+H]^+$ (found $[M+H]^+$, 431.0887, $C_{24}H_{18}N_2O_2S_2$ requires $[M+H]^+$ 431.0876).

General Procedure for Buchwald-Hartwig Reactions



[0129] To a solution of bromoisoquinoline (0.035 g, 0.093 mmol, 1.0 eq) in *N*-methylpyrrolidinone (0.7 mL) was added the amine (0.18 mmol, 2.0 eq). The solution was degassed by bubbling argon through for three minutes before adding potassium carbonate (0.033 g, 0.29 mmol, 3.1 eq), X-Phos (0.004 g, 0.009 mmol, 0.09 eq) and tris(dibenzylideneacetone)dipalladium (0.004 g, 0.009 mmol, 0.09 eq). The reaction mixture was further degassed by bubbling argon through for three minutes and the reaction vessel sealed. The reaction was heated to 140°C in a microwave for 10 minutes. After cooling the reaction mixture was poured onto aqueous NH_4Cl solution (5 mL). The resulting precipitate was collected and dissolved in CH_2Cl_2 (30 mL). The organics were washed with brine (30 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The samples were isolated by reversed phase HPLC.

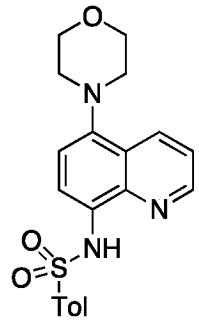
Compound **9**: N-(5-(4-benzylpiperidin-1-yl)quinolin-8-yl)-4-methylbenzenesulfonamide



[0130] ^1H NMR ($CDCl_3$) δ 9.01 (1H, br s, SO_2NH), 8.69 (1H, dd, J 4.0, 1.5 Hz, quinolineH-2), 8.40 (1H, dd, J 8.5, 1.5 Hz, quinolineH-4), 7.75 (2H, d, J 8.0 Hz, 2H of $SO_2C_6H_4Me$), 7.71 (1H, d, J 8.5 Hz, quinolineH-6 or H-7), 7.37 (1H, dd, J 8.5, 4.5 Hz, quinolineH-3), 7.33-7.28 (2H, m, 2H of C_6H_5), 7.23-7.18 (3H, m, 3H of C_6H_5), 7.11 (2H, d, J 8.5 Hz, 2H of $SO_2C_6H_4Me$), 6.97 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 3.20 (2H, m, 2H

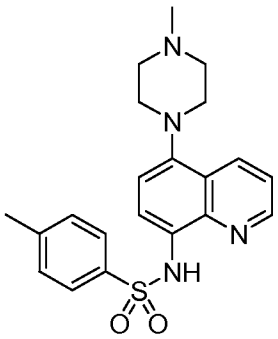
of pipH-2, H-6), 2.70-2.60 (4H, m, 2H of pipH-2, H-6, C<u>H</u>$_2$C$_6$H$_5$), 2.28 (3H, s, C$_6$H$_4$C<u>H</u>$_3$), 1.78 (2H, m, 2H of pipH-3, H-5), 1.74-1.65 (1H, m pipH-4), 1.56 (2H, m, 2H of pipH-3, H-5); ^{13}C NMR ($CDCl_3$) δ 148.4, 146.0, 143.4, 140.4, 139.7, 136.6, 132.7, 129.4, 129.1, 128.2, 127.2, 125.9, 124.2, 120.9, 115.6, 115.1, 54.0, 43.3, 38.0, 32.8, 21.4; *m/z*: 472 $[M+H]^+$ (found $[M+H]^+$, 472.2047, $C_{28}H_{29}N_3O_2S$ requires $[M+H]^+$ 472.2053).

Compound **10**: 4-methyl-N-(5-morpholinoquinolin-8-yl)benzenesulfonamide



[0131] ^{1}H NMR ($CDCl_3$) δ 9.06 (1H, br s, SO_2NH), 8.74 (1H, dd, J 4.0, 0.5 Hz, quinolineH-2), 8.46 (1H, dd, J 8.5, 1.0 Hz, quinolineH-4), 7.78 (2H, d, J 8.5 Hz, 2H of $SO_2C_6H_4Me$), 7.34 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.41 (1H, dd, J 8.5, 4.0 Hz, quinolineH-3), 7.15 (2H, d, J 8.0 Hz, 2H of $SO_2C_6H_4Me$), 7.05 (1H, d, J 8.5 Hz, quinolineH-6 or H-7), 3.93, 3.92 (4H, 2d AB system, J 4.5 Hz, 4H of morpholine), 3.01, 2.99 (4H, 2d AB system, J 4.5 Hz, 4H of morpholine), 2.30 (3H, s, C$_6$H$_4$C<u>H</u>$_3$); ^{13}C NMR ($CDCl_3$) δ 148.6, 144.6, 143.5, 139.6, 136.6, 132.3, 129.9, 129.4, 127.2, 124.0, 121.2, 115.5, 115.2, 67.3, 53.6, 21.5; *m/z*: 384 $[M+H]^+$ (found $[M+H]^+$, 384.1338, $C_{20}H_{21}N_3O_3S$ requires $[M+H]^+$ 384.1377).

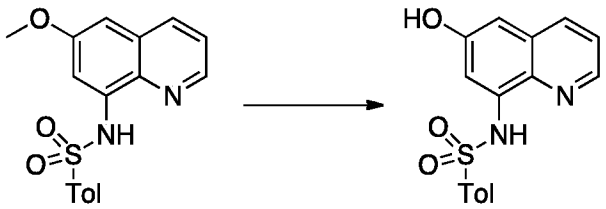
Compound **11**: 4-methyl-N-(5-(4-methylpiperazin-1-yl)quinolin-8-yl)benzenesulfonamide



[0132] ^{1}H NMR ($CDCl_3$) δ 9.02 (1H, br s, SO_2NH), 8.70 (1H, br s, quinolineH-2), 8.42 (1H, d, J 8.5 Hz, quinolineH-4), 7.77 (2H, d, J 8.0 Hz, 2H of $SO_2C_6H_4Me$), 7.70 (1H, m, quinolineH-3, H-6 or H-7), 7.37 (1H, m, quinolineH-3, H-6 or H-7), 7.12 (1H, m,

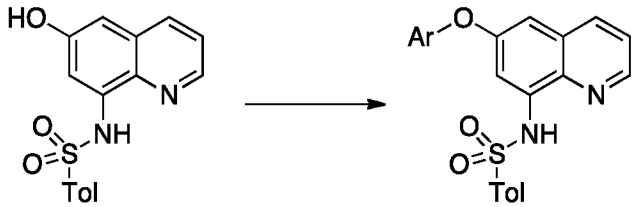
quinolineH-3, H-6 or H-7), 7.02 (2H, d, J 8.5 Hz, 2H of $SO_2C_6H_4Me$), 3.02 (4H, m, 4H of piperazine), 2.65 (4H, m, 4H of piperazine), 2.39 (3H, s, NCH_3), 2.27 (3H, s, $C_6H_4C\underline{H}_3$); ^{13}C NMR ($CDCl_3$) δ 148.5, 144.9, 143.5, 139.7, 136.6, 132.5, 129.6, 129.4, 127.2, 124.1, 121.0, 115.5, 115.4, 55.5, 53.1, 46.2, 21.4; *m/z*: 397 $[M+H]^+$ (found $[M+H]^+$, 397.1694, $C_{20}H_{21}N_3O_3S$ requires $[M+H]^+$ 397.1693).

Demethylation of 6-methoxy-8-tosylsulfonamidoquinoline to form 6-hydroxy-8-tosylsulfonamidoquinoline



[0133] To a solution of the 6-methoxyquinoline (0.300 g, 2.43 mmol, 1.0 eq) in dichloromethane (25 mL) was cooled to -78°C and boron tribromide (0.38 mL, 2.92 mmol, 1.2 eq) added dropwise. The yellow solution was stirred at -78°C for 1.5 hours and 0°C for 3 hours. Further boron tribromide (0.20 mL, 2.12 mmol, 0.9 eq) was added and the reaction stirred at 0°C for 1 hour before adding $NaHCO_3$ (50 mL). The organics were extracted with CH_2Cl_2 (2 x 60 mL), combined, washed with brine (60 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (silica, 0→5% MeOH-CH_2Cl_2) yielded the 6-hydroxy-8-tosylsulfonamidoquinoline.

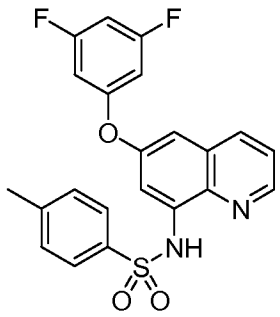
General Procedure for Evans-Chan-Lam Reaction



[0134] To a solution of the 6-hydroxyquinoline (0.020 g, 0.064 mmol, 1.0 eq) and the arylboronic acid (0.127 mmol, 2.0 eq) in dichloromethane (1.0 mL) was added freshly crushed 4Å molecular sieves. Copper acetate (0.012 g, 0.064 mmol, 1.0 eq) was added followed by triethylamine (0.044 mL, 0.318 mmol, 5.0 eq) and the reactions stirred at room temperature for 24 hours. If LC-MS analysis showed only partial reaction, further boronic acid (0.127 mmol, 1.0 eq), triethylamine (0.018 mL, 0.128 mmol, 2.0 eq) and copper acetate (0.006 g, 0.032 mmol, 0.5 eq) was added and the reaction stirred for a further 14 hours before diluting with CH_2Cl_2 (20 mL). The solution was washed with $NaHCO_3$ (20 mL),

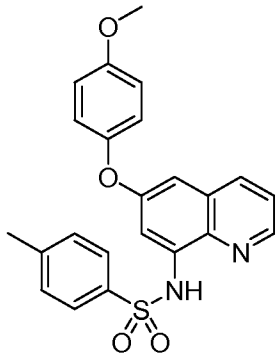
dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (silica, 0→3% MeOH-CH_2Cl_2) yielded the aryl ethers.

Compound **12**: N-(6-(3,5-difluorophenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide



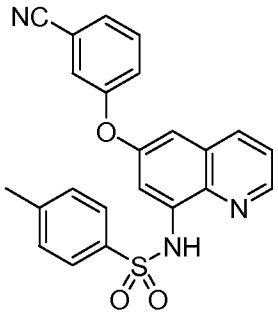
[0135] ^{1}H NMR ($CDCl_3$) δ 9.27 (1H, br s, NH), 8.71 (1H, dd, J 4.0, 1.5 Hz, quinolineH-2), 8.00 (1H, d, J 8.5 Hz, quinolineH-4), 7.76 (2H, d, J 8.5 Hz, 2H of $C_6H_4SO_2Me$), 7.54 (1H, d, J 2.5 Hz, quinolineH-5 or H-7), 7.42 (1H, dd, J 8.5, 4.0 Hz, quinolineH-3), 7.18 (2H, d, J 8.5 Hz, 2H of $C_6H_4SO_2Me$), 6.99 (1H, d, J 2.5 Hz, quinolineH-5 or H-7), 6.60 (1H, br t, J 9.0 Hz, $C_6H_3F_2H$-4), 6.43 (2H, d, J 8.5 Hz, $C_6H_3F_2H$-2, H-6), 2.34 (3H, s, SO_2CH_3); *m/z*: 427 $[M+H]^+$.

Compound **13**: N-(6-(4-methoxyphenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide



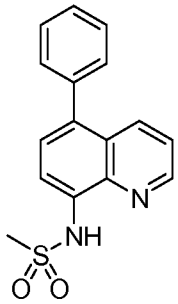
[0136] ^{1}H NMR ($CDCl_3$) δ 9.23 (1H, br s, NH), 8.62 (1H, m, quinolineH-2), 7.86 (1H, d, J 7.5 Hz, quinolineH-4), 7.78 (2H, d, J 7.5 Hz, 2H of $C_6H_4SO_2Me$), 7.53 (1H, m, quinolineH-5 or H-7), 7.33 (2H, m, quinolineH-3, quinolineH-5 or H-7), 7.19 (2H, d, J 7.5 Hz, 2H of $C_6H_4SO_2Me$), 6.99 (2H, d, J 9.5 Hz, 2H of C_6H_4OMe), 6.92 (2H, d, J 9.5 Hz, 2H of C_6H_4OMe), 3.85 (3H, s, OCH_3), 2.35 (3H, s, SO_2CH_3); *m/z*: 421 $[M+H]^+$.

Compound **14**: N-(6-(3-cyanophenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide



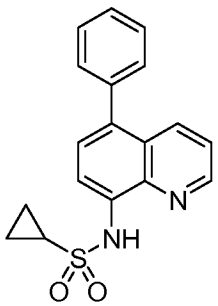
[0137] *m/z*: 416 $[M+H]^+$.

Compound **15**: N-(5-phenylquinolin-8-yl)methanesulfonamide



[0138] ^1H NMR ($CDCl_3$) δ 9.02 (1H, br s, SO_2NH), 8.84 (1H, dd, J 4.5, 1.5 Hz, quinolineH-2), 8.30 (1H, dd, J 9.0, 1.5 Hz, quinolineH-4), 7.92 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.55-7.43 (7H, m, quinolineH-3, quinolineH-6 or H-7, C_6H_5), 3.08 (3H, s, SO_2CH_3); *m/z*: 299 $[M+H]^+$ (found $[M+H]^+$, 299.0824, $C_{16}H_{14}N_2O_2S$ requires $[M+H]^+$ 299.0849).

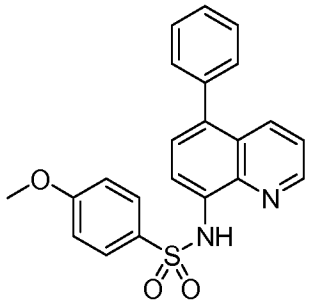
Compound **16**: N-(5-phenylquinolin-8-yl)cyclopropanesulfonamide



[0139] ^1H NMR ($CDCl_3$) δ 9.02 (1H, br s, SO_2NH), 8.83 (1H, dd, J 4.5, 1.5 Hz, quinolineH-2), 8.29 (1H, dd, J 9.0, 1.5 Hz, quinolineH-4), 7.96 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.54-7.42 (7H, m, quinolineH-3, quinolineH-6 or H-7, C_6H_5), 2.59 (1H, tt, J 8.0, 5.0 Hz, cPrH-1), 1.31 (2H, m, 2H of cPrH-2, H-3), 0.92 (2H, m, 2H of cPrH-2, H-3); ^{13}C NMR ($CDCl_3$) δ 148.6, 138.9, 138.8, 135.1, 134.8, 133.7, 130.0, 128.6, 127.7,

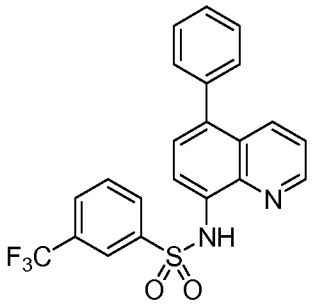
127.5, 126.7, 122.0, 115.1, 30.1, 5.7; *m/z*: 325 $[M+H]^+$ (found $[M+H]^+$, 325.0956, $C_{18}H_{16}N_2O_2S$ requires $[M+H]^+$ 325.1005).

Compound **17**: 4-methoxy-N-(5-phenylquinolin-8-yl)benzenesulfonamide



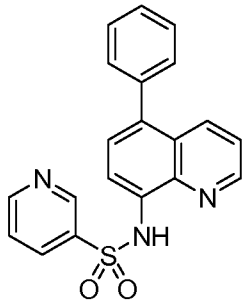
[0140] ^1H NMR ($CDCl_3$) δ 9.30 (1H, br s, SO_2NH), 8.87 (1H, dd, J 4.5, 1.5 Hz, quinolineH-2), 8.20 (1H, dd, J 8.5, 1.5 Hz, quinolineH-4), 7.90 (2H, d, J 9.5 Hz, 2H of C_6H_4OMe), 7.85 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.50-7.35 (7H, m, quinolineH-3, quinolineH-6 or H-7, C_6H_5), 6.86 (2H, d, J 9.5 Hz, 2H of C_6H_4OMe), 3.78 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$) δ 163.0, 152.2, 148.4, 138.8, 138.5, 134.7, 133.3, 131.2, 130.0, 129.4, 128.5, 127.6, 127.3, 126.6, 121.8, 114.2, 114.1, 55.5; *m/z*: 391 $[M+H]^+$ (found $[M+H]^+$, 391.1111, $C_{22}H_{18}N_2O_3S$ requires $[M+H]^+$ 391.1111).

Compound **18**: N-(5-phenylquinolin-8-yl)-3-(trifluoromethyl)benzenesulfonamide



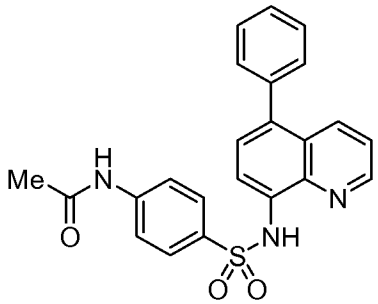
[0141] ^1H NMR ($CDCl_3$) δ 9.34 (1H, s, SO_2NH), 8.75 (1H, dd, J 4.0, 1.5 Hz, quinolineH-2), 8.20 (1H, dd, J 8.5, 1.5 Hz, quinolineH-4), 8.19 (1H, s, $C_6H_4CF_3H$-2), 8.11 (1H, d, J 8.0 Hz, $C_6H_4CF_3H$-4, H-5 or H-6), 7.90 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.69 (1H, d, J 7.5 Hz, $C_6H_4CF_3H$-4, H-5 or H-6), 7.55-7.43 (5H, m, 5 x ArH), 7.40-7.36 (3H, m, 3 x ArH); ^{13}C NMR ($CDCl_3$) δ 148.7, 140.6, 138.8, 138.6, 135.9, 134.9, 132.4, 131.5 (d, J 33.5 Hz), 130.4, 129.9, 129.7, 129.5 (m), 128.6, 127.7, 127.2, 126.7, 124.4 (d, J 3.5 Hz), 122.0, 115.6; ^{19}F NMR ($CDCl_3$) δ -63.0; *m/z*: 429 $[M+H]^+$ (found $[M+H]^+$, 429.0872, $C_{22}H_{15}F_3N_2O_2S$ requires $[M+H]^+$ 429.0879).

Compound 19: N-(5-phenylquinolin-8-yl)pyridine-3-sulfonamide



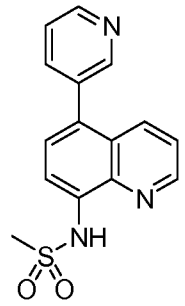
[0142] ^{1}H NMR ($CDCl_3$) δ 9.40 (1H, br s, NH), 9.13 (1H, d, J 2.0 Hz, pyH-2), 8.76 (1H, dd, J 4.0, 3.0 Hz, quinolineH-2), 8.67 (1H, dd, J 5.0, 1.5 Hz, pyH-4 or H-6), 8.24-8.20 (2H, m, quinolineH-4, pyH-5), 7.92 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.51-7.32 (8H, m, quinolineH-3, quinolineH-6 or H-7, pyH-4 or H-6, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 153.4, 148.7, 148.0, 138.6, 136.1, 135.8, 134.9, 132.3, 129.9, 128.6, 127.7, 127.3, 126.7, 123.6, 122.0, 115.2; *m/z*: 362 $[M+H]^+$ (found $[M+H]^+$, 362.0969, $C_{20}H_{15}N_3O_2S$ requires $[M+H]^+$ 362.0958).

Compound **20**: N-(4-(N-(5-phenylquinolin-8-yl)sulfamoyl)phenyl)acetamide



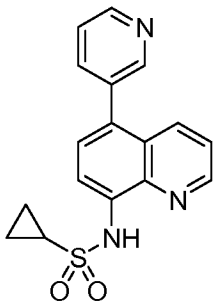
[0143] ^{1}H NMR ($CDCl_3$) δ 9.32 (1H, br s, NH), 8.77 (1H, dd, J 8.0, 1.5 Hz, quinolineH-2), 8.20 (1H, dd, J 8.5, 1.5 Hz, quinolineH-4), 7.90 (2H, d, J 8.5 Hz, 2H of C_6H_4NHCO), 7.85 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.53 (2H, d, J 9.0 Hz, 2H of C_6H_4NHCO), 7.49-7.35 (7H, m, quinolineH-3, quinolineH-6 or H-7, C_6H_5), 7.31 (1H, br s, NHCO), 2.15 (3H, s, $COCH_3$); ^{13}C NMR ($CDCl_3$) δ 148.5, 142.0, 138.8, 138.5, 134.9, 134.8, 133.0, 130.0, 126.8, 128.5, 127.6, 127.3, 126.6, 121.9, 119.1, 114.4, 24.7; *m/z*: 418 $[M+H]^+$ (found $[M+H]^+$, 418.1180, $C_{23}H_{19}N_3O_3S$ requires $[M+H]^+$ 418.1220).

Compound **21**: N-(5-(pyridin-3-yl)quinolin-8-yl)methanesulfonamide



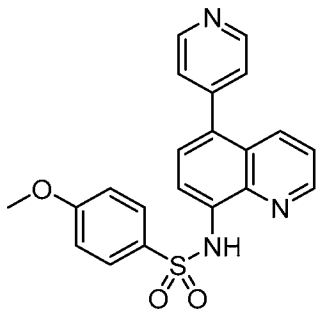
[0144] ^{1}H NMR ($CDCl_3$) δ 9.08 (1H, br s, SO_2NH), 8.87 (1H, m, quinolineH-2), 8.72 (2H, m, pyH-2, H-6), 8.20 (1H, dd, J 8.5, 1.5 Hz, quinolineH-4), 7.94 (1H, d, J 7.5 Hz, quinolineH-6 or H-7), 7.79 (1H, br d, J 7.5 Hz, pyH-4), 7.53-7.45 (3H, m, quinolineH-3, quinolineH-6 or H-7, pyH-5), 3.10 (3H, s, SO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 150.5, 149.0 (2C), 138.6, 137.3, 134.5, 134.4, 134.2, 131.2, 128.1, 126.7, 123.5, 122.6, 114.4, 39.5; *m/z*: 300 $[M+H]^+$ (found $[M+H]^+$, 300.0788, $C_{15}H_{13}N_3O_2S$ requires $[M+H]^+$ 300.0801).

Compound **22**: N-(5-(pyridin-3-yl)quinolin-8-yl)cyclopropanesulfonamide



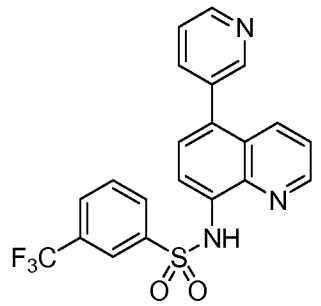
[0145] ^{1}H NMR ($CDCl_3$) δ 9.06 (1H, br s, SO_2NH), 8.88 (1H, dd, J 4.0, 1.5 Hz, quinolineH-2), 8.73-8.70 (2H, m, pyH-2, H-6), 8.20 (1H, dd, J 8.5, 1.5 Hz, quinolineH-4), 8.00 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.79 (1H, dt, J 7.5, 2.0 Hz, pyH-4), 7.51-7.44 (3H, m, quinolineH-3, quinolineH-6 or H-7, pyH-5), 2.62 (1H, tt, J 8.0, 5.0 Hz, cPrH-1), 1.33 (2H, m, 2H of cPrH-2, H-3), 0.95 (2H, m, 2H of cPrH-2, H-3); ^{13}C NMR ($CDCl_3$) δ 150.5, 149.0, 148.9, 138.8, 137.3, 134.6, 134.1, 130.9, 128.1, 126.7, 123.4, 122.4, 114.7, 30.3, 5.8; *m/z*: 326 $[M+H]^+$ (found $[M+H]^+$, 326.0949, $C_{17}H_{15}N_3O_2S$ requires $[M+H]^+$ 326.0958).

Compound **23**: 4-methoxy-N-(5-(pyridin-4-yl)quinolin-8-yl)benzenesulfonamide



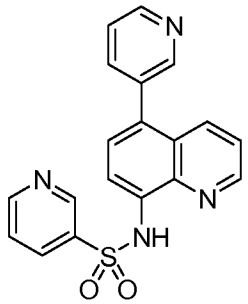
[0146] ^{1}H NMR ($CDCl_3$) δ 9.34 (1H, br s, SO_2NH), 8.81 (1H, dd, J 4.0, 1.5 Hz, quinolineH-2), 8.67 (2H, m, pyH-2, H-6), 8.12 (1H, dd, J 8.5, 1.0 Hz, quinolineH-4), 7.91 (2H, d, J 8.5 Hz, 2H of C_6H_4OMe), 7.87 (1H, d, J 8.5 Hz, quinolineH-6 or H-7 or pyH-4), 7.72 (1H, dt, J 8.0, 2.0 Hz, quinolineH-6 or H-7 or pyH-4), 7.45-7.39 (3H, m, quinolineH-3, quinolineH-6 or H-7, pyH-5), 6.87 (2H, d, J 9.0 Hz, 2H of C_6H_4OMe), 3.78 (3H, s, OCH_3); ^{13}C NMR ($CDCl_3$) δ 163.1, 150.5, 148.9, 148.7, 138.5, 137.2, 134.1, 134.0, 131.0, 130.5, 129.4, 128.0, 126.5, 123.4, 122.3, 114.2, 113.9, 55.5; *m/z*: 392 $[M+H]^+$ (found $[M+H]^+$, 392.1040, $C_{21}H_{17}N_3O_3S$ requires $[M+H]^+$ 392.1063).

Compound **24**: N-(5-(pyridin-3-yl)quinolin-8-yl)-3-(trifluoromethyl)benzenesulfonamide



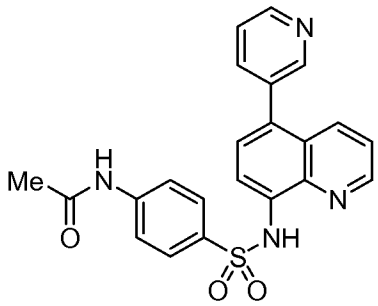
[0147] ^{1}H NMR ($CDCl_3$) δ 9.39 (1H, br s, SO_2NH), 8.81 (1H, dd, J 4.0, 1.5 Hz, quinolineH-2), 8.69 (1H, dd, J 5.0, 1.5 Hz, pyH-6), 8.66 (1H, d, J 2.0 Hz, pyH-2), 8.20 (1H, s, $C_6H_4CF_3H$-2), 8.12 (2H, m, quinolineH-2, $C_6H_4CF_3H$-4 or H-6), 7.93 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.74-7.70 (2H, m, pyH-5, $C_6H_4CF_3H$-4 or H-6), 7.55 (1H, t, J 8.0 Hz, $C_6H_4CF_3H$-5), 7.46-7.41 (4H, m, quinolineH-3, H-6 or H-7, pyH-4); ^{13}C NMR ($CDCl_3$) δ 150.4, 149.0, 140.5, 138.7, 137.2, 134.4, 134.1, 133.3, 131.7, 130.3 (d, J 1.0 Hz), 129.8, 129.6, 127.9, 126.6, 124.5 (q, J 3.5 Hz), 123.4, 122.5; ^{19}F NMR ($CDCl_3$) δ -63.0; *m/z*: 430 $[M+H]^+$ (found $[M+H]^+$, 430.0804, $C_{21}H_{14}F_3N_3O_2S$ requires $[M+H]^+$ 430.0832).

Compound **25**: N-(5-(pyridin-3-yl)quinolin-8-yl)pyridine-3-sulfonamide



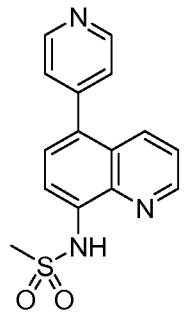
[0148] ^{1}H NMR ($CDCl_3$) δ 9.45 (1H, br s, SO_2NH), 9.15 (1H, dd, J 2.5, 1.0 Hz, 1 x pyH-2), 8.81 (1H, m, quinolineH-2), 8.69 (2H, dd, J 5.0, 1.5 Hz, 2H of 2 x pyH-4, H-6), 8.66 (1H, dd, J 2.0, 1.0 Hz, 1 x pyH-2), 8.24 (1H, ddd, J 7.5, 2.5, 2.0 Hz, 1 x pyH-4 or H-6), 8.13 (1H, dd, J 8.5, 1.5 Hz, quinolineH-4), 7.95 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.73 (1H, ddd, J 8.0, 2.0, 1.5 Hz, 1 x pyH-4 or H-6), 7.46-7.41 (3H, m, quinolineH-3, quinolineH-6 or H-7, 1 x pyH-5), 7.35 (1H, ddd, J 8.0, 5.0, 1.0 Hz, 1 x pyH-5); ^{13}C NMR ($CDCl_3$) δ 153.5, 150.4, 149.1, 149.0, 148.0, 138.6, 137.2, 136.0, 137.2, 136.0, 134.9, 134.3, 134.2, 133.2, 131.7, 127.9, 126.6, 123.7, 123.4, 122.5, 114.9; *m/z*: 363 $[M+H]^+$ (found $[M+H]^+$, 363.0807, $C_{19}H_{14}N_4O_2S$ requires $[M+H]^+$ 363.0910).

Compound **26**: N-(4-(N-(5-(pyridin-3-yl)quinolin-8-yl)sulfamoyl)phenyl)acetamide



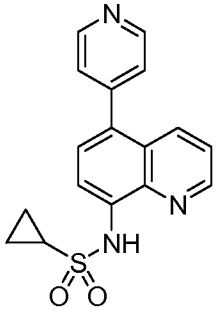
[0149] ^{1}H NMR ($CDCl_3$) δ 9.36 (1H, br s, SO_2NH), 8.81 (1H, dd, 4.0, 2.0 Hz, quinolineH-2), 8.66 (2H, m, pyH-2, H-6), 8.11 (1H, dd, J 8.5, 12.0 Hz, quinolineH-4), 7.91 (2H, d, J 9.0 Hz, 2H of $C_6\underline{H}_4NHAc$), 7.87 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.73 (1H, ddd, J 8.5, 2.0, 1.5 Hz, pyH-4), 7.55 (2H, d, J 9.0 Hz, 2H of $C_6\underline{H}_4NHAc$), 7.45-7.39 (4H, m, quinolineH-3, quinolineH-6 or H-7, pyH-5, NHAc), 2.15 (3H, s, $COCH_3$); ^{13}C NMR ($CDCl_3$) δ 160.8, 150.5, 148.9, 148.8, 142.1, 138.5, 137.3, 134.6, 134.1, 134.0, 133.9, 130.8, 128.6, 127.9, 126.5, 123.4, 122.3, 119.2, 114.1, 24.7; *m/z*: 419 $[M+H]^+$ (found $[M+H]^+$, 419.1172, $C_{22}H_{18}N_4O_3S$ requires $[M+H]^+$ 419.1164).

Compound **27**: N-(5-(pyridin-4-yl)quinolin-8-yl)methanesulfonamide



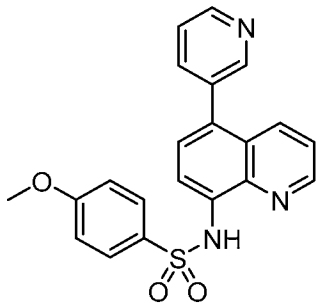
[0150] ^{1}H NMR ($CDCl_3$) δ 9.08 (1H, br s, SO_2NH), 8.87 (1H, m, quinolineH-2), 8.75 (2H, d, J 5.5 Hz, 2H of py), 8.25 (1H, dd, J 8.5, 1.0 Hz, quinolineH-4), 7.93 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.51 (2H, m, quinolineH-3, quinolineH-6 or H-7), 7.39 (2H, d, J 5.5 Hz, 2H of py), 3.10 (3H, s, SO_2CH_3); ^{13}C NMR ($CDCl_3$) δ 150.1, 149.0, 146.6, 138.5, 134.7, 134.0, 132.1, 127.7, 126.1, 124.8, 122.6, 114.2, 39.5; *m/z*: 300 $[M+H]^+$ (found $[M+H]^+$, 300.0789, $C_{15}H_{13}N_3O_2S$ requires $[M+H]^+$ 300.0801).

Compound **28**: N-(5-(pyridin-4-yl)quinolin-8-yl)cyclopropanesulfonamide



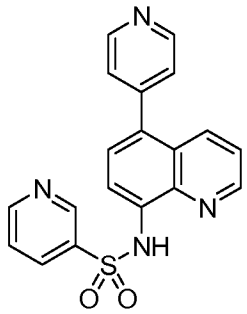
[0151] ^{1}H NMR ($CDCl_3$) δ 9.08 (1H, br s, SO_2NH), 8.88 (1H, m, quinolineH-2), 8.75 (2H, d, J 5.5 Hz, pyH-2, H-6), 8.25 (1H, br d, J 8.5 Hz, quinolineH-4), 7.98 (1H, d, J 7.5 Hz, quinolineH-6 or H-7), 7.52-7.48 (2H, m, quinolineH-3, quinolineH-6 or H-7), 7.40 (2H, d, J 5.5 Hz, pyH-3, H-5), 2.61 (1H, tt, J 8.0, 5.0 Hz, cPrH-1), 1.34 (2H, m, 2H of cPrH-2, H-3), 0.95 (2H, m, 2H of cPrH-2, H-3); ^{13}C NMR ($CDCl_3$) δ 150.1, 148.9, 146.7, 138.7, 135.0, 134.0, 131.8, 127.7, 126.0, 124.9, 122.5, 114.5, 30.3, 5.8; *m/z*: 326 $[M+H]^+$ (found $[M+H]^+$, 326.0953, $C_{17}H_{15}N_3O_2S$ requires $[M+H]^+$ 326.0958).

Compound **29**: 4-methoxy-N-(5-(pyridin-3-yl)quinolin-8-yl)benzenesulfonamide



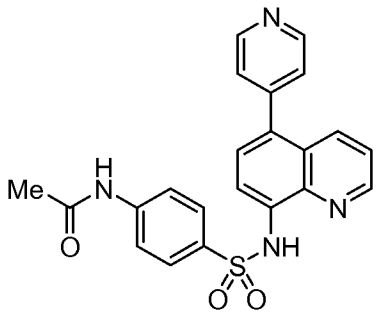
[0152] ^{1}H NMR ($CDCl_3$) δ 9.33 (1H, br s, SO_2NH), 8.82 (1H, m, quinolineH-2), 8.71 (2H, d, J 5.5 Hz, pyH-2, H-6), 8.17 (1H, dd, J 8.0, 1.5 Hz, quinolineH-4), 7.91 (2H, d, J 9.0 Hz, 2H of C_6H_4OMe), 7.86 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.43 (2H, m, quinolineH-3, quinolineH-6 or H-7), 7.34 (2H, d, J 5.5 Hz, pyH-3, H-5), 6.88 (2H, d, J 9.5 Hz, 2H of C_6H_4OMe), 3.79 (3H, s, OCH_3); *m/z*: 392 $[M+H]^+$ (found $[M+H]^+$, 392.1086, $C_{21}H_{17}N_3O_3S$ requires $[M+H]^+$ 392.1063).

Compound **30**: N-(5-(pyridin-4-yl)quinolin-8-yl)pyridine-3-sulfonamide



[0153] ^{1}H NMR ($CDCl_3$) δ 9.45 (1H, br s, SO_2NH), 9.14 (1H, dd, J 2.5, 1.0 Hz, pyH-2), 8.82 (1H, dd, J 4.0, 1.5 Hz, quinolineH-2), 8.73 (2H, d, J 6.0 Hz, pyH-2, H-6), 8.70 (1H, dd, J 5.0, 1.5 Hz, pyH-6), 8.24 (1H, ddd, J 8.0, 2.5, 1.5 Hz, pyH-4), 8.18 (1H, dd, J 8.5, 1.5 Hz, quinolineH-4), 7.95 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.45 (2H, m, quinolineH-3, quinolineH-6 or H-7), 7.37 (1H, m, pyH-5), 7.34 (2H, d, J 6.0 Hz, pyH-3, H-5); ^{13}C NMR ($CDCl_3$) δ 153.5, 150.1, 149.0, 148.0, 146.4, 138.5, 136.1, 134.8, 134.0, 133.6, 132.6, 127.5, 126.0, 124.7, 123.6, 122.5, 114.8; *m/z*: 363 $[M+H]^+$ (found $[M+H]^+$, 363.0913, $C_{19}H_{14}N_4O_2S$ requires $[M+H]^+$ 363.0910).

Compound **31**: N-(4-(N-(5-(pyridin-4-yl)quinolin-8-yl)sulfamoyl)phenyl)acetamide



[0154] ^{1}H NMR ($CDCl_3$) δ 9.38 (1H, br s, SO_2NH), 8.81 (1H, dd, J 4.5, 1.5 Hz, quinolineH-2), 8.71 (2H, d, J 6.0 Hz, pyH-2, H-6), 8.17 (1H, dd, J 8.5, 1.5 Hz, quinolineH-4), 7.89 (2H, d, J 9.0 Hz, 2H of C_6H_4NHAc), 7.86 (1H, d, J 8.5 Hz, quinolineH-6 or H-7), 7.81 (1H, s, NH), 7.56 (2H, d, J 9.0 Hz, 2H of C_6H_4NHAc), 7.44 (1H, dd, J 8.5, 4.5 Hz, quinolineH-3), 7.41 (1H, d, J 8.0 Hz, quinolineH-6 or H-7), 7.35 (2H, d, J 5.5 Hz, pyH-3, H-5), 2.14 (3H, s, $COCH_3$); ^{13}C NMR ($CDCl_3$) δ 168.7, 150.0, 148.8, 146.8, 142.4, 138.4, 134.2, 133.9, 131.7, 128.6, 127.6, 125.9, 124.9, 122.5, 119.3, 113.9, 24.6; *m/z*: 419 $[M+H]^+$ (found $[M+H]^+$, 419.1224, $C_{22}H_{18}N_4O_3S$ requires $[M+H]^+$ 419.1173).

Example 2: Cks1-Skp2 Protein-Protein Interaction

[0155] In vitro binding of Skp2 to Cks1 was established in an ELISA assay format, with Cks1 protein immobilized on a 384-well plate and binding of Skp1/Skp2 to Cks1 detected by anti-Skp2 immunoreaction.

Table 1. Potency of compounds in the interaction assay.

Compound	Cks1-Skp2 (μM)	GFP-p27
1	0.84	++
4	0.54	+
5	0.55	+
6	1.73	+
7	5.54	+
8	7.84	+
12	3.57	+
13	1.15	NA
14	1.74	NA

Example 3: p27-GFP Stabilization

[0156] A constitutively degraded mutant p27(T187D) is fused to GFP and used as a reporter for SCF-Skp2 E3 ligase activity in Hela cells. Inhibition of Cks1-Skp2 interaction by the compounds will inhibit p27 ubiquitination and degradation, thus stabilizing p27-GFP protein levels within the cells.

Table 2. Potency of the sulfonamide analogues in the Cks1-Skp2 interaction assay (μM).

Compound	Potency (μM)	Compound	Potency (μM)	Compound	Potency (μM)
15	2.20	**21**	15.13		
16	12.10	**22**	7.16	**28**	10.94
17	8.02	**23**	0.58	**29**	2.45
18	6.70	**24**	0.17	**30**	1.21
19	2.20	**25**	1.67	**31**	6.55
20	7.60	**26**	14.49		

Example 4: Inhibition of Tumor Cell Growth

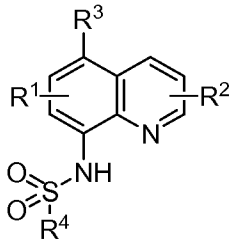
[0157] Compounds that were able to inhibit the interaction of Cks1-Skp2 were screened in both the lung tumor cell line A549 and the fibrosarcoma HT1080, which have been shown to be sensitive to p27.

Table 3. Potency of selected compounds against two cancer cell lines.

Compound	IC_{50} (μM)		
	Cks1-Skp2	A549	HT1080
4	0.54	2.36	1.64
5	0.55	26.01	9.78
6	1.73	6.02	4.22
7	5.54	2.36	0.64
8	7.84	0.39	0.15
12	3.57	4.11	0.08
13	1.15	4.09	0.74
14	1.74	6.48	6.83
23	0.58	1.24	0.44
24	0.17	0.91	0.40
25	1.67	5.24	1.07
29	2.45	3.06	1.32
30	1.21	5.88	1.07

WHAT IS CLAIMED:

1. A compound having structural formula (I):



(I)

or a pharmaceutically acceptable salt, prodrug or *N*-oxide thereof, or solvate or hydrate thereof,

wherein

R^1 is -hydrogen, -(C_1-C_6 haloalkyl), -Y-(C_1-C_6 haloalkyl), -Y-(C_0-C_6 alkyl)-Ar, -Y-(C_0-C_6 alkyl)-Het, -Y-(C_0-C_6 alkyl)-Cak, -Y-(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN,

wherein Y is O, S, N(R^5), and R^5 is -hydrogen or -(C_1-C_6 alkyl);

R^2 is -hydrogen, -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -Y-(C_1-C_6 alkyl), -Y-(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN;

wherein Y is O, S, N(R^5), and R^5 is -hydrogen or -(C_1-C_6 alkyl);

R^3 is -hydrogen, -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN; and

R^4 is -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het or -(C_0-C_6 alkyl)-Cak,

wherein

each Ar (aryl), Het (heteroaryl), Cak (cycloalkyl), Hca (heterocycloalkyl), alkyl, and haloalkyl is optionally substituted,

provided that:

at least one of R^1 and R^3 is not hydrogen, and

the compound is not:

N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
N-(6-chloroquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
N-(6-fluoroquinolin-8-yl)benzenesulfonamide;

N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
2,6-difluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
4-chloro-2-fluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(7-chloroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-bromoquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
2,4-dichloro-N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)pyridine-3-sulfonamide;
2-amino-N-(5-chloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(5-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide;
N-(5-bromoquinolin-8-yl)-5-(oxazol-5-yl)thiophene-2-sulfonamide; or
N-(5-bromoquinolin-8-yl)-4-(2-methylpyrimidin-4-yl)benzenesulfonamide.

2. The compound of claim 1,

wherein

R^1 is -(C_1-C_6 haloalkyl), -Y-(C_1-C_6 haloalkyl), -Y-(C_0-C_6 alkyl)-Ar, -Y-(C_0-C_6 alkyl)-Het, -Y-(C_0-C_6 alkyl)-Cak, -Y-(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN,

wherein Y is O, S, N(R^5), and R^5 is -hydrogen or -(C_1-C_6 alkyl).

3. The compound of claim 1,

wherein

R^3 is -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN.

4. The compound of claim 1,

wherein

R^1 is -(C_1-C_6 haloalkyl), -Y-(C_1-C_6 haloalkyl), -Y-(C_0-C_6 alkyl)-Ar, -Y-(C_0-C_6 alkyl)-Het, -Y-(C_0-C_6 alkyl)-Cak, -Y-(C_0-C_6 alkyl)-Hca, -NO_2 or -CN,

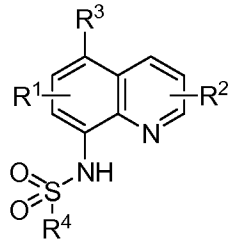
wherein Y is O, S, N(R^5), and R^5 is -hydrogen or -(C_1-C_6 alkyl).

5. The compound of claim 1,

wherein

R^3 is -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -(C_0-C_6 alkyl)-Hca, -NO_2 or -CN.

6. A compound having the structure of formula (I):



(I)

or a pharmaceutically acceptable salt, prodrug or *N*-oxide thereof, or solvate or hydrate thereof,

wherein

R^1 is -hydrogen, -(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -NO_2 or -CN;

R^2 is -hydrogen, -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN;

R^3 is -hydrogen, -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -NO_2 or -CN; and

R^4 is -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het or -(C_0-C_6 alkyl)-Cak,

wherein

each Ar (aryl), Het (heteroaryl), Cak (cycloalkyl), Hca (heterocycloalkyl), alkyl, and haloalkyl is optionally substituted,

provided that:

at least one of R^1 and R^3 is not hydrogen.

7. The compound of any of claims 1-6, wherein

R^2 is -hydrogen, -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl), -O-(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN,

wherein -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl) and -O-(C_1-C_6 haloalkyl) are each optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

8. The compound of any of claims 1-8, wherein

R^2 is -hydrogen, -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

9. The compound of any of claims 1-8, wherein

R^2 is -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

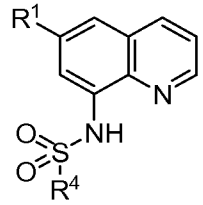
10. The compound of any of claims 1-8 or 10, wherein

R^2 is - hydrogen.

11. The compound of any of claims 1-9, wherein

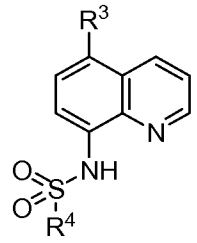
R^2 is - halogen.

12. The compound of any of claims 1, 2, 4 or 6, having the structure of formula (II):



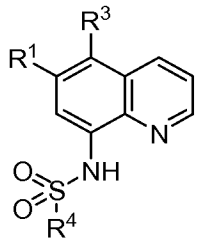
(II).

13. The compound of any of claims 1, 3, 5 or 6, having the structure of formula (III):



(III).

14. The compound of any of claims 1-6, having structural formula (IV):



(IV)

or a pharmaceutically acceptable salt, prodrug or *N*-oxide thereof, or solvate or hydrate thereof,

wherein

R^1 is -hydrogen or -O-(C_0-C_6 alkyl)-Ar,

R^3 is -hydrogen, -(C_0-C_6 alkyl)-Ar or -(C_0-C_6 alkyl)-Het; and

R^4 is -(C_0-C_6 alkyl)-Ar or -(C_0-C_6 alkyl)-Het.

15. The compound of any of claims 1-5 or 7-12, wherein

R^1 is -hydrogen, -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN,

wherein -(C_1-C_6 haloalkyl), -O-(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak and -O-(C_0-C_6 alkyl)-Hca are each optionally substituted with one or more -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

16. The compound of any of claims 1-5 or 7-12, wherein

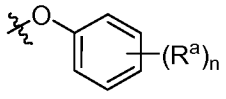
R^1 is -hydrogen, -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN.

17. The compound of any of claims 1-5 or 7-12, wherein
R^1 is -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN.

18. The compound of any of claims 1-5 or 7-12, wherein
R^1 is -hydrogen, -(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -NO_2 or -CN.

19. The compound of any of claims 1-12, wherein
R^1 is -(C_1-C_6 haloalkyl), -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -NO_2 or -CN.

20. The compound of any of claims 1-5 or 7-12, wherein
R^1 is -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak, -O-(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN, wherein -O-(C_0-C_6 alkyl)-Ar, -O-(C_0-C_6 alkyl)-Het, -O-(C_0-C_6 alkyl)-Cak and -O-(C_0-C_6 alkyl)-Hca are each optionally substituted with one or more -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN.

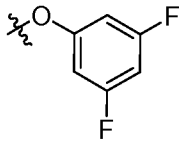
21. The compound of any of claims 1-12 or 14, wherein
R^1 is  ,
wherein
R^a is independently hydrogen, -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN, and n is 1, 2, 3, 4 or 5.

22. The compound of claim 21, wherein
R^a is independently -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen or -CN, and n is 1, 2, 3 or 4.

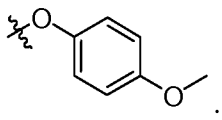
23. The compound of claim 21, wherein

R^a is independently -OMe, fluoro, chloro, bromo or -CN, and n is 1 or 2.

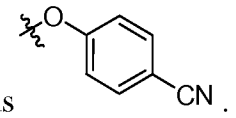
24. The compound of any of claims 1-12 or 14, wherein

R^1 is  .

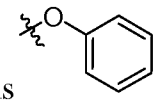
25. The compound of any of claims 1-12 or 14, wherein

R^1 is  .

26. The compound of any of claims 1-12 or 14, wherein

R^1 is  .

27. The compound of any of claims 1-12 or 14, wherein

R^1 is  .

28. The compound of any of claims 1-5, 7-11, 13 or 15-27, wherein

R^3 is -hydrogen, -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak, -(C_0-C_6 alkyl)-Hca, -halogen, -NO_2 or -CN,

wherein -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak and -(C_0-C_6 alkyl)-Hca are each optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

29. The compound of any of claims 1-5, 7-11, 13 or 15-27, wherein

R^3 is -hydrogen, -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het, -(C_0-C_6 alkyl)-Cak or -(C_0-C_6 alkyl)-Hca.

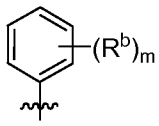
30. The compound of any of claims 1-5, 7-11, 13 or 15-27, wherein
R^3 is -hydrogen, -halogen, $-NO_2$ or -CN.

31. The compound of any of claims 1-11 or 13-27, wherein
R^3 is -hydrogen .

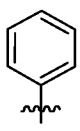
32. The compound of any of claims 1-5, 7-11, 13 or 15-27, wherein
R^3 is -halogen.

33. The compound of any of claims 1-11 or 13-27, wherein
R^3 is $-(C_0\text{-}C_6$ alkyl)-Ar or $-(C_0\text{-}C_6$ alkyl)-Het.

34. The compound of any of claims 1-11 or 13-27, wherein
R^3 is -Ar.

35. The compound of any of claims 1-11 or 13-27, wherein
R^3 is  ,
wherein
R^b is independently hydrogen, $-(C_1\text{-}C_6$ alkyl), $-O\text{-}(C_1\text{-}C_6$ alkyl), $-(C_1\text{-}C_6$ haloalkyl), -halogen, $-NO_2$ or -CN, and m is 1, 2, 3, 4 or 5.

36. The compound of claim 35, wherein
R^b is independently $-O\text{-}(C_1\text{-}C_6$ alkyl), -halogen or -CN, and m is 1 or 2.

37. The compound of any of claims 1-11 or 13-27, wherein
R^3 is  .

38. The compound of any of claims 1-11 or 13-27, wherein

R^3 is -(C_0-C_6 alkyl)-Het.

39. The compound of any of claims 1-11 or 13-27, wherein
R^3 is -(C_0-C_6 alkyl)-pryidyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

40. The compound of any of claims 1-11 or 13-27, wherein
R^3 is -(C_0-C_6 alkyl)-furanyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

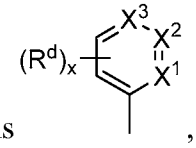
41. The compound of any of claims 1-11 or 13-27, wherein
R^3 is -(C_0-C_6 alkyl)-thiophenyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

42. The compound of any of claims 1-11 or 13-27, wherein
R^3 is -(C_0-C_6 alkyl)-benzofuranyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

43. The compound of any of claims 1-11 or 13-27, wherein
R^3 is -(C_0-C_6 alkyl)- benzothiaphenyl optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

44. The compound of any of claims 1-11 or 13-27, wherein
R^3 is -Het.

45. The compound of any of claims 1-11 or 13-27, wherein

R^3 is 

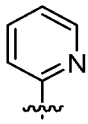
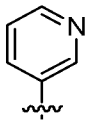
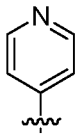
,

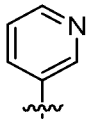
wherein

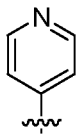
R^d is independently -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN, x is 1, 2, 3, 4 or 5, and one of X^1, X^2 and X^3 is N.

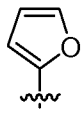
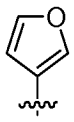
46. The compound of claim 45, wherein
R^d is independently -O-(C_1-C_6 alkyl), -halogen or -CN, x is 1 or 2, and one of X^1, X^2 and X^3 is N.

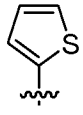
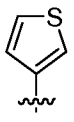
47. The compound of claim 45, wherein
R^d is R^d is independently -OMe, fluoro, chloro, bromo or -CN, x is 1 or 2, and one of X^3 is N.

48. The compound of any of claims 1-11 or 13-27, wherein
R^3 is  ,  or  .

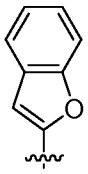
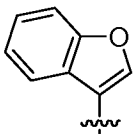
49. The compound of any of claims 1-11 or 13-27, wherein
R^3 is  .

50. The compound of any of claims 1-11 or 13-27, wherein
R^3 is  .

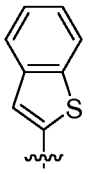
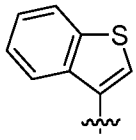
51. The compound of any of claims 1-11 or 13-27, wherein
R^3 is  or  .

52. The compound of any of claims 1-11 or 13-27, wherein
R^3 is  or  .

53. The compound of any of claims 1-11 or 13-27, wherein

R^3 is  or  .

54. The compound of any of claims 1-11 or 13-27, wherein

R^3 is  or  .

55. The compound of any of claims 1-11 or 13-27, wherein

R^3 is -Cak.

56. The compound of any of claims 1-11 or 13-27, wherein

R^3 is cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

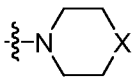
57. The compound of any of claims 1-11 or 13-27, wherein

R^3 is cyclopentyl or cyclohexyl.

58. The compound of any of claims 1-5, 7-11, 13 or 15-27, wherein

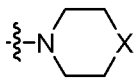
R^3 is -(C_0-C_6 alkyl)-Hca.

59. The compound of any of claims 1-5, 7-11, 13 or 15-27, wherein

R^3 is  ,

wherein

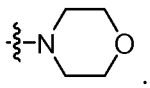
X is -O-, -S-, N(R^5) or -C(H)-CH_2-Ar; and

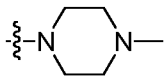
the  group is optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_1-C_6 alkyl)-Ar, -halogen, -NO_2 or -CN.

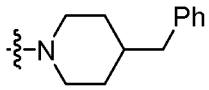
60. The compound of claim 59, wherein

X is -O-, N(R^5) or -C(H)-CH_2-Ar.

61. The compound of claim 59, wherein
X is N(R^5) or -C(H)-CH_2-Ar.

62. The compound of any of claims 1-5, 7-11, 13 or 15-27, wherein
R^3 is  .

63. The compound of any of claims 1-5, 7-11, 13 or 15-27, wherein
R^3 is  .

64. The compound of any of claims 1-5, 7-11, 13 or 15-27, wherein
R^3 is  .

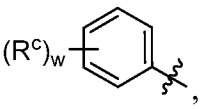
65. The compound of any of claims 1-64, wherein
R^4 is -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het or -(C_0-C_6 alkyl)-Cak,
wherein
-(C_1-C_6 haloalkyl), -(C_0-C_6 alkyl)-Ar, -(C_0-C_6 alkyl)-Het and -(C_0-C_6 alkyl)-Cak are each optionally substituted with one or more -(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -O-(C_1-C_6 alkyl), N(R^5)(R^6), -halogen, -NO_2 or -CN, wherein R^5 and R^6 are independently -hydrogen, -(C_1-C_6 alkyl) or -C(O)-(C_1-C_6 alkyl).

66. The compound of any of claims 1-64, wherein
R^4 is -(C_1-C_6 alkyl).

67. The compound of any of claims 1-64, wherein
R^4 is -methyl.

68. The compound of any of claims 1-64, wherein
R^4 is -(C_1-C_6 haloalkyl).

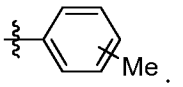
69. The compound of any of claims 1-64, wherein
R^4 is -CF_3.

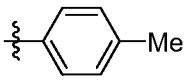
70. The compound of any of claims 1-64, wherein
R^4 is  ,
wherein
R^c is independently -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN, and w is 1, 2, 3, 4 or 5.

71. The compound of claim 70, wherein
R^c is independently -O-(C_1-C_6 alkyl), -halogen or -CN, and w is 1 or 2.

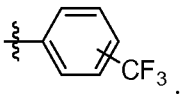
72. The compound of claim 70, wherein
R^c is independently -OMe, fluoro, chloro, bromo or -CN, and w is 1 or 2.

73. The compound of claim 70, wherein
R^c is -Me, and w is 1, 2 or 3.

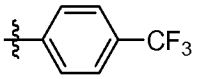
74. The compound of any of claims 1-64, wherein
R^4 is  .

75. The compound of any of claims 1-64, wherein
R^4 is  .

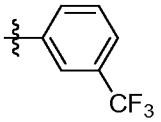
76. The compound of any of claims 1-64, wherein

R^4 is  .

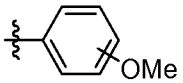
77. The compound of any of claims 1-64, wherein

R^4 is  .

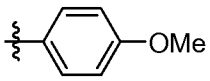
78. The compound of any of claims 1-64, wherein

R^4 is  .

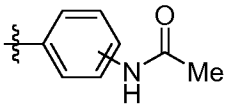
79. The compound of any of claims 1-64, wherein

R^4 is  .

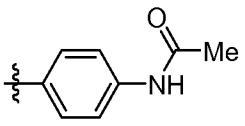
80. The compound of any of claims 1-64, wherein

R^4 is  .

81. The compound of any of claims 1-64, wherein

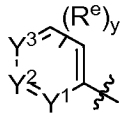
R^4 is  .

82. The compound of any of claims 1-64, wherein

R^4 is  .

83. The compound of any of claims 1-64, wherein R^4 is -(C_0-C_6 alkyl)-Het.

84. The compound of any of claims 1-64, wherein

R^4 is  ,

wherein

R^e is independently -(C_1-C_6 alkyl), -O-(C_1-C_6 alkyl), -(C_1-C_6 haloalkyl), -halogen, -NO_2 or -CN, y is 1, 2, 3, 4 or 5, and one of X^1, X^2 and X^3 is N.

85. The compound of claim 84, wherein

R^e is independently -O-(C_1-C_6 alkyl), -halogen or -CN, y is 1 or 2, and one of Y^1, Y^2 and Y^3 is N.

86. The compound of claim 84, wherein

R^e is independently -OMe, fluoro, chloro, bromo, iodo or -CN, y is 1 or 2, and Y^2 or Y^3 is N.

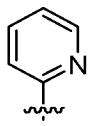
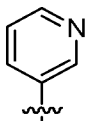
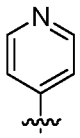
87. The compound of claim 84, wherein

R^e is independently -OMe, fluoro, chloro, bromo or -CN, y is 1 or 2, and Y^2 is N.

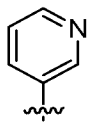
88. The compound of claim 84, wherein

R^e is independently -OMe, fluoro, chloro, bromo or -CN, y is 1 or 2, and Y^3 is N.

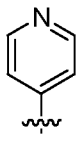
89. The compound of any of claims 1-64, wherein

R^4 is  ,  or  .

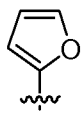
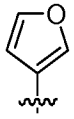
90. The compound of any of claims 1-64, wherein

R^4 is  .

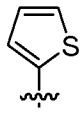
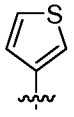
91. The compound of any of claims 1-64, wherein

R^4 is  .

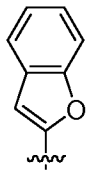
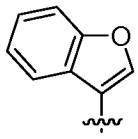
92. The compound of any of claims 1-64, wherein

R^4 is  or  .

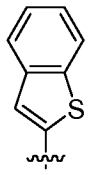
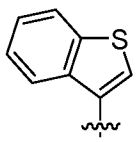
93. The compound of any of claims 1-64, wherein

R^4 is  or  .

94. The compound of any of claims 1-64, wherein

R^4 is  or  .

95. The compound of any of claims 1-64, wherein

R^4 is  or  .

96. The compound of claim 1, wherein the compound is:

4-methyl-N-(5-phenylquinolin-8-yl)benzenesulfonamide;
N-(5-(furan-2-yl)quinolin-8-yl)-4-methylbenzenesulfonamide;
4-methyl-N-(5-(pyridin-3-yl)quinolin-8-yl)benzenesulfonamide;
4-methyl-N-(5-(thiophen-3-yl)quinolin-8-yl)benzenesulfonamide;
N-(5-(benzo[b]thiophen-2-yl)quinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-(4-benzylpiperidin-1-yl)quinolin-8-yl)-4-methylbenzenesulfonamide;
4-methyl-N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
4-methyl-N-(5-(4-methylpiperazin-1-yl)quinolin-8-yl)benzenesulfonamide;
N-(6-(3,5-difluorophenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide;
N-(6-(4-methoxyphenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide;

N-(6-(3-cyanophenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-phenylquinolin-8-yl)methanesulfonamide;
N-(5-phenylquinolin-8-yl)cyclopropanesulfonamide;
4-methoxy-N-(5-phenylquinolin-8-yl)benzenesulfonamide;
N-(5-phenylquinolin-8-yl)-3-(trifluoromethyl)benzenesulfonamide;
N-(5-phenylquinolin-8-yl)pyridine-3-sulfonamide;
N-(4-(N-(5-phenylquinolin-8-yl)sulfamoyl)phenyl)acetamide;
N-(5-(pyridin-3-yl)quinolin-8-yl)methanesulfonamide;
N-(5-(pyridin-3-yl)quinolin-8-yl)cyclopropanesulfonamide;
4-methoxy-N-(5-(pyridin-4-yl)quinolin-8-yl)benzenesulfonamide;
N-(5-(pyridin-3-yl)quinolin-8-yl)-3-(trifluoromethyl)benzenesulfonamide;
N-(5-(pyridin-3-yl)quinolin-8-yl)pyridine-3-sulfonamide;
N-(4-(N-(5-(pyridin-3-yl)quinolin-8-yl)sulfamoyl)phenyl)acetamide;
N-(5-(pyridin-4-yl)quinolin-8-yl)methanesulfonamide;
N-(5-(pyridin-4-yl)quinolin-8-yl)cyclopropanesulfonamide;
4-methoxy-N-(5-(pyridin-3-yl)quinolin-8-yl)benzenesulfonamide;
N-(5-(pyridin-4-yl)quinolin-8-yl)pyridine-3-sulfonamide; or
N-(4-(N-(5-(pyridin-4-yl)quinolin-8-yl)sulfamoyl)phenyl)acetamide.

97. The compound of claim 14, wherein the compound is:

4-methyl-N-(5-phenylquinolin-8-yl)benzenesulfonamide;
N-(5-(furan-2-yl)quinolin-8-yl)-4-methylbenzenesulfonamide;
4-methyl-N-(5-(pyridin-3-yl)quinolin-8-yl)benzenesulfonamide;
4-methyl-N-(5-(thiophen-3-yl)quinolin-8-yl)benzenesulfonamide;
N-(5-(benzo[b]thiophen-2-yl)quinolin-8-yl)-4-methylbenzenesulfonamide;
N-(6-(3,5-difluorophenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide;
N-(6-(4-methoxyphenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide;
N-(6-(3-cyanophenoxy)quinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-phenylquinolin-8-yl)methanesulfonamide;
N-(5-phenylquinolin-8-yl)pyridine-3-sulfonamide;
4-methoxy-N-(5-(pyridin-4-yl)quinolin-8-yl)benzenesulfonamide;
N-(5-(pyridin-3-yl)quinolin-8-yl)-3-(trifluoromethyl)benzenesulfonamide;
N-(5-(pyridin-3-yl)quinolin-8-yl)pyridine-3-sulfonamide;
4-methoxy-N-(5-(pyridin-3-yl)quinolin-8-yl)benzenesulfonamide; or
N-(5-(pyridin-4-yl)quinolin-8-yl)pyridine-3-sulfonamide.

98. A pharmaceutical composition comprising a pharmaceutically acceptable diluent, carrier, or excipient and a compound according to any one of claims 1-97 or a compound selected from:

N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
N-(6-chloroquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;

N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
2,6-difluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
4-chloro-2-fluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(7-chloroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-bromoquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
2,4-dichloro-N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)pyridine-3-sulfonamide;
2-amino-N-(5-chloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(5-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide;
N-(5-bromoquinolin-8-yl)-5-(oxazol-5-yl)thiophene-2-sulfonamide; and
N-(5-bromoquinolin-8-yl)-4-(2-methylpyrimidin-4-yl)benzenesulfonamide.

99. The pharmaceutical composition of claim 98, wherein the compound is according to any one of claims 1-97.

100. The pharmaceutical composition of claim 98, wherein the compound is selected from:

N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
N-(6-chloroquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;

N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
2,6-difluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
4-chloro-2-fluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(7-chloroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-bromoquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
2,4-dichloro-N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)pyridine-3-sulfonamide;
2-amino-N-(5-chloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(5-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide;
N-(5-bromoquinolin-8-yl)-5-(oxazol-5-yl)thiophene-2-sulfonamide; and
N-(5-bromoquinolin-8-yl)-4-(2-methylpyrimidin-4-yl)benzenesulfonamide.

101. A pharmaceutical composition comprising a pharmaceutically acceptable diluent, carrier, or excipient and a compound according to claim 96.

102. A method for treating a disease or condition mediated by or involving Cks1-Skp2 PPI in a subject in need thereof, comprising administering an effective Cks1-Skp2 PPI inhibiting amount of a compound according to any one of claims 1-97 or a compound selected from:

N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
N-(6-chloroquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
N-(6-fluoroquinolin-8-yl)benzenesulfonamide;

N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
2,6-difluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
4-chloro-2-fluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(7-chloroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-bromoquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
2,4-dichloro-N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)pyridine-3-sulfonamide;
2-amino-N-(5-chloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(5-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide;
N-(5-bromoquinolin-8-yl)-5-(oxazol-5-yl)thiophene-2-sulfonamide; and
N-(5-bromoquinolin-8-yl)-4-(2-methylpyrimidin-4-yl)benzenesulfonamide,
or the pharmaceutical composition according to claim 98.

103. The method of claim 102, wherein the compound is according to any one of claims 1-97.

104. The method of claim 102, wherein the compound is selected from:

N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
N-(6-chloroquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;

2,6-difluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
4-chloro-2-fluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(7-chloroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-bromoquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
2,4-dichloro-N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)pyridine-3-sulfonamide;
2-amino-N-(5-chloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(5-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide;
N-(5-bromoquinolin-8-yl)-5-(oxazol-5-yl)thiophene-2-sulfonamide; and
N-(5-bromoquinolin-8-yl)-4-(2-methylpyrimidin-4-yl)benzenesulfonamide,

105. A method for treating a disease or condition mediated by or involving Cks1-Skp2 PPI in a subject in need thereof, comprising administering an effective Cks1-Skp2 PPI inhibiting amount of a compound according to claim 96 or a pharmaceutical composition according to claim 101.

106. The method of claim 102 or 105, wherein the effective Cks1-Skp2 PPI inhibiting amount is sufficient to inhibit protein ubiquitination in the subject.

107. The method of claim 102 or 105, wherein the effective Cks1-Skp2 PPI inhibiting amount is sufficient to increase the p27 levels in the subject.

108. The method of any one of claims 102-107, wherein the subject is human.

109. The method of any one of claims 102-108, wherein the disease or condition mediated by or involving Cks1-Skp2 PPI involves a process selected from the group consisting of inflammation, adaptive immunity, innate immunity, bone metabolism, LPS-induced angiogenesis, osteoporosis, osteopinneal diseases, lymph node development, mammary gland development, skin development, and central nervous system development.

110. The method of any one of claims 102-108, wherein the disease or condition mediated by or involving Cks1-Skp2 PPI is cancer.

111. The method of claim 110, wherein the cancer is colon, pancreas, breast, prostate, lung, brain, ovary, cervix, testes, renal, head, or neck cancer, or lymphoma, leukemia, or melanoma.

112. A method for inhibiting Cks1-Skp2 PPI in a cell, comprising contacting the cell with an effective Cks1-Skp2 PPI inhibiting amount of a compound according to any one of claims 1-97, a compound selected from:

N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
N-(6-chloroquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
2,6-difluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
4-chloro-2-fluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(7-chloroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-bromoquinolin-8-yl)benzenesulfonamide;

N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
2,4-dichloro-N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)pyridine-3-sulfonamide;
2-amino-N-(5-chloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(5-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide;
N-(5-bromoquinolin-8-yl)-5-(oxazol-5-yl)thiophene-2-sulfonamide; and
N-(5-bromoquinolin-8-yl)-4-(2-methylpyrimidin-4-yl)benzenesulfonamide,
or a pharmaceutical composition according to claim 98.

113. The method of claim 112, wherein the compound is according to any one of claims 1-97.

114. The method of claim 112, wherein the compound is selected from:

N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
N-(6-chloroquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
2,6-difluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
4-chloro-2-fluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(7-chloroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-bromoquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)benzenesulfonamide;

N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
2,4-dichloro-N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)pyridine-3-sulfonamide;
2-amino-N-(5-chloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(5-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide;
N-(5-bromoquinolin-8-yl)-5-(oxazol-5-yl)thiophene-2-sulfonamide; and
N-(5-bromoquinolin-8-yl)-4-(2-methylpyrimidin-4-yl)benzenesulfonamide.

115. A method for inhibiting Cks1-Skp2 PPI in a cell, comprising contacting the cell with an effective Cks1-Skp2 PPI inhibiting amount of a compound according to claim 96 or a pharmaceutical composition according to claim 101.

116. A method for inhibiting ubiquitination in a cell, comprising contacting the cell with an effective ubiquitination-inhibiting amount of a compound according to any one of claims 1-97, a compound selected from:

N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
N-(6-chloroquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
2,6-difluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
4-chloro-2-fluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(7-chloroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-bromoquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)benzenesulfonamide;

N-(5-bromoquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
2,4-dichloro-N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)pyridine-3-sulfonamide;
2-amino-N-(5-chloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(5-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide;
N-(5-bromoquinolin-8-yl)-5-(oxazol-5-yl)thiophene-2-sulfonamide; and
N-(5-bromoquinolin-8-yl)-4-(2-methylpyrimidin-4-yl)benzenesulfonamide,
or a pharmaceutical composition according to claim 98.

117. The method of claim 116, wherein the compound is according to any one of claims 1-97.

118. The method of claim 116, wherein the compound is selected from:

N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
N-(6-chloroquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
2,6-difluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
4-chloro-2-fluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(7-chloroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-bromoquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;

N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
2,4-dichloro-N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)pyridine-3-sulfonamide;
2-amino-N-(5-chloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(5-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide;
N-(5-bromoquinolin-8-yl)-5-(oxazol-5-yl)thiophene-2-sulfonamide; and
N-(5-bromoquinolin-8-yl)-4-(2-methylpyrimidin-4-yl)benzenesulfonamide.

119. A method for increasing p27 levels in a cell, comprising contacting the cell with an effective p27-increasing amount of a compound according to any one of claims 1-97, a compound selected from:

N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
N-(6-chloroquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
2,6-difluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
4-chloro-2-fluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(7-chloroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-bromoquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
2,4-dichloro-N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)pyridine-3-sulfonamide;
2-amino-N-(5-chloroquinolin-8-yl)-4-methylbenzenesulfonamide;

N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(5-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide;
N-(5-bromoquinolin-8-yl)-5-(oxazol-5-yl)thiophene-2-sulfonamide; and
N-(5-bromoquinolin-8-yl)-4-(2-methylpyrimidin-4-yl)benzenesulfonamide,
or a pharmaceutical composition according to claim 98.

120. The method of claim 119, wherein the compound is according to any one of claims 1-97.

121. The method of claim 119, wherein the compound is selected from:

N-(5-bromoquinolin-8-yl)-4-methylbenzenesulfonamide
N-(6-chloroquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)benzenesulfonamide;
2,6-difluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
4-chloro-2-fluoro-N-(6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;
N-(7-chloroquinolin-8-yl)benzenesulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)-6-(trifluoromethyl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-2-sulfonamide;
N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-(trifluoromethoxy)quinolin-8-yl)pyridine-3-sulfonamide;
6-cyano-N-(6-fluoroquinolin-8-yl)pyridine-3-sulfonamide;
N-(6-bromoquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)benzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5,7-dichloroquinolin-8-yl)-2,4,6-trimethylbenzenesulfonamide;
2,4-dichloro-N-(5-chloroquinolin-8-yl)benzenesulfonamide;
N-(5-chloroquinolin-8-yl)pyridine-3-sulfonamide;
2-amino-N-(5-chloroquinolin-8-yl)-4-methylbenzenesulfonamide;
N-(5-chloro-6-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5,6-difluoroquinolin-8-yl)benzenesulfonamide;

N-(5-fluoroquinolin-8-yl)benzenesulfonamide;
N-(5-morpholinoquinolin-8-yl)benzenesulfonamide;
N-(5-bromoquinolin-8-yl)-5-(2-(methylthio)pyrimidin-4-yl)thiophene-2-sulfonamide;
N-(5-bromoquinolin-8-yl)-5-(oxazol-5-yl)thiophene-2-sulfonamide; and
N-(5-bromoquinolin-8-yl)-4-(2-methylpyrimidin-4-yl)benzenesulfonamide.

122. A method for increasing p27 levels in a cell, comprising contacting the cell with an effective p27-increasing amount of a compound according to claim 96 or a pharmaceutical composition according to claim 101.

123. The method of any one of claims 112-122, wherein the cell is a human cell.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2015/045174

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 C07D215/40 C07D401/04 C07D401/12 C07D405/04
C07D409/04 A61K31/4706 A61K31/496 A61K31/5377 A61P35/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2007/254894 A1 (KANE JOHN L JR [US] ET AL) 1 November 2007 (2007-11-01)	1,3,5-8, 10, 13-16, 18,28, 29, 58-61, 63,65, 83,89, 98,99, 102-113, 116,117, 119,120, 122,123
Y	compound 110 on page 36, compound 109 on page 35 and compound 73 in Table 5 on page 31; paragraphs [0029], [0034], [0041] - [0043]; claims 1,6,41	1

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
24 September 2015	12/10/2015

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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Y	last two compounds on page 60, 2nd and 3rd compound on page 62, compound 226 on page 25, intermediates 272 and 273 on page 145; paragraphs [0023], [0614]; claims 1,10,12	1
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