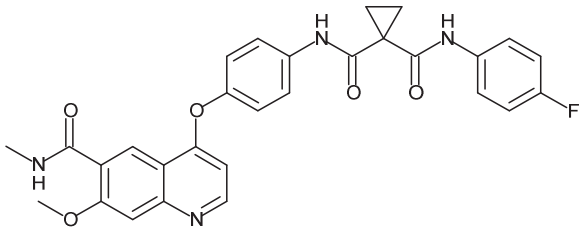
receptor. Tumor cells secrete a soluble form of the extracellular Mer receptor which reduces the ability of soluble Gas-6 ligand to activate Mer on endothelial cells, leading to cancer progression.

[0005] Therefore a need exists for compounds that inhibit TAM receptor tyrosine kinases such as Axl and Mer for the treatment of selected cancers.

Summary of the ~~Invention~~Disclosure

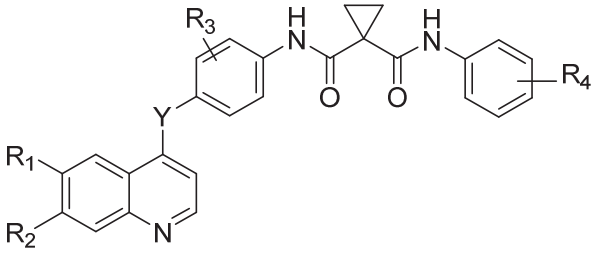
[0005a] In one aspect, provided herein is a compound which is:



or a pharmaceutically acceptable salt thereof.

[0005b] In one aspect, provided herein is a compound which is 1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(methylcarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide or a pharmaceutically acceptable salt thereof.

[0006] In one ~~aspect~~example, the present ~~invention~~ disclosure provides a compound of formula I:



I

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from the group consisting of -H, -CN, -CO-NR_5R_6, -CO_2R_7, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted (C_1-C_6) alkyl, optionally substituted (C_3-C_8) cycloalkyl, optionally substituted (C_3-C_6) heterocycloalkyl, -$SO_2NR_8R_9$, and -(SO_2)-(C_1-C_6) alkyl;

wherein when R_1 is selected from the group consisting of -CN, -CO-NR_5R_6, -CO_2R_7, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted (C_3-C_8) cycloalkyl, optionally substituted (C_3-C_6) heterocycloalkyl, -$SO_2NR_8R_9$, and -(SO_2)-(C_1-C_6) alkyl, R_2 is -H, halo, -NR_5R_6, or optionally substituted (C_1-C_6) alkoxy;

wherein when R_1 is -H, optionally substituted (C_1-C_6) alkyl, or optionally substituted (C_1-C_6) alkoxy, R_2 is -CO-NR_5R_6; or -CO_2R_7;

or R_1 and R_2 taken together with the atoms to which they are attached to form optionally substituted cycloalkyl or optionally substituted heterocyloalkyl;

R_3 is selected from the group consisting of -H, optionally substituted (C_1.C_6) alkyl, -CN, and halo;

R_4 is -H or halo;

 is optionally substituted with one, two, three, or four groups independently selected from the group consisting of halo and (C_1-C_6) alkyl, wherein "〰" indicate points of attachment;

R_5 and R_6 are each independently -H, optionally substituted (C_1-C_6) alkyl, or optionally substituted (C_1-C_6) alkoxy;

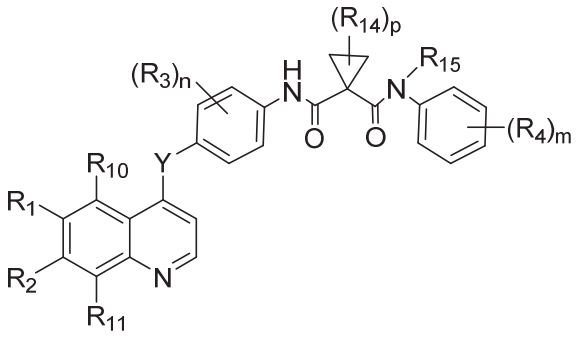
R_7 is -H or optionally substituted (C_1-C_6) alkyl

R_8 and R_9 are each independently -H or optionally substituted (C_1-C_6) alkyl;

or R_8 and R_9 may connect to form an optionally substituted heterocycle; and

Y is selected from the group consisting of O, S, SO, SO_2, NH, and N-(C_1-C_6 alkyl).

[0007] Another ~~aspect~~ example provides a compound of formula A:



A

or a pharmaceutically acceptable salt thereof, wherein

(i) R_1 is selected from the group consisting of (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_6-C_{10}) aryl, (C_3-C_{10}) cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, -CN,-NHOH, -C(O)R^a, -C(O)NR^aR^a, -C(O)NHOR^a, -C(O)OR^a, -C(O)$NR^aS(O)_2R^a$, -OC(O)NR^aR^a, C(=NR^a)R^a, -C(=NOH)R^a, -C(=NOH)NR^a, -C(=NCN)NR^aR^a, -C(=NR^a)NR^aR^a, -S(O)NR^aR^a, -$S(O)_2NR^aC(O)R^a$, -P(O)R^aR^a, -P(O)(OR^a)(OR^a), -$B(OH)_2$, -$B(OR^a)_2$, and $S(O)_2NR^aR^a$; and

R_2 is selected from -H, halo, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, (C_6-C_{10}) aryl-(C_1-C_4) alkylene-, (C_3-C_{10}) cycloalkyl-(C_1-C_4) alkylene-, (5-14 membered heteroaryl)-(C_1-C_4) alkylene-, (4-14 membered heterocycloalkyl)-(C_1-C_4) alkylene-, -CN, -NO_2, -OR^a, -SR^a, -NHOR^a, -C(O)R^a, -C(O)NR^aR^a, -C(O)NHOR^a, -C(O)OR^a, -C(O)$NR^aS(O)_2R^a$, -OC(O)R^a, -OC(O)NR^aR^a, -NHR^a, -NR^aR^a, -$NR^aC(O)R^a$, -$NR^aC(=NR^a)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^aR^a$, -C(=NR^a)R^a, -C(=NOH)R^a, -C(=NOH)NR^a, -C(=NCN)NR^aR^a, -$NR^aC(=NCN)NR^aR^a$, -C(=NR^a)NR^aR^a, -$NR^aC(=NR^a)NR^aR^a$, -$NR^aS(O)R^a$, -

each R^g is independently selected from the group consisting of halo, -OH, -CN, -COOH, -COO-(C_1-C_4) alkyl, -NH_2, -NH-(C_1-C_6) alkyl, -N((C_1-C_6) alky)$_2$, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) alkylthio, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and (C_3-C_6) cycloalkyl;

Y is selected from -O-, -S-, -SO-, -SO_2-, -NH-, and –N((C_1-C_6) alkyl)-;

the ring nitrogen atom on the quinoline moiety in Formula A is optionally oxidized;

the subscript n is an integer of 1, 2, 3, or 4;

the subscript m is an integer of 1, 2, 3, 4, or 5; and

the subscript p is an integer of 0, 1, 2, 3, or 4.

[0008] Another ~~aspect~~example provides methods of using compounds of formula I or a pharmaceutically acceptable salt thereof for the treatment of a disease, disorder, or syndrome mediated at least in part by modulating in vivo activity of a protein kinase.

[0009] A further ~~aspect~~example provides processes for making compounds of formula A and of formula I.

[00010] These and other ~~aspect~~examples ~~and embodiments~~ are described below.

Detailed Description of the Invention

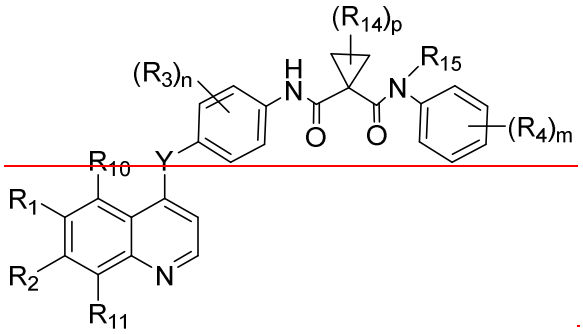
Abbreviations and Definitions

[00011] The following abbreviations and terms have the indicated meanings throughout:

Abbreviation	Meaning
Ac	Acetyl
anhyd	Anhydrous
Aq	Aqueous
Ar	Argon
Boc	Tert-butoxycarbonyl
Br	Broad
°C	Degrees Celsius
c-	Cyclo
calcd	Calculated
CBZ	CarboBenZoxy = benzyloxycarbonyl
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublets of doublets
dt	Doublet of triplets
DCM	Dichloromethane

Claims

1. A compound of formula A:



A

or a pharmaceutically acceptable salt thereof, wherein:

(i) R_1 is selected from the group consisting of $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, -CN, -NHOH, $-C(O)R^a$, $-C(O)NR^aR^a$, $-C(O)NHOR^a$, $-C(O)OR^a$, $-C(O)NR^aS(O)_2R^a$, $-OC(O)NR^aR^a$, $C(=NR^a)R^a$, $-C(=NOH)R^a$, $-C(=NOH)NR^a$, $-C(=NCN)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(O)NR^aR^a$, $-S(O)_2NR^aC(O)R^a$, $-P(O)R^aR^a$, $-P(O)(OR^a)(OR^a)$, $-B(OH)_2$, $-B(OR^a)_2$, and $S(O)_2NR^aR^a$; and

R_2 is selected from -H, halo, $(C_1$-$C_6)$ alkyl, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_1$-$C_6)$ haloalkyl, $(C_1$-$C_6)$ haloalkoxy, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (5-14 membered heteroaryl)-$(C_1$-$C_4)$ alkylene-, (4-14 membered heterocycloalkyl)-$(C_1$-$C_4)$ alkylene-, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NHOR^a$, $-C(O)R^a$, $-C(O)NR^aR^a$, $-C(O)NHOR^a$, $-C(O)OR^a$, $-C(O)NR^aS(O)_2R^a$, $-OC(O)R^a$, $-OC(O)NR^aR^a$, $-NHR^a$, $-NR^aR^a$, $-NR^aC(O)R^a$, $-NR^aC(=NR^a)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^aR^a$, $-C(=NR^a)R^a$, $-C(=NOH)R^a$, $-C(=NOH)NR^a$, $-C(=NCN)NR^aR^a$, $-NR^aC(=NCN)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-NR^aC(=NR^a)NR^aR^a$, $-NR^aS(O)R^a$, $-NR^aS(O)_2R^a$, $-NR^aS(O)_2NR^aR^a$, $-S(O)R^a$, $-S(O)NR^aR^a$, $-S(O)_2R^a$, $-S(O)_2NR^aC(O)R^a$, $-P(O)R^aR^a$, $-P(O)(OR^a)(OR^a)$, $-B(OH)_2$, $-B(OR^a)_2$, and $-S(O)_2NR^aR^a$, wherein the $(C_1$-$C_6)$ alkyl, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (5-14 membered heteroaryl)-$(C_1$-$C_4)$ alkylene-, and (4-14 membered heterocycloalkyl)-$(C_1$-$C_4)$ alkylene- of R_1 or R_2 are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^b substituents, provided when R_1 is 5-7 membered heteroaryl or 5-7 membered heterocycloalkyl and R_2 is C_{1-6} alkoxy, then the 5-7 membered heteroaryl or 5-7 membered

heterocycloalkyl does not connect to the fused phenyl ring of the quinoline moiety through a ring nitrogen atom; or

(ii) R_1 is selected from -H, halo, $(C_1$-$C_6)$ alkyl, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_1$-$C_6)$ haloalkyl, $(C_1$-$C_6)$ haloalkoxy, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (5-14 membered heteroaryl)-$(C_1$-$C_4)$ alkylene-, (4-14 membered heterocycloalkyl)-$(C_1$-$C_4)$ alkylene-, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NHOR^a$, $-C(O)R^a$, $-C(O)NR^aR^a$, $-C(O)NHOR^a$, $-C(O)OR^a$, $-C(O)NR^aS(O)_2R^a$, $-OC(O)R^a$, $-OC(O)NR^aR^a$, $-NHR^a$, $-NR^aR^a$, $-NR^aC(O)R^a$, $-NR^aC(=NR^a)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^aR^a$, $-C(=NR^a)R^a$, $-C(=NOH)R^a$, $-C(=NOH)NR^a$, $-C(=NCN)NR^aR^a$, $-NR^aC(=NCN)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-NR^aC(=NR^a)NR^aR^a$, $-NR^aS(O)R^a$, $-NR^aS(O)_2R^a$, $-NR^aS(O)_2NR^aR^a$, $-S(O)R^a$, $-S(O)NR^aR^a$, $-S(O)_2R^a$, $-S(O)_2NR^aC(O)R^a$, $-P(O)R^aR^a$, $-P(O)(OR^a)(OR^a)$, $-B(OH)_2$, $-B(OR^a)_2$, and $-S(O)_2NR^aR^a$, wherein the $(C_1$-$C_6)$ alkyl, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (5-14 membered heteroaryl)-$(C_1$-$C_4)$ alkylene-, and (4-14 membered heterocycloalkyl)-$(C_1$-$C_4)$ alkylene- of R_1 or R_2 are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^b substituents; and

R_2 is selected from the group consisting of $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, -CN, -NHOH, $-C(O)R^a$, $-C(O)NR^aR^a$, $-C(O)NHOR^a$, $-C(O)OR^a$, $-C(O)NR^aS(O)_2R^a$, $-OC(O)NR^aR^a$, $-C(=NR^a)R^a$, $-C(=NOH)R^a$, $-C(=NOH)NR^a$, $-C(=NCN)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(O)NR^aR^a$, $-S(O)_2NR^aC(O)R^a$, $-P(O)R^aR^a$, $-P(O)(OR^a)(OR^a)$, $-B(OH)_2$, $-B(OR^a)_2$, and $S(O)_2NR^aR^a$, provided when R_1 is 5-7 membered heteroaryl or 5-7 membered heterocycloalkyl and R_2 is C_{1-6} alkoxy, then the 5-7 membered heteroaryl or 5-7 membered heterocycloalkyl of R_1 does not connect to the fused phenyl ring of the quinoline moiety through a ring nitrogen atom;

(iii) R_1 and R_2 taken together with the atoms to which they are attached form a fused $(C_3$-$C_7)$ cycloalkyl ring or a fused 4- to 10-membered heterocycloalkyl ring, wherein the fused $(C_3$-$C_7)$ cycloalkyl ring and fused 4- to 10-membered heterocycloalkyl ring are each optionally substituted with 1, 2, or 3 independently selected R^b substituents, provided that the compound is not 1-[2-(4-Fluoro-phenyl)-acetyl]-cyclopropanecarboxylic acid [3-fluoro-4-(7,8,10,11,13,14-hexahydro-6,9,12,15-tetraoxa-1-aza-cyclododeca[b]naphthalen-4-yloxy)-phenyl]-amide;

R_{10} and R_{11} are each independently selected from the group consisting of -H, halo, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, (C_6-C_{10}) aryl, (C_3-C_{10}) cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, (C_6-C_{10}) aryl-(C_1-C_4) alkylene-, (C_3-C_{10}) cycloalkyl-(C_1-C_4) alkylene-, (5-14 membered heteroaryl)-(C_1-C_4) alkylene-, (4-14 membered heterocycloalkyl)-(C_1-C_4) alkylene-, -CN, -NO_2, -OR^a, -SR^a, -$NHOR^a$, -$C(O)R^a$, -$C(O)NR^aR^a$, -$C(O)OR^a$, -$C(O)NR^aS(O)_2R^a$, -$OC(O)R^a$, -$OC(O)NR^aR^a$, -NHR^a, -NR^aR^a, -$NR^aC(O)R^a$, -$NR^aC(=NR^a)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^aR^a$, -$C(=NR^a)R^a$, -$C(=NOH)R^a$, -$C(=NOH)NR^a$, -$C(=NCN)NR^aR^a$, -$NR^aC(=NCN)NR^aR^a$, -$C(=NR^a)NR^aR^a$, -$NR^aC(=NR^a)NR^aR^a$, -$NR^aS(O)R^a$, -$NR^aS(O)_2R^a$, -$NR^aS(O)_2NR^aR^a$, -$S(O)R^a$, -$S(O)NR^aR^a$, -$S(O)_2R^a$, -$S(O)_2NR^aC(O)R^a$, -$P(O)R^aR^a$, -$P(O)(OR^a)(OR^a)$, -$B(OH)_2$, -$B(OR^a)_2$, and $S(O)_2NR^aR^a$, wherein the (C_1-C_6) alkyl, (C_6-C_{10}) aryl, (C_3-C_{10}) cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, (C_6-C_{10}) aryl-(C_1-C_4) alkylene-, (C_3-C_{10}) cycloalkyl-(C_1-C_4) alkylene-, (5-14 membered heteroaryl)-(C_1-C_4) alkylene-, and (4-14 membered heterocycloalkyl)-(C_1-C_4) alkylene- of R_1 or R_2 are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^b substituents;

each R_3 is independently selected from the group consisting of -H, halo, -OH, -CN, optionally substituted (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkoxy, -NH_2, -NH(C_1-C_6)alkyl, -N(C_1-C_6-alkyl)$_2$, and (C_3-C_6) cycloalkyl, wherein the (C_1-C_6) alkoxy, -NH(C_1-C_6)alkyl, -N(C_1-C_6-alkyl)$_2$, and (C_3-C_6) cycloalkyl of R_3 are each optionally substituted with 1, 2, or 3 independently selected R^g substituents;

each R_{14} is independently selected from the group consisting of halo, -OH, -NH_2, -CN, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, -COOH, -NH(C_1-C_6)alkyl, -N(C_1-C_6-alkyl)$_2$, phenyl, phenyl-(C_1-C_2) alkylene, (C_3-C_6) cycloalkyl, (C_3-C_6) cycloalkyl-(C_1-C_4) alkylene-, 4- to 6-membered heterocycloalkyl, (4- to 6-membered heterocycloalkyl)-(C_1-C_4) alkylene-, 5- to 6-membered heteroaryl, (5- to 6-membered heteroaryl)-(C_1-C_4) alkylene-, and -OR^e, wherein the (C_1-C_6) alkyl, phenyl, phenyl-(C_1-C_2) alkylene, (C_3-C_6) cycloalkyl, (C_3-C_6) cycloalkyl-(C_1-C_4) alkylene-, 4- to 6-membered heterocycloalkyl, (4- to 6-membered heterocycloalkyl)-(C_1-C_4) alkylene-, 5- to 6-membered heteroaryl, and (5- to 6-membered heteroaryl)-(C_1-C_4) alkylene- of R_{14} are each optionally substituted with 1, 2, or 3 independently selected R^g substituents,

R_{15} is H or C_{1-6} alkyl;

each R_4 is independently selected from the group consisting of -H, halo, -OH, -$COOR^e$, -$CONR^eR^e$, -CN, -NH_2, -NH($(C_1$-$C_6)$ alkyl), -N($(C_1$-$C_6)$ alkyl)$_2$, $(C_1$-$C_6)$ alkyl, $(C_1$-$C_6)$ alkoxy, $(C_1$-$C_6)$ haloalkyl, $(C_1$-$C_6)$ haloalkoxy, -$CONR^aR^a$, -NR^aCOR^a, -$NR^aCONR^aR^a$, -SO_2R^a, -$NR^aS(O)_2R^a$, -$NR^aS(O)_2NR^aR^a$, $(C_3$-$C_6)$ cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl, $(C_3$-$C_6)$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (4- to 6-membered heterocycloalkyl)-$(C_1$-$C_4)$ alkylene-, phenyl-$(C_1$-$C_2)$ alkylene, and (5- or 6-membered heteroaryl)-$(C_1$-$C_4)$ alkylene-, wherein the $(C_1$-$C_6)$ alkyl, $(C_3$-$C_6)$ cycloalkyl, 4- to 6-membered heterocycloalkyl, phenyl, 5- or 6-membered heteroaryl, $(C_3$-$C_6)$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (4- to 6-membered heterocycloalkyl)-$(C_1$-$C_4)$ alkylene-, phenyl-$(C_1$-$C_2)$ alkylene, and (5- or 6-membered heteroaryl)-$(C_1$-$C_4)$ alkylene- of R_4 are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^a is independently selected from the group consisting of -H, -CN, $(C_1$-$C_6)$ alkyl, $(C_1$-$C_6)$ haloalkyl, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (5-14 membered heteroaryl)-$(C_1$-$C_4)$ alkylene-, and (4-14 membered heterocycloalkyl)-$(C_1$-$C_4)$ alkylene-, wherein the $(C_1$-$C_6)$ alkyl, $(C_1$-$C_6)$ haloalkyl, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (5-14 membered heteroaryl)-$(C_1$-$C_4)$ alkylene-, and (4-14 membered heterocycloalkyl)-$(C_1$-$C_4)$ alkylene- of R^a are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^d substituents;

each R^b is independently selected from the group consisting of halo, oxo, $(C_1$-$C_6)$ alkyl, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_1$-$C_6)$ haloalkyl, $(C_1$-$C_6)$ haloalkoxy, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (5-10 membered heteroaryl)-$(C_1$-$C_4)$ alkylene-, (4-10 membered heterocycloalkyl)-$(C_1$-$C_4)$ alkylene-, -CN, -OH, -NH_2, -NO_2, -$NHOR^e$, -OR^e, -SR^e, -$C(O)R^e$, -$C(O)NR^eR^e$, -$C(O)OR^e$, -$C(O)NR^eS(O)_2R^e$, -$OC(O)R^e$, -$OC(O)NR^eR^e$, -$C(=NOH)R^e$, -$C(=NOH)NR^e$, -$C(=NCN)NR^eR^e$, -$NR^eC(=NCN)NR^eR^e$, -$C(=NR^e)NR^eR^e$, -$NR^eC(=NR^e)NR^eR^e$, -NHR^e, -NR^eR^e, -$NR^eC(O)R^e$, -$NR^eC(=NR^e)R^e$, -$NR^eC(O)OR^e$, -$NR^eC(O)NR^eR^e$, -$NR^eS(O)R^e$, -$NR^eS(O)_2R^e$, -$NR^eS(O)_2NR^eR^e$, -$S(O)R^e$, -$S(O)NR^eR^e$, -$S(O)_2R^e$, -$S(O)_2NR^eC(O)R^e$, -$Si(R^e)_3$, -$P(O)R^eR^e$, -$P(O)(OR^e)(OR^e)$, -$B(OH)_2$, -$B(OR^e)_2$, and -

~~$S(O)_2NR^eR^e$, wherein the $(C_1$-$C_6)$ alkyl, $(C_1$-$C_6)$ haloalkyl, $(C_1$-$C_6)$ haloalkoxy, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $(C_6$-$C_{10})$ aryl $(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalky $(C_1$-$C_4)$ alkylene-, (5-10 membered heteroaryl) $(C_1$-$C_4)$ alkylene-, and (4-10 membered heterocycloalkyl) $(C_1$-$C_4)$ alkylene- of R^b are each further optionally substituted with 1, 2, or 3 independently selected R^d substituents;~~

~~each R^e is independently selected from the group consisting of -H, $(C_1$-$C_6)$ alkyl, $(C_1$-$C_6)$ haloalkyl, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $(C_6$-$C_{10})$ aryl $(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl $(C_1$-$C_4)$ alkylene-, (5-10 membered heteroaryl) $(C_1$-$C_4)$ alkylene-, and (4-10 membered heterocycloalkyl) $(C_1$-$C_4)$ alkylene-, wherein the $(C_1$-$C_6)$ alkyl, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-10 membered heteroaryl, 4-10 membered heterocycloalkyl, $(C_6$-$C_{10})$ aryl $(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl $(C_1$-$C_4)$ alkylene-, (5-10 membered heteroaryl) $(C_1$-$C_4)$ alkylene-, and (4-10 membered heterocycloalkyl) $(C_1$-$C_4)$ alkylene- of R^e are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^f substituents;~~

~~each R^d is independently selected from the group consisting of $(C_1$-$C_6)$ alkyl, $(C_1$-$C_6)$ haloalkyl, halo, $(C_6$-$C_{10})$ aryl, 5-10 membered heteroaryl, $(C_3$-$C_{10})$ cycloalkyl, 4-10 membered heterocycloalkyl, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (5-10 membered heteroaryl) $(C_1$-$C_4)$ alkylene-, (4-10 membered heterocycloalkyl) $(C_1$-$C_4)$ alkylene-, -CN, $-NH_2$, -NHOR^e, -OR^e, -SR^e, -C(O)R^e, -C(O)NR^{e}R^e, -C(O)OR^e, -OC(O)R^e, -OC(O)NR^{e}R^e, -NHR^e, -NR^{e}R^e, -NR^{e}C(O)R^e, -NR^{e}C(O)NR^{e}R^e, -NR^{e}C(O)OR^e, -C(=NR^e)NR^{e}R^e, -NR^{e}C(=NR^e)NR^{e}R^e, -NR^{e}C(=NOH)NR^{e}R^e, -NR^{e}C(=NCN)NR^{e}R^e, -S(O)R^e, -S(O)NR^{e}R^e, -$S(O)_2$R^e, -NR^{e}S(O)$_2$R^e, -NR^{e}S(O)$_2$NR^{e}R^e, and -$S(O)_2$NR^{e}R^e, wherein the $(C_1$-$C_6)$ alkyl, $(C_1$-$C_6)$ haloalkyl, $(C_6$-$C_{10})$ aryl, 5-10 membered heteroaryl, $(C_3$-$C_{10})$ cycloalkyl, 4-10 membered heterocycloalkyl, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (5-10 membered heteroaryl) $(C_1$-$C_4)$ alkylene-, and (4-10 membered heterocycloalkyl) $(C_1$-$C_4)$ alkylene- of R^d are each optionally substituted with 1, 2, or 3 independently selected R^f substituents;~~

~~each R^e is independently selected from the group consisting of -H, $(C_1$-$C_6)$ alkyl, $(C_3$-$C_6)$ cycloalkyl, $(C_3$-$C_6)$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, $(C_6$-$C_{10})$ aryl, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$ alkylene-, 5- or 6-membered heteroaryl, (5- or 6-membered heteroaryl)-$(C_1$-C4) alkylene-, 4-7-membered~~

heterocycloalkyl, (4-7-membered heterocycloalkyl)-(C_1-C_4)-alkylene-, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, (C_2-C_4) alkenyl, and (C_2-C_4) alkynyl, wherein the (C_1-C_4) alkyl, (C_3-C_6) cycloalkyl, (C_6-C_{10}) aryl, 5- or 6-membered heteroaryl, 4-7-membered heterocycloalkyl, (C_6-C_{10}) aryl-(C_1-C_4) alkylene-, (5- or 6-membered heteroaryl)-(C_1-C_4) alkylene-, (4-7-membered heterocycloalkyl)-(C_1-C_4) alkylene-, (C_2-C_4) alkenyl, and (C_2-C_4) alkynyl of R^e are each optionally substituted with 1, 2, or 3 R^f substituents,

or any two R^a substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

or any two R^e substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents,

or any two R^e substituents together with the nitrogen atom to which they are attached form 4-, 5-, 6-, 7-, 8-, 9-, or 10-membered heterocycloalkyl, each of which is optionally substituted with 1, 2, or 3 independently selected R^f substituents;

each R^f is independently selected from the group consisting of halo, -OH, -CN, -COOH, -NH_2, -NH-(C_1-C_6) alkyl, -N((C_1-C_6) alky)$_2$, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) alkylthio, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and (C_3-C_6) cycloalkyl, wherein the (C_1-C_6) alkyl, phenyl, (C_3-C_6) cycloalkyl, 4-6 membered heterocycloalkyl, and 5-6 membered heteroaryl of R^f are each optionally substituted with 1, 2, or 3 substituents selected from halo, -OH, -CN, -COOH, -NH_2, (C_1-C_4) alkyl, (C_1-C_4) alkoxy, (C_1-C_4) haloalkyl, (C_1-C_4) haloalkoxy, phenyl, (C_3-C_{10}) cycloalkyl, 5-6 membered heteroaryl, and 4-6 membered heterocycloalkyl;

each R^g is independently selected from the group consisting of halo, -OH, -CN, -COOH, -COO-(C_1-C_4) alkyl, -NH_2, -NH-(C_1-C_6) alkyl, -N((C_1-C_6) alky)$_2$, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, (C_1-C_6) alkylthio, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, phenyl, 5-6 membered heteroaryl, 4-6 membered heterocycloalkyl, and (C_3-C_6) cycloalkyl;

Y is selected from -O-, -S-, -SO-, -SO_2-, -NH-, and -N((C_1-C_6) alkyl)-;

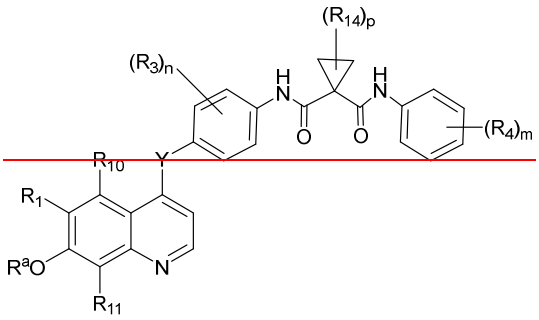
the ring nitrogen atom on the quinoline moiety in Formula A is optionally oxidized;

the subscript n is an integer of 1, 2, 3, or 4;

the subscript m is an integer of 1, 2, 3, 4, or 5; and

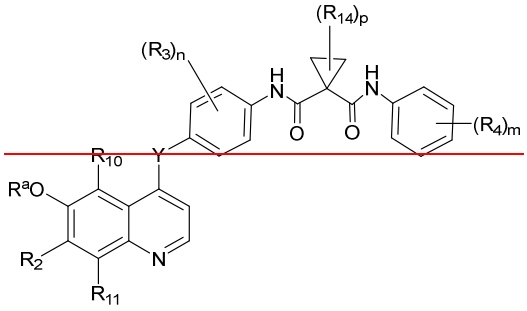
the subscript p is an integer of 0, 1, 2, 3, or 4.

2. The compound of claim 1, having formula A-1:



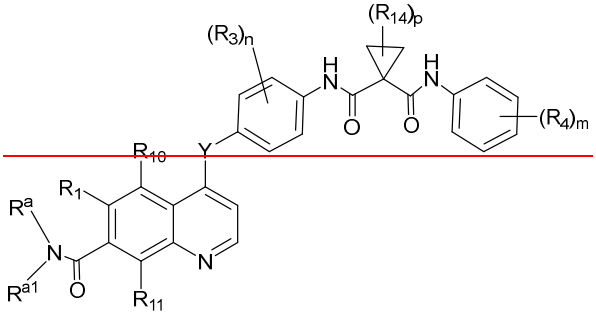
A-1.

3. The compound of claim 1, having formula A-2:



A-2.

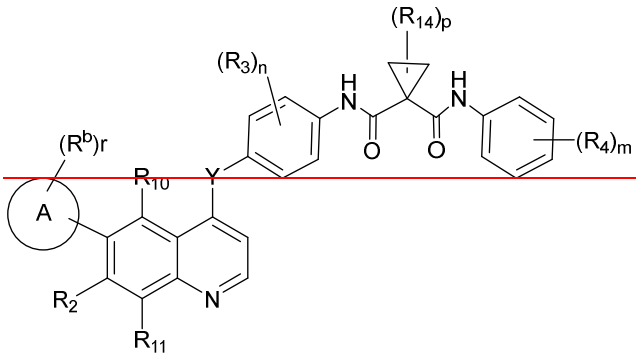
4. The compound of claim 1, having formula A-3:



A-3

wherein R^{a1} is H or (C_1-C_6) alkyl.

5. The compound of claim 1, having formula A-4:



A-4

wherein ring A is 5- to 14-membered heteroaryl; and the subscript r is 1, 2, 3, or 4.

6. The compound of claim 1, wherein:

R_1 is selected from the group consisting of $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, -CN, -NHOH, $-C(O)R^a$, $-C(O)NR^aR^a$, $-C(O)NHOR^a$, $-C(O)OR^a$, $-C(O)NR^aS(O)_2R^a$, $-OC(O)NR^aR^a$, $C(=NR^a)R^a$, $-C(=NOH)R^a$, $-C(=NOH)NR^a$, $-C(=NCN)NR^aR^a$, $-NR^aC(=NCN)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-S(O)NR^aR^a$, $-S(O)_2NR^aC(O)R^a$, $-P(O)R^aR^a$, $-P(O)(OR^a)(OR^a)$, $-B(OH)_2$, $-B(OR^a)_2$, and $S(O)_2NR^aR^a$; and

R_2 is selected from -H, halo, $(C_1$-$C_6)$ alkyl, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_1$-$C_6)$ haloalkyl, $(C_1$-$C_6)$ haloalkoxy, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (5-14 membered heteroaryl)-$(C_1$-$C_4)$ alkylene-, (4-14 membered heterocycloalkyl)-$(C_1$-$C_4)$ alkylene-, -CN, $-NO_2$, $-OR^a$, $-SR^a$, $-NHOR^a$, $-C(O)R^a$, $-C(O)NR^aR^a$, $-C(O)NHOR^a$, $-C(O)OR^a$, $-C(O)NR^aS(O)_2R^a$, $-OC(O)R^a$, $-OC(O)NR^aR^a$, $-NHR^a$, $-NR^aR^a$, $-NR^aC(O)R^a$, $-NR^aC(=NR^a)R^a$, $-NR^aC(O)OR^a$, $-NR^aC(O)NR^aR^a$, $-C(=NR^a)R^a$, $-C(=NOH)R^a$, $-C(=NOH)NR^a$, $-C(=NCN)NR^aR^a$, $-NR^aC(=NCN)NR^aR^a$, $-C(=NR^a)NR^aR^a$, $-NR^aC(=NR^a)NR^aR^a$, $-NR^aS(O)R^a$, $-NR^aS(O)_2R^a$, $-NR^aS(O)_2NR^aR^a$, $-S(O)R^a$, $-S(O)NR^aR^a$, $-S(O)_2R^a$, $-S(O)_2NR^aC(O)R^a$, $-P(O)R^aR^a$, $-P(O)(OR^a)(OR^a)$, $-B(OH)_2$, $-B(OR^a)_2$, and $-S(O)_2NR^aR^a$, wherein the $(C_1$-$C_6)$ alkyl, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (5-14 membered heteroaryl)-$(C_1$-$C_4)$ alkylene-, and (4-14 membered heterocycloalkyl)-$(C_1$-$C_4)$ alkylene- of R_1 or R_2 are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^b substituents, provided when R_1 is 5-7 membered heteroaryl or 5-7 membered heterocycloalkyl and

R_2 is C_{1-6} alkoxy, then the 5-7 membered heteroaryl or 5-7 membered heterocycloalkyl of R_1 does not connect to the fused phenyl ring of the quinoline moiety through a ring nitrogen atom.

7. The compound of claim 1, wherein:

R_1 is selected from -H, halo, $(C_1$-$C_6)$ alkyl, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_1$-$C_6)$ haloalkyl, $(C_1$-$C_6)$ haloalkoxy, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (5-14 membered heteroaryl)-$(C_1$-$C_4)$ alkylene-, (4-14 membered heterocycloalkyl)-$(C_1$-$C_4)$ alkylene-, -CN, -NO_2, -OR^a, -SR^a, -NHOR^a, -C(O)R^a, -C(O)NR^aR^a, -C(O)NHOR^a, -C(O)OR^a, -C(O)$NR^aS(O)_2R^a$, -OC(O)R^a, -OC(O)NR^aR^a, -NHR^a, -NR^aR^a, -$NR^aC(O)R^a$, -$NR^aC(=NR^a)R^a$, -$NR^aC(O)OR^a$, -$NR^aC(O)NR^aR^a$, -C(=NR^a)R^a, -C(=NOH)R^a, -C(=NOH)NR^a, -C(=NCN)NR^aR^a, -$NR^aC(=NCN)NR^aR^a$, -C(=NR^a)NR^aR^a, -$NR^aC(=NR^a)NR^aR^a$, -$NR^aS(O)R^a$, -$NR^aS(O)_2R^a$, -$NR^aS(O)_2NR^aR^a$, -S(O)R^a, -S(O)NR^aR^a, -$S(O)_2R^a$, -$S(O)_2NR^aC(O)R^a$, -P(O)R^aR^a, -P(O)$(OR^a)(OR^a)$, -$B(OH)_2$, -$B(OR^a)_2$, and -$S(O)_2NR^aR^a$, wherein the $(C_1$-$C_6)$ alkyl, $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$ alkylene-, $(C_3$-$C_{10})$ cycloalkyl-$(C_1$-$C_4)$ alkylene-, (5-14 membered heteroaryl)-$(C_1$-$C_4)$ alkylene-, and (4-14 membered heterocycloalkyl)-$(C_1$-$C_4)$ alkylene- of R_1 or R_2 are each optionally substituted with 1, 2, 3, 4, or 5 independently selected R^b substituents; and

R_2 is selected from the group consisting of $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, -CN, -NHOH, -C(O)R^a, -C(O)NR^aR^a, -C(O)NHOR^a, -C(O)OR^a, -C(O)$NR^aS(O)_2R^a$, -OC(O)NR^aR^a, -C(=NR^a)R^a, -C(=NOH)R^a, -C(=NOH)NR^a, -C(=NCN)NR^aR^a, -$NR^aC(=NCN)NR^aR^a$, -C(=NR^a)NR^aR^a, -S(O)NR^aR^a, -$S(O)_2NR^aC(O)R^a$, -P(O)R^aR^a, -P(O)$(OR^a)(OR^a)$, -$B(OH)_2$, -$B(OR^a)_2$, and -$S(O)_2NR^aR^a$, provided when R_1 is 5-7 membered heteroaryl or 5-7 membered heterocycloalkyl and R_2 is C_{1-6} alkoxy, then the 5-7 membered heteroaryl or 5-7 membered heterocycloalkyl of R_1 does not connect to the fused phenyl ring of the quinoline moiety through a ring nitrogen atom.

8. The compound of claim 1, wherein:

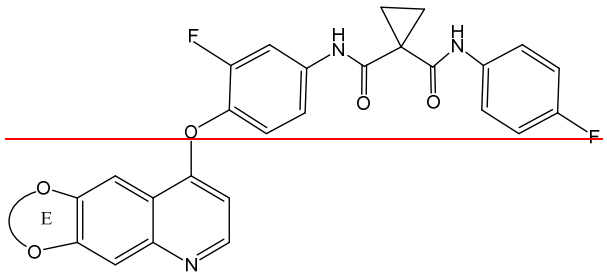
R_1 and R_2 taken together with the atoms to which they are attached form a fused $(C_3$-$C_7)$ cycloalkyl ring or a fused 4- to 10-membered heterocycloalkyl ring, wherein the fused $(C_3$-$C_7)$ cycloalkyl ring and fused 4- to 10-membered heterocycloalkyl ring are each optionally substituted

with 1, 2, or 3 independently selected R^b substituents, provided that the compound is not 1-[2-(4-Fluoro-phenyl)-acetyl]-cyclopropanecarboxylic acid [3-fluoro-4-(7,8,10,11,13,14-hexahydro-6,9,12,15-tetraoxa-1-aza-cyclododeca[b]naphthalen-4-yloxy)-phenyl]-amide .

9. The compound of claim 1, 6, 7 or 8, wherein:

R_{15} is H or CH_3.

10. The compound of claim 1 or 9, wherein R_1 and R_2 taken together with the atoms to which they are attached form a fused (C_3-C_7) cycloalkyl ring or a fused 4- to 10-membered heterocycloalkyl ring, wherein the fused (C_3-C_7) cycloalkyl ring or a fused 4- to 10-membered heterocycloalkyl ring are each optionally substituted with 1, 2, or 3 independently selected R^b substituents, provided that the compound is not a compound having the formula:



wherein ring E is fused 4- to 10-membered heterocycloalkyl.

11. The compound of any of claims 2, 4, 7, and 9, wherein R_1 is -H.

12. The compound of any of claims 1, 3, 5 and 6, wherein R_2 is -H.

13. The compound of any of claims 1, 2, 4, 5, and 7-9, wherein R_1 is selected from the group consisting of -H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, -C(=NO-(C_1-C_6) alkyl)R^a, -CN, -C(O)OR^a, -C(O)N$R^a R^a$, -C(O)NHOR^a, -S(O)$_2$N$R^a R^a$, phenyl, 5- to 6-membered heteroaryl, (C_3-C_6) cycloalkyl, and 4- to 6-membered heterocycloalkyl.

14. The compound of claim 13, wherein R_1 is -H, R^aNHC(O) , R^aOC(O) , (C_1-C_6) alkyl, (C_1-C_6) alkoxy or C(=NO-CH_3)R^a; and

R_2 is selected from 2-methoxyethylamino, methylamino, 3-morpholinopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, propoxy, 2-hydroxypropoxy, methoxycarbonyl, carboxy, carbamoyl, methylcarbamoyl, (2-hydroxyethoxy)carbamoyl, (2,2-dihydroxyethoxy)carbamoyl, (oxetan-3-yloxy)carbamoyl, methoxycarbamoyl, 2-trimethylsilylethynyl, ethynyl, sulfamoyl, acetyl, and $-C(=NOCH_3)CH_3$.

15. The compound of any of claims 1, 3, 5, and 6, wherein R_2 is selected from the group consisting of -H, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, $-C(=NO-(C_1-C_6)\text{alkyl})R^a$, -CN, $-C(O)OR^a$, $-C(O)NR^aR^a$, $-C(O)NHOR^a$, and $-S(O)_2NR^aR^a$.

16. The compound claim 15, wherein R_1 is selected from 2-methoxyethylamino, azetidin-1-yl, methylamino, 3-morpholinopropoxy, 2-methoxyethoxy, 2-hydroxyethoxy, propoxy, 2-hydroxypropoxy, methoxycarbonyl, carboxy, carbamoyl, methylcarbamoyl, 2-oxazolyl, pyrazol-3-yl, pyrazol-4-yl, 4-isoxazolyl, 3,5-dimethylisoxazol-4-yl, 1-methyl-pyrazol-4-yl, 2-methyl-pyrazol-3-yl, 2-ethyl-pyrazol-3-yl, 2-(2-hydroxyethyl)-pyrazol-3-yl, 2-(2,2,2-trifluoroethyl)-pyrazol-3-yl, 2-(2-fluoroethyl)-pyrazol-3-yl, 2-(2,2-difluoroethyl)-pyrazol-3-yl, 2-trifluoromethyl-pyrazol-3-yl, 2-difluoromethyl-pyrazol-3-yl, 1-methyl-imidazol-4-yl, 1-methyl-imidazol-2-yl, 1H-imidazol-2-yl, (2-hydroxyethoxy)carbamoyl, (2,2-dihydroxyethoxy)carbamoyl, (oxetan-3-yloxy)carbamoyl, methoxycarbamoyl, 2-trimethylsilylethynyl, ethynyl, 1,3,4-oxadiazol-3-yl, 1H-1,2,3-triazol-5-yl, sulfamoyl, acetyl, and $-C(=NOCH_3)CH_3$, and R_2 is -H, $R^aNHC(O)$-, $R^aOC(O)$-, (C_1-C_6) alkyl, (C_1-C_6) alkoxy, or $-C(=NO-CH_3)R^a$.

17. The compound of claim 5, wherein the subscript r is 1 or 2.

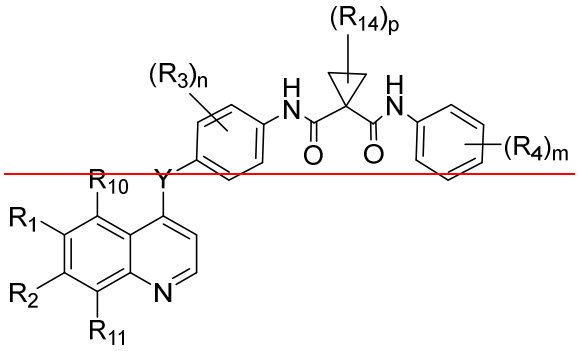
18. The compound of any of claims 1-17, wherein R_{10} and R_{11} are each H.

19. The compound of any of claims 1-18, wherein the subscript n is 1.

20. The compound of any of claims 1-19, wherein the subscript m is 1.

21. The compound of any of claims 1-20, wherein the subscript p is 1.

22. The compound of any of claims 1-21, having formula B:



B

or a pharmaceutically acceptable salt thereof, wherein:

(i) R_2 is:

H or a group selected from the group consisting of:

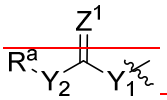
$(C_1$-$C_6)$ alkyl, halo, $-NO_2$, $-X_1R^a$, wherein X_1 is -O-, -S-, -SO-, $-SO_2$-, $-SO_2NH$-, $-SO_2NR^a$-, -NH-, and -N-$(C_1$-$C_6)$ alkyl-, wherein $(C_1$-$C_6)$ alkyl is optionally substituted; and

R_1 is selected from the group consisting of:

$(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein the $(C_2$-$C_6)$ alkenyl, $(C_2$-$C_6)$ alkynyl, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl are each independently optionally substituted;

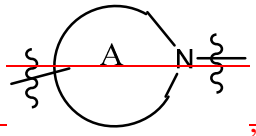
-CN, $-P(O)R^aR^a$, $-P(O)(OR^a)_2$, $-B(OH)_2$, $-B(OR^a)_2$,

X_2R^a, wherein X_2 is -NHO-, -NH-S(O)-, -N-$(C_1$-$C_6)$alkyl-S(O)-, -NH-$S(O)_2$-, -N-$(C_1$-$C_6)$-alkyl-$S(O)_2R^a$-, -NH-S(O)-NH-, -N-$(C_1$-$C_6)$-alkyl-S(O)NH-, -NH-$S(O)_2NH$-, -N-$(C_1$-$C_6)$-alkyl-$S(O)_2NH$-, $-S(O)_2NHC(O)$-; and

 wherein "〰" indicates the point of attachment, wherein:

Y_1 is absent, or is -NH-, -N-$(C_1$-$C_6)$-alkyl-, or -O-;

Y_2 is absent, or is -O-, -NH-, -NHO-, -N-$(C_1$-$C_6)$-alkyl-, $-N_2H_2$-, -NH-S(O)-, -NH-$S(O)_2$-; or

Y_2 is or optionally substituted 

, wherein "〰" indicates points of attachment, wherein ring A is a 3, 4, 5, 6, or 7-membered ring; and

Z^1 is O, NH, N-(C_1-C_6) alkyl, NOH, NO-(C_1-C_6) alkyl, or NCN; or

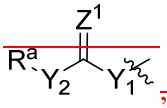
(ii)

R_1 is selected from the group consisting of:

(C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_6-C_{10}) aryl, (C_3-C_{10}) cycloalkyl, 5-10 membered heteroaryl, and 4-10 membered heterocycloalkyl, wherein (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_6-C_{10}) aryl, (C_3-C_{10}) cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl are each independently optionally substituted;

$P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$, CN,

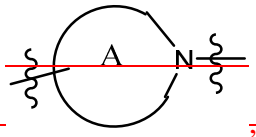
X_2R^a, wherein X_2 is -NHO-, -NH-S(O)-, -N-(C_1-C_6)alkyl-S(O)-, -NH-$S(O)_2$-, -N-(C_1-C_6) alkyl-$S(O)_2R^a$-, -NH-S(O)-NH-, -N-(C_1-C_6) alkyl-S(O)NH-, -NH-$S(O)_2$NH-, -N-(C_1-C_6) alkyl-$S(O)_2$NH-, -S(O)-, -$S(O)_2$-, -$S(O)_2$NHC(O); and



, wherein:

Y_1 is absent, or is -NH-, -N-(C_1-C_6) alkyl-, or -O-;

Y_2 is absent, or is -O-, -NH-, -NHO-, -N-(C_1-C_6) alkyl-, N_2H_2-, -NH-S(O)-, or -NH-$S(O)_2$; or

Y_2 is optionally substituted 

, wherein "〰" indicates points of attachment, wherein ring A is a 3, 4, 5, 6, or 7-membered ring; and

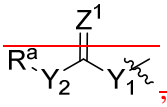
Z^1 is -O-, -NH-, -N-(C_1-C_6) alkyl-, -NOH-, -NO-(C_1-C_6) alkyl-, or -NCN-; or

R_2 is selected from the group consisting of:

H, halo, (C_1-C_6) alkyl, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, (C_6-C_{10}) aryl-(C_1-C_4) alkylene-, (C_3-C_{10}) cycloalkyl-(C_1-C_4) alkylene-, (5-14 membered heteroaryl)-(C_1-C_4) alkylene-, and (4-14 membered heterocycloalkyl)-(C_1-C_4) alkylene-, wherein (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, (C_6-C_{10}) aryl-(C_1-C_4) alkylene-, (C_3-C_{10}) cycloalkyl-(C_1-C_4) alkylene-, (5-14 membered heteroaryl)-(C_1-C_4) alkylene-, and (4-14 membered heterocycloalkyl)-(C_1-C_4) alkylene- are each independently optionally substituted;

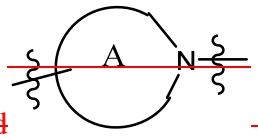
CN, NO_2, $P(O)R^aR^a$, $P(O)(OR^a)(OR^a)$, $B(OH)_2$, $B(OR^a)_2$;

X_1R^a, wherein X_1 is -O-, -S-, -NH-, or -N(C_1-C_6)-, -NHO-, -NH-S(O)-, -N(C_1-C_6)alkyl-S(O)-, -NH-S(O)$_2$-, -N-(C_1-C_6) alkyl-S(O)$_2$-, -NH-S(O)-NH-, -N-(C_1-C_6) alkyl-S(O)NH-, -NH-S(O)$_2$NH-, -N-(C_1-C_6) alkyl-S(O)$_2$NH-, -S(O)$_2$NHC(O)-, -NH-S(O)R^a-, -N-(C_1-C_6) alkyl-S(O)R^a-, -NH-S(O)$_2R^a$-, or -N-(C_1-C_6) alkyl-S(O)$_2R^a$-;


, wherein

Y_1 is absent or is -NH-, -N-(C_1-C_6) alkyl-, or -O-;

Y_2 is absent or is -O-, -NH-, -NHO-, -N-(C_1-C_6) alkyl-, -N_2H_2-, -NH-S(O)-, or -NH-S(O)$_2$-; or

Y_2 is optionally substituted 
, wherein ring A is a 3-, 4-, 5-, 6-, or 7-membered ring and wherein "〰" indicates points of attachment; and

Z^1 is O, NH, N-(C_1-C_6) alkyl, NOH, NO-(C_1-C_6) alkyl, or NCN; or

(iii)

R_1 and R_2 taken together with the atoms to which they are attached form a 4- to 10-membered heterocycloalkyl ring optionally substituted with 1, 2, or 3 groups independently selected from the group consisting of halo, (C_1-C_6) alkyl, (C_1-C_6) haloalkyl, (C_1-C_6) haloalkoxy, -CN, -OH, -NH_2, provided that the compound is

not 1-[2-(4-Fluoro-phenyl)-acetyl]-cyclopropanecarboxylic acid [3-fluoro-4-(7,8,10,11,13,14-hexahydro-6,9,12,15-tetraoxa-1-aza-cyclododeca[b]naphthalen-4-yloxy)-phenyl]-amide;

and R_{10}, R_{11}, R_3, R_{14}, R_4, n, p, m and Y are as defined as follows:

each R_3 is independently selected from the group consisting of -H, halo, -OH, -CN, optionally substituted $(C_1$-$C_6)$ alkyl, $(C_1$-$C_6)$ alkoxy, $(C_1$-$C_6)$ haloalkoxy, $-NH_2$, $-NH(C_1$-$C_6)$alkyl, $-N(C_1$-C_6-alkyl$)_2$, and $(C_3$-$C_6)$ cycloalkyl, wherein $(C_1$-$C_6)$ alkoxy, $-NH(C_1$-$C_6)$alkyl, $-N(C_1$-C_6-alkyl$)_2$, and $(C_3$-$C_6)$ cycloalkyl are each optionally substituted;

each of R_{10} and R_{11} is indepdendently selected from the group consisting of -H, $(C_1$-$C_6)$ alkyl, $(C_1$-$C_6)$ alkoxy, and $(C_1$-$C_6)$ haloalkoxy;

each R_{14} is independently selected from the group consisting of -halo, -OH, $-NH_2$, -CN, $(C_1$-$C_6)$ alkyl, $(C_1$-$C_6)$ alkoxy, $(C_1$-$C_6)$ haloalkyl, $(C_1$-$C_6)$ haloalkoxy, -COOH, $-NH(C_1$-$C_6)$alkyl, $-N(C_1$-C_6-alkyl$)_2$, phenyl, phenyl-$(C_1$-$C_2)$-alkylene, $(C_3$-$C_6)$ cycloalkyl, $(C_3$-$C_6)$ cycloalkyl-$(C_1$-$C_4)$-alkylene-, 4- to 6-membered heterocycloalkyl, (4- to 6-membered heterocycloalkyl)-$(C_1$-$C_4)$-alkylene-, 5- to 6-membered heteroaryl, (5- to 6-membered heteroaryl)-$(C_1$-$C_4)$-alkylene-, and $-OR^e$, wherein the $(C_1$-$C_6)$ alkyl, phenyl, phenyl-$(C_1$-$C_2)$-alkylene, $(C_3$-$C_6)$ cycloalkyl, $(C_3$-$C_6)$ cycloalkyl-$(C_1$-$C_4)$-alkylene-, 4- to 6-membered heterocycloalkyl, (4- to 6-membered heterocycloalkyl)-$(C_1$-$C_4)$-alkylene-, 5- to 6-membered heteroaryl, and (5- to 6-membered heteroaryl)-$(C_1$-$C_4)$-alkylene- of R_{14} are each optionally substituted;

each R_4 is independently selected from -H, halo, -OH, $(C_1$-$C_6)$ alkyl, $(C_1$-$C_6)$ alkoxy, $(C_1$-$C_6)$ haloalkyl, and $(C_1$-$C_6)$ haloalkoxy, wherein the $(C_1$-$C_6)$ alkyl are each $(C_1$-$C_6)$ alkoxy, $(C_1$-$C_6)$ haloalkyl, and $(C_1$-$C_6)$ haloalkoxy are each independently optionally substituted;

each R^a is independently selected from -H, $(C_1$-$C_6)$ alkyl, $(C_1$-$C_6)$ haloalkyl, $(C_6$-$C_{10})$ aryl, $(C_3$-$C_{10})$ cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, $(C_6$-$C_{10})$ aryl-$(C_1$-$C_4)$-alkylene-, $(C_3$-$C_{10})$ cycloalkyl-$(C_1$-$C_4)$-alkylene-, (5-14 membered heteroaryl)-$(C_1$-$C_4)$-alkylene-, and (4-14 membered heterocycloalkyl)-$(C_1$-$C_4)$-alkylene-, wherein $(C_1$-$C_6)$ alkyl, $(C_1$-$C_6)$ haloalkyl,

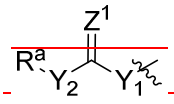
~~(C_6-C_{10}) aryl, (C_3-C_{10}) cycloalkyl, 5-14 membered heteroaryl, 4-14 membered heterocycloalkyl, (C_6-C_{10}) aryl-(C_1-C_4) alkylene-, (C_3-C_{10}) cycloalkyl-(C_1-C_4) alkylene-, (5-14 membered heteroaryl)-(C_1-C_4) alkylene-, and (4-14 membered heterocycloalkyl)-(C_1-C_4) alkylene- are each independently optionally substituted;~~

~~n, p, and m are each independently integers of 0 to 3; and~~

~~Y is selected from -O-, -S-, -SO-, -SO_2-, -NH-, and -N((C_1-C_6) alkyl)-.~~

~~23. The compound of claim 22, wherein:~~

~~R_1 is -H, -CN, (C_1-C_6) alkyl, (C_3-C_{10}) cycloalkyl, (C_6-C_{10}) aryl, 4-10 membered heterocycloalkyl, 5-10 membered heteroaryl, -$S(O)_2NHR^a$, -$P(O)R^aR^a$, -OR^a, or~~



~~, wherein "~~ ~~" indicates the point of attachment, wherein:~~

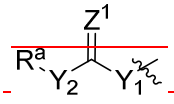
~~Y_1 is absent or is -NH-, -N-(C_1-C_6) alkyl-, or -O-;~~

~~Y_2 is absent or is -O-, -NH-, -NHO-, -N-(C_1-C_6) alkyl-, -NH-NH-, -NH-S(O)-, or -NH-$S(O)_2$-; and~~

~~Z^1 is -O, -NH, -N-(C_1-C_6) alkyl, -N-OH, or -N-O(C_1-C_6)alkyl;~~

~~24. The compound of claim 23, wherein:~~

~~R_2 is -H, halo, -X_1R^a, (C_2-C_6) alkenyl, (C_2-C_6) alkynyl, or~~



~~wherein "~~ ~~" indicates the point of attachment, wherein:~~

~~Y_1 is absent or is NH, N-(C_1-C_6) alkyl, or O;~~

~~Y_2 is absent or is O, NH, NHO, N-(C_1-C_6) alkyl, N_2H_2, NH-S(O), or NH-$S(O)_2$-; and~~

~~Z^1 is -O, -NH, -N-(C_1-C_6) alkyl, -NOH-, or -N-O(C_1-C_6)alkyl.~~

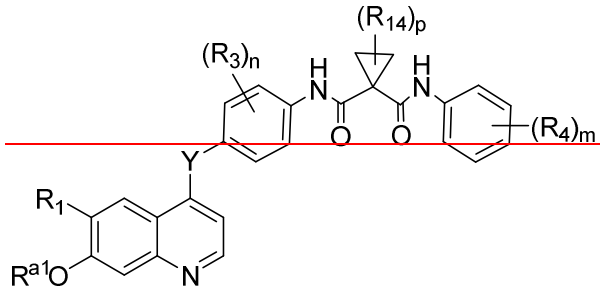
~~25. The compound of any of claims 22-24, wherein R_3 is -H or halo.~~

~~26. The compound of any of claims 22-25, wherein R_4 is -H or halo.~~

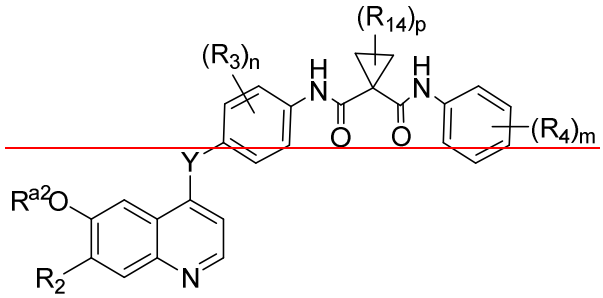
27. The compound of any of claims 22-26, wherein, wherein R_{14} is -H or halo.

28. The compound of any of claims 22-27, wherein Y is -O-.

29. The compound of any of claims 22-28, which is a compound of either formula B-1 or B-2:



B-1



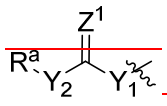
B-2

or a pharmaceutically acceptable salt thereof.

30. The compound of claim 29 of formula B-1, wherein:

R^{a1} is optionally substituted (C_1-C_6) alkyl;

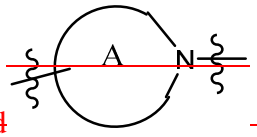
R_1 is -H, -CN, optionally substituted 3-6 membered cycloalkyl, optionally substituted phenyl, optionally substituted 4-6 membered heterocycloalkyl, optionally substituted 5-6 membered heteroaryl, $-SO_2$-(C_1-C_6) alkyl, $-SO_2NH_2$, $-SO_2$-NH(C_1-C_6) alkyl, or P(O)((C_1-C_6) alkyl)$_2$; or



wherein "〰" indicates the point of attachment, wherein:

Y_1 is absent;

Y_2 is absent or is -O-, -NH-, -NHO-, -NH-NH-, or -N-(C_1-C_6) alkyl-; or

Y_2 is optionally substituted 

, wherein ring A is a 3, 4, 5, 6, or 7-membered ring, wherein "〰" indicates points of attachment,

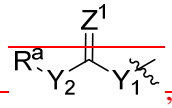
Z^1 is O, NH, N-(C_1-C_6) alkyl, NHO, or NO-(C_1-C_6) alkyl; and

R^a is -H, -(C_1-C_6) alkyl, 4-6-membered heterocycloalkyl, 3-6-membered cycloalkyl, -(C_2-C_6) alkylene-OH, -CH_2CHOH-(C_2-C_6) alkylene-OH, -(C_2-C_6) alkylene-NH_2, -(C_2-C_6) alkylene-NH(C_1-C_6), -(C_2-C_6) alkylene-N(C_1-C_6)$_2$, or -(C_2-C_6) alkylene-N-(4-6-membered heterocycloalkyl);

31. The compound of claim 30 of formula B-1, wherein:

R^{a1} is (C_1-C_6) alkyl;

R_1 is -H, -CN, optionally substituted cyclopropyl, optionally substituted phenyl, optionally substituted 4-6 membered azetidinyl, optionally substituted pyrollidinyl, optionally substituted piperidinyl, optionally substituted oxetanyl, optionally substituted oxazolyl, optionally substituted pyridinyl, optionally substituted imidazolyl, optionally substituted pyrrolyl, optionally substituted furnayl, optionally substituted pyrazolyl, optionally substituted oxadiazolyl, -SO_2-(C_1-C_6) alkyl, -SO_2NH_2, -SO_2-NH(C_1-C_6) alkyl, or P(O)((C_1-C_6) alkyl)$_2$; or

R_1 is 

, wherein:

Y_1 is absent;

Y_2 is O, NH, NHO, NH-NH, or N-(C_1-C_6) alkyl; or

Y_2 is optionally substituted azetidinyl;

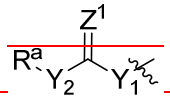
Z is O, NH, or N-(C_1-C_6) alkyl; and

R^a is H, (C_1-C_6) alkyl, -(C_2-C_6) alkylene-OH, -CH_2CHOH-(C_2-C_6) alkylene-OH, -(C_2-C_6) alkylene-NH_2, -(C_2-C_6) alkylene-NH(C_1-C_6) alkyl, -(C_2-C_6) alkylene-N((C_1-C_6) alkyl)$_2$, -(C_2-C_6) alkylene-

heterocycloalkyl), and 4-6 membered heterocycloalkyl, wherein heterocycloalkyl is optionally substituted.

32. The compound of claim 30 of formula B-2, wherein:

R^{a2} is optionally substituted (C_1-C_6) alkyl;

R_2 is  wherein "〰" indicates the point of attachment, wherein:

Y_1 is absent;

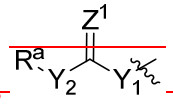
Y_2 is absent or is -O- or -NH-; and

Z^1 is O; and

R^a is -H or -(C_1-C_6) alkyl.

33. The compound of claim 32 of formula B-2, wherein:

R^{a2} is (C_1-C_6) alkyl;

R_2 is  wherein "〰" indicates the point of attachment, wherein:

Y_1 is absent;

Y_2 is absent or is -O- or -NH-; and

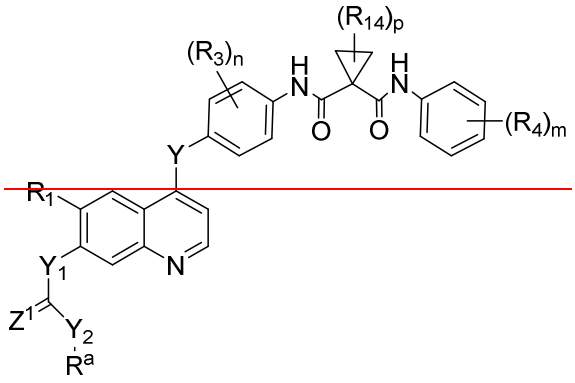
Z^1 is O or NO-(C_1-C_6) alkyl; and

R^a is -H or -(C_1-C_6) alkyl.

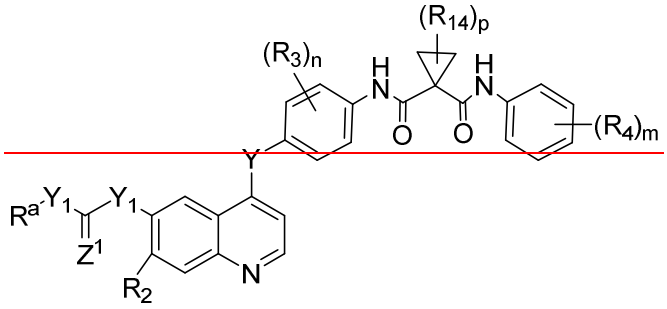
34. The compound of any of claims 29-31 of formula B-1, R^{a1} is methoxy.

35. The compound of any of claims 29 and 32-33 of formula B-2, R^{a2} is methoxy.

36. The compound of any of claims 22-28, which is a compound of either formula B-3 or B-4:



B-3



B-4

or a pharmaceutically acceptable salt thereof.

37. The compound of claim 36 which is a compound of formula B-3, wherein:

R_1 is -H or $(C_1$-$C_6)$ alkyl; and

Y_1 is absent;

Y_2 is absent or is -O-, -NHO-, or -NH-; and

Z^1 is O or NO $(C_1$-$C_6)$ alkyl; and

R^a is -H or $-(C_1$-$C_6)$ alkyl.

38. The compound of claim 37 which is a compound of formula B-3, wherein:

R_1 is -H or methyl;

Y_1 is absent;

Y_2 is absent or is -O-, -NHO-, or -NH-; and

Z^1 is O or NO-Me; and

R^a is -H, or Me.

39. The compound of claim 36 which is a compound of formula B-3, wherein:

R_1 and R^a, together with the atoms to which they are attached, form a 4-6 membered hereocycloalkly ring optionally substituted with halo; (C_1-C_6) alkyl; and (C_1-C_6) haloalkyl.

40. The compound of claim 36 which is a compound of formula B-4, wherein:

Y_1 is absent;

Y_2 is O, NH, NHO, NH-NH, or N-(C_1-C_6) alkyl; or

Y_2 is optionally substituted azetidinyl;

Z^1 is O, NH, NO-(C_1-C_6) alkyl, N-(C_1-C_6) alkyl; and

R^a is H, (C_1-C_6) alkyl, -(C_2-C_6) alkylene-OH, -CH_2CHOH-(C_2-C_6) alkylene-OH, -(C_2-C_6) alkylene-NH_2, -(C_2-C_6) alkylene-NH(C_1-C_6) alkyl, -(C_2-C_6) alkylene-N$((C_1-C_6)$ alkyl$)_2$, -(C_2-C_6) alkylene-optionally substituted 4-6 membered heterocycloalkyl), and optionally substituted 4-6 membered heterocycloalkyl;

R_2 is -H, F, Cl, Br, (C_1-C_6)alkoxy, -O-(C_2-C_6)alkylene-OH, -O-(C_2-C_6)alkylene-O-$(C_1-C_6$-alkyl), (C_2-C_6)alkylene-O-(C_1-C_6) alkyl, -NH_2, -NH-$(C_1-C_6$-alkyl), -NH-(C_1-C_6)alkylene-(optionally substituted 4-6 membered heterocycloalkyl), -NH-(C_2-C_6)alkylene-O-$(C_1-C_6$-alkyl).

41. The compound of claim 40 which is a compound of formula B-4, wherein:

Y_1 is absent;

Y_2 is O, NH, NHO, NH-NH, or N-(C_1-C_6) alkyl; or

Y_2 is optionally substituted azetidinyl;

Z^1 is O, NH, NO-(C_1-C_6) alkyl, N-(C_1-C_6) alkyl; and

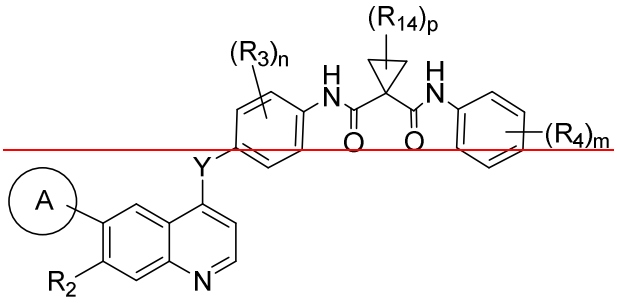
R^a is H, methyl, ethyl, -(C_2-C_6) alkylene-OH, -CH_2CHOH-(C_2-C_6) alkylene-OH, -(C_2-C_6) alkylene-NH_2, -(C_2-C_6) alkylene-NHMe, -(C_2-C_6) alkylene-N$(Me)_2$, -(C_1-C_6) alkylene-morpholinyl), -(C_1-C_6) alkylene-piperidinyl), (C_1-C_6)alkylene-(optionally substituted pyrrolidinyl), optionally substituted azetidinyl, or optionally substituted oxetanyl;

R_2 is -H, H, F, Cl, Br, methoxy, -O-(C_2-C_6)alkylene-OH, O-(C_2-C_6)alkylene-OMe, -NH_2, -NH-$(C_1-C_6$-alkyl), -NH-(C_2-C_6)alkylene-OMe, -NH-(C_2-C_6)alkylene-(optionally substituted morpholinyl), or -NH-(C_2-C_6)alkylene-O-$(C_1-C_6$-alkyl).

42. The compound of claim 36 which is a compound of formula B-4, wherein:

R_2 and R^a, together with the atoms to which they are attached, form a 4-6 membered hereocycloalkly ring optionally substituted with halo, (C_1-C_6) alkyl, and (C_1-C_6) haloalkyl.

43. The compound of claims 22-28 which is a compound of formula B-5:



B-5

or a pharmaceutically acceptable salt thereof, wherein ring A in formula B-5 is an optionally substituted 5-10 membered heteroaryl or C_{6-10} aryl, .

44. The compound of claim 43 which is a compound of formula B-5, wherein:

Ring A is an optionally substituted (C_6-C_{10}) aryl, optionally substituted (C_3-C_{10}) cycloalkyl, optionally substituted 5-10 membered heteroaryl, or optionally substituted 4-10 membered heterocycloalkyl; and

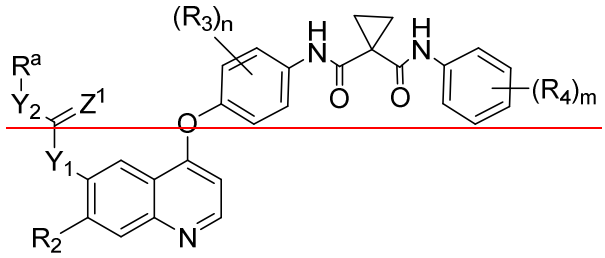
R_2 is H, or (C_1-C_6)alkoxy.

45. The compound of claim 44 which is a compound of formula B-5, wherein:

Ring A is an optionally substituted phenyl, optionally substituted cyclopropyl, optionally substituted pyridyl, optionally substituted imidazolyl, optionally substituted pyrrolyl, optionally substituted furanyl, optionally substituted pyrazolyl, optionally substituted oxazolyl, optionally substituted azetidinyl, or optionally substituted oxetanyl; and

R_2 is H or methoxy.

46. The compound of any one of claims 22-28, which is a compound of formula C:



C

or a pharmaceutically acceptable salt thereof, wherein:

Y_1 is absent;

Y_2 is O, NH, NHO, NH-NH, or N-(C_1-C_6) alkyl; or

Y_2 is optionally substituted azetidinyl;

Z^1 is O, NH, NO-(C_1-C_6) alkyl, or N-(C_1-C_6) alkyl;

R^a is H, (C_1-C_6) alkyl, -(C_2-C_6) alkylene-OH, -CH_2CHOH-(C_2-C_6) alkylene-OH, -(C_2-C_6) alkylene-NH_2, -(C_2-C_6) alkylene-NH(C_1-C_6) alkyl, -(C_2-C_6) alkylene-N((C_1-C_6) alkyl)$_2$, -(C_2-C_6) alkylene-optionally substituted 4-6 membered heterocycloalkyl), or optionally substituted 4-6 membered heterocycloalkyl;

R_2 is -H, F, Cl, Br, (C_1-C_6)alkoxy, -O-(C_2-C_6)alkylene-OH, -O-(C_2-C_6)alkylene-O-(C_1-C_6-alkyl), (C_2-C_6)alkylene-O-(C_1-C_6) alkyl, -NH_2, -NH-(C_1-C_6-alkyl), -NH-(C_1-C_6)alkylene-(optionally substituted 4-6 membered heterocycloalkyl), or -NH-(C_2-C_6)alkylene-O-(C_1-C_6-alkyl); and

n and m are each independently integers of 0 to 3

47. The compound of claim 46, wherein:

Y_1 is absent;

Y_2 is O, NH, NHO, NH-NH, or N-(C_1-C_6) alkyl; or

Y_2 is optionally substituted azetidinyl;

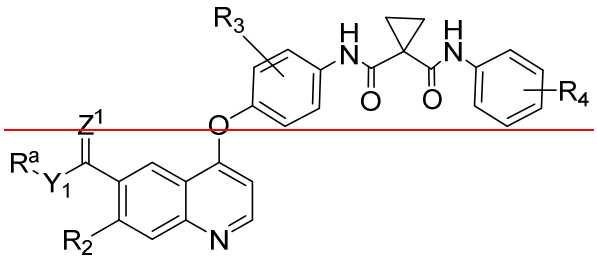
Z^1 is O, NH, NO-(C_1-C_6) alkyl, or N-(C_1-C_6) alkyl;

R^a is H, methyl, ethyl, -(C_2-C_6) alkylene-OH, -CH_2CHOH-(C_2-C_6) alkylene-OH, -(C_2-C_6) alkylene-NH_2, -(C_2-C_6) alkylene-NHMe, -(C_2-C_6) alkylene-N(Me)$_2$, -(C_1-C_6) alkylene-morpholinyl), -(C_1-C_6) alkylene-piperidinyl), (C_1-C_6)alkylene-(optionally substituted pyrrolidinyl), optionally substituted azetidinyl, or optionally substituted oxetanyl;

~~R_2 is -H, H, F, Cl, Br, methoxy, -O-(C_2-C_6)alkylene-OH, O-(C_2-C_6)alkylene-OMe, -NH_2, -NH-(C_1-C_6-alkyl), -NH-(C_2-C_6)alkylene-OMe, -NH-(C_2-C_6)alkylene-(optionally substituted morpholinyl), or -NH-(C_2-C_6)alkylene-O-(C_1-C_6-alkyl); and~~

~~and n and m or each 0 or 1.~~

~~48. The compound of any one of claims 46-47, which is a compound of formula C-1.~~



~~C-1~~

~~or a pharmaceutically acceptable salt thereof, wherein:~~

~~Y_2 is O, NH, NHO, NH-NH, or N-(C_1-C_6) alkyl; or~~

~~Y_2 is optionally substituted azetidinyl,~~

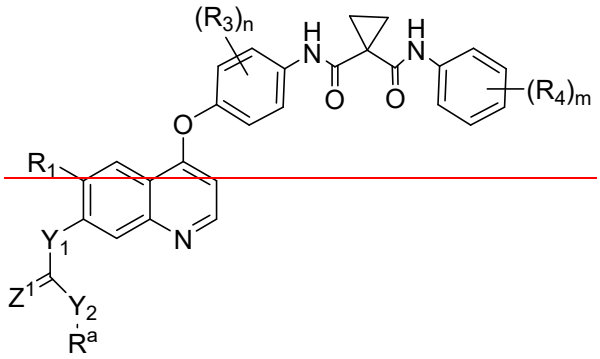
~~Z^1 is O, NH, NO-(C_1-C_6) alkyl, or N-(C_1-C_6) alkyl;~~

~~R^a is H, methyl, ethyl, -(C_2-C_6) alkylene-OH, -CH_2CHOH-(C_2-C_6) alkylene-OH, -(C_2-C_6) alkylene-NH_2, -(C_2-C_6) alkylene-NHMe, -(C_2-C_6) alkylene-N(Me)$_2$, -(C_1-C_6) alkylene-morpholinyl), -(C_1-C_6) alkylene-piperidinyl), (C_1-C_6)alkylene-(optionally substituted pyrrolidinyl), optionally substituted azetidinyl, or optionally substituted oxetanyl;~~

~~R_2 is -H, H, F, Cl, Br, methoxy, -O-(C_2-C_6)alkylene-OH, O-(C_2-C_6)alkylene-OMe, -NH_2, -NH-(C_1-C_6-alkyl), -NH-(C_2-C_6)alkylene-OMe, -NH-(C_2-C_6)alkylene-(optionally substituted morpholinyl), or -NH-(C_2-C_6)alkylene-O-(C_1-C_6-alkyl); and~~

~~and n and m are each indepenenently 0 or 1.~~

49. The compound of any one of claims 22-28, which is a compound of formula D:



D

50. The compound of any one of claim 49, wherein:

R_1 is H, or (C_1-C_6) alkyl; and

Y_1 is absent;

Y_2 is absent or is -O-, -NHO-, or -NH-; and

Z^1 is O or NO (C_1-C_6) alkyl,

R^a is H or (C_1-C_6) alkyl; and

n and m are each independently integers of 0 to 3.

51. The compound of any one of claim 50, wherein:

R_1 is H or methyl;

Y_1 is absent;

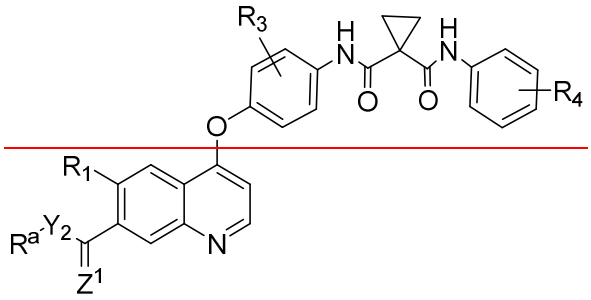
Y_2 is absent or is -O-, -NHO-, or -NH-; and

Z^1 is O or NO-Me; and

R^a is -H or Me.

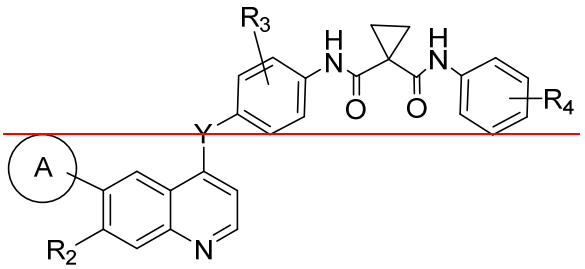
n and m are each independently integers of 0 to 1.

52. The compound of any one of claims 49-51, which a compound of formula D-1:



D-1.

53. The compound of any one of claims 22-28, which is a compound of formula E:



E

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted (C_6-C_{10}) aryl, optionally substituted (C_3-C_{10}) cycloalkyl, optionally substituted 5-10 membered heteroaryl, or optionally substituted 4-10 membered heterocycloalkyl; and

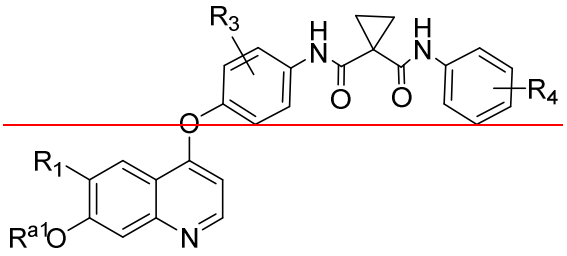
R_2 is H or (C_1-C_6)alkoxy.

54. The compound of claim 53, wherein:

Ring A is an optionally substituted phenyl, optionally substituted cyclopropyl, optionally substituted pyridyl, optionally substituted imidazolyl, optionally substituted pyrrolyl, optionally substituted furanyl, optionally substituted pyrazolyl, optionally substituted oxazolyl, optionally substituted azetidinyl, or optionally substituted oxetanyl; and

R_2 is H or methoxy.

55. The compound of any one of claims 22-28, which is a compound of formula F:

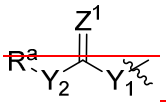


F

or a pharmaceutically acceptable salt thereof, wherein

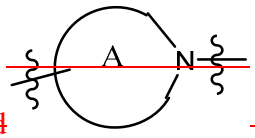
R^{a1} is optionally substituted (C_1-C_6) alkyl;

R_1 is -H, -CN, optionally substituted 3-6 membered cycloalkyl, optionally substituted phenyl, optionally substituted 4-6 membered heterocycloalkyl, optionally substituted 5-6 membered heteroaryl, $-SO_2$-(C_1-C_6) alkyl, $-SO_2NH_2$, $-SO_2$-NH(C_1-C_6) alkyl, or P(O)((C_1-C_6) alkyl)$_2$; or

 wherein "~~~" indicates the point of attachment; wherein:

Y_1 is absent;

Y_2 is absent or is -O-, -NH-, -NHO-, -NH-NH-, -N-(C_1-C_6) alkyl-; or

 Y_2 is optionally substituted , wherein ring A is a 3, 4, 5, 6, or 7-membered ring, wherein "~~~" indicates points of attachment;

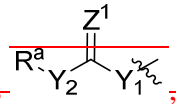
Z^1 is O, NH, N-(C_1-C_6) alkyl, NHO, or NO-(C_1-C_6) alkyl; and

R^a is -H, -(C_1-C_6) alkyl, 4-6 membered heterocycloalkyl, 3-6 membered cycloalkyl, -(C_2-C_6) alkylene-OH, $-CH_2CHOH$-(C_2-C_6) alkylene-OH, -(C_2-C_6) alkylene-NH_2, -(C_2-C_6) alkylene-NH(C_1-C_6), -(C_2-C_6) alkylene-N(C_1-C_6)$_2$, -(C_2-C_6) alkylene-N-(4-6 membered heterocycloalkyl);

56. The compound of any one of claim 55, wherein:

R^{a1} is methyl;

R_1 is -H, -CN, optionally substituted cyclopropyl, optionally substituted phenyl, optionally substituted 4-6 membered azetidinyl, optionally substituted pyrollidinyl, optionally substituted piperidinyl, optionally substituted oxetanyl, optionally substituted oxazolyl, optionally substituted pyridinyl, optionally substituted imidazolyl, optionally substituted pyrrolyl, optionally substituted furnayl, optionally substituted pyrazolyl, optionally substituted oxadiazolyl, $-SO_2-(C_1-C_6)$ alkyl, $-SO_2NH_2$, $-SO_2-NH(C_1-C_6)$ alkyl, or $P(O)((C_1-C_6)\text{ alkyl})_2$; or

R_1 is , wherein:

Y_1 is absent;

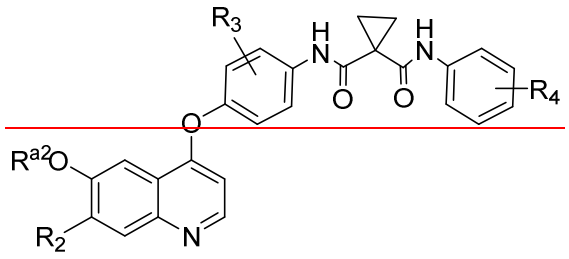
Y_2 is O, NH, NHO, NH-NH, or N-(C_1-C_6) alkyl; or

Y_2 is optionally substituted azetidinyl;

Z^1 is O, NH, or N-(C_1-C_6) alkyl; and

R^a is H, (C_1-C_6) alkyl, $-(C_2-C_6)$ alkylene-OH, $-CH_2CHOH-(C_2-C_6)$ alkylene-OH, $-(C_2-C_6)$ alkylene-NH_2, $-(C_2-C_6)$ alkylene-$NH(C_1-C_6)$ alkyl, $-(C_2-C_6)$ alkylene-$N((C_1-C_6)\text{ alkyl})_2$, $-(C_2-C_6)$ alkylene-heterocycloalkyl), and 4-6 membered heterocycloalkyl, wherein heterocycloalkyl is optionally substituted.

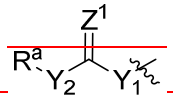
57. The compound of any one of claims 22-28, which is a compound of formula G:



G

or a pharmaceutically acceptable salt thereof, wherein:

R^{a1} is optionally substituted (C_1-C_6) alkyl;

R_2 is  wherein "〰" indicates the point of attachment, wherein:

Y_1 is absent;

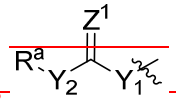
Y_2 is absent or is -O- or -NH-; and

Z^1 is O; and

R^a is -H or -(C_1-C_6) alkyl.

58. The compound of claim 57, wherein:

R^{a2} is methyl;

R_2 is  wherein "~~~" indicates the point of attachment, wherein:

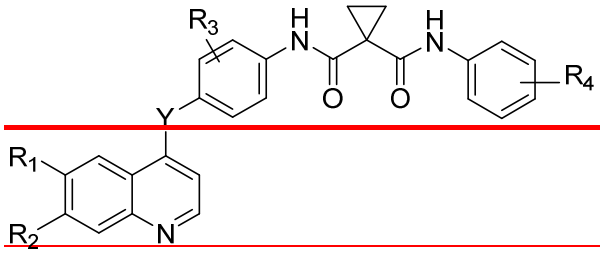
Y_1 is absent;

Y_2 is absent or is -O- or -NH-; and

Z^1 is O or NO (C_1-C_6) alkyl; and

R^a is -H or -(C_1-C_6) alkyl.

59. The compound any one of claims 1-58 which is a compound of formula H:



H

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is selected from the group consisting of -H, -CN, -CO NR_5R_6, -CO_2R_7, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_1-C_6 alkyl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_3-C_6 heterocycloalkyl, $SO_2NR_8R_9$, and (SO_2)-C_1-C_6 alkyl;

wherein when R_1 is selected from the group consisting of -CN, -CO NR_5R_6, -CO_2R_7, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted C_3-C_8 cycloalkyl, optionally substituted C_3-C_6 heterocycloalkyl, $SO_2NR_8R_9$, and (SO_2)-C_1-C_6 alkyl, R_2 is H, halo, NR_5R_6, or optionally substituted C_1-C_6 alkoxy;

wherein when R_1 is H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 alkoxy, R_2 is $-CO-NR_5R_6$ or $-CO_2R_7$;

or R_1 and R_2 taken together with the atoms to which they are attached to form optionally substituted cycloalkyl or optionally substituted heterocyloalkyl;

R_3 is selected from the group consisting of –H, optionally substituted C_{1-6} alkyl, –CN, and halo;

R_4 is –H or halo;

 is optionally substituted with one, two, three, or four groups independently selected from the group consisting of halo and C_1-C_6 alkyl, wherein "~~~~" indicate points of attachment;

R_5 and R_6 are each independently H, optionally substituted C_1-C_6 alkyl, or optionally substituted C_1-C_6 alkoxy;

R_7 is H or optionally substituted C_1-C_6 alkyl;

R_8 and R_9 are each independently H and optionally substituted C_1-C_6 alkyl or R_8; or

R_8 and R_9 may connect to form optionally substituted heterocycle; and

Y is selected from the group consisting of O, S, SO, SO_2, NH, and N-(C_1-C_6 alkyl).

60. The compound of claim 59, wherein Y is O.

61. The compound of claim 60, wherein R_3 is H.

62. The compound of claim 61, wherein  is not substituted.

63. The compound of claim 62, wherein R_4 is halo.

64. The compound of claim 63, wherein R_4 is para fluoro.

65. The compound of any one of claims 59-64, wherein R_2 is –H, halo, or optionally substituted (C_1-C_6)-alkoxy.

66. The compound of claim 63, wherein R_1 is -CN.

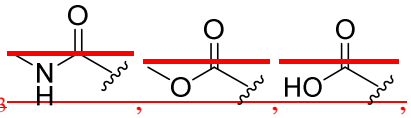
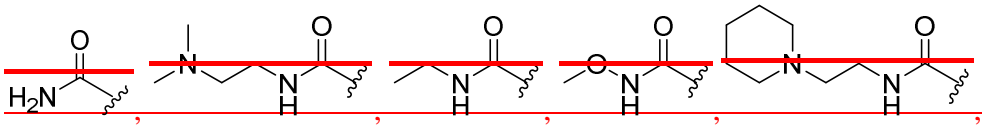
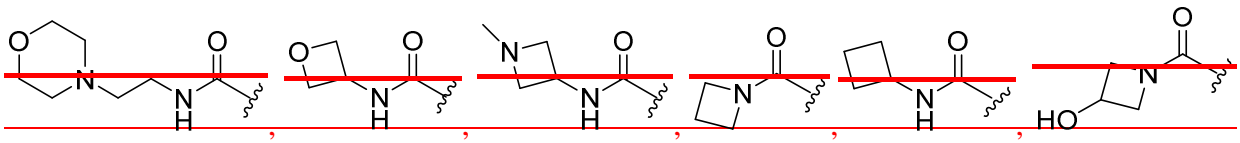
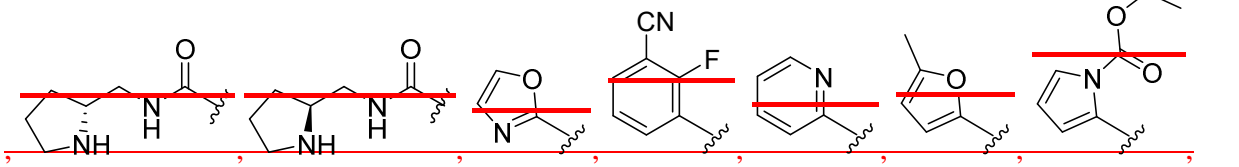
67. The compound of claim 63, wherein R_1 is $-CO_2H$.

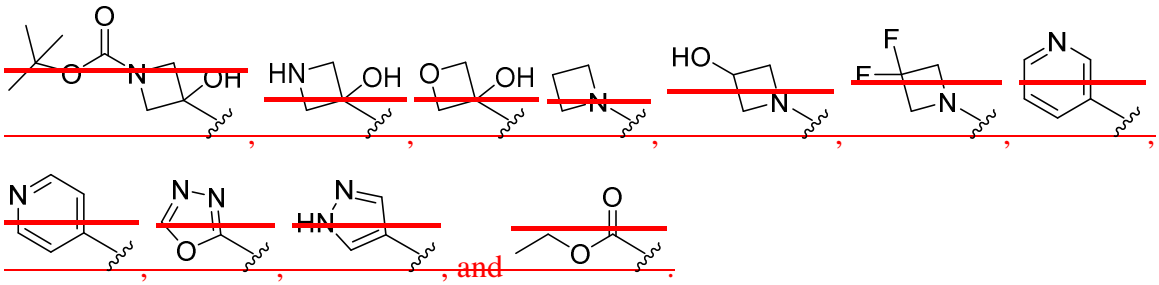
68. The compound of claim 63, wherein R_1 is $-CO_2$-Me.

69. The compound of claim 63, wherein R_1 is $-CO-NHR_6$.

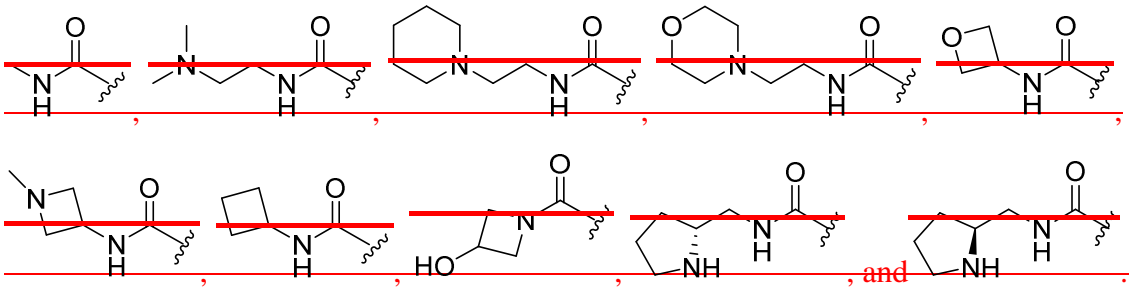
70. The compound of claim 69, wherein R_1 is $-CO-NH_2$.

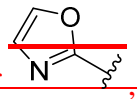
71. The compound of claim 69, wherein R_1 is $-CO-NMeR_6$.

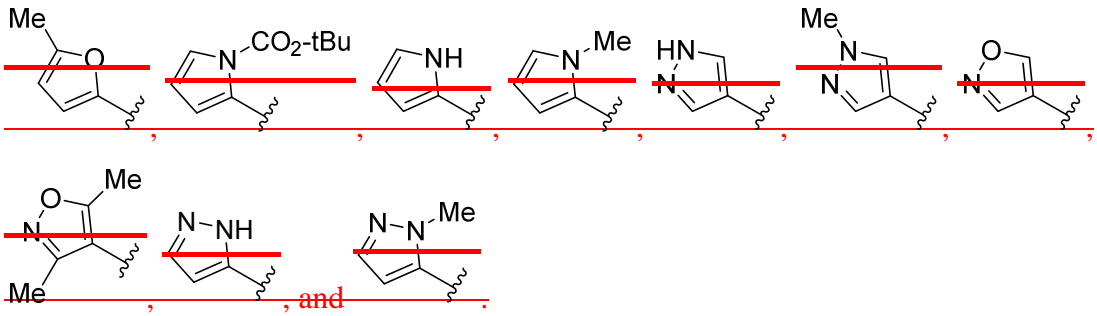
72. The compound of any one of claims 1, 2, 4, 5, 7, 8, 9, and 63, wherein R_1 is selected from the group consisting of -CN, $-(SO_2)NH_2$, -OMe, $-(SO_2)CH_3$ , , , ,

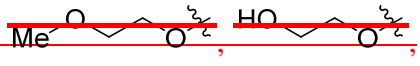


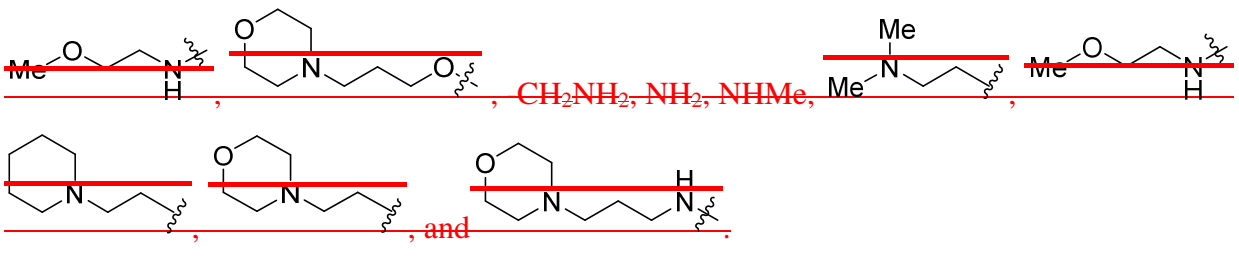
73. The compound of claim 72, wherein R_1 is selected from the group consisting of



74. The compound of claim 72, wherein R_1 selected from the group consisting of ,



75. The compound of any one of claims 1, 2, 3, 5, 6, 9, and 63-74, wherein R_2 is selected from the group consisting of H, CN, Br, F, Cl, OMe, CH_3, ,



76. The compound of any one of claims 59-65, wherein R_1 is -H, methyl, or methoxy.

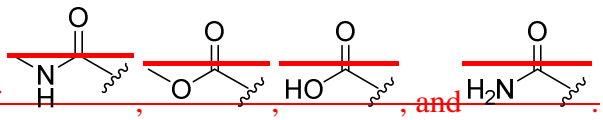
77. The compound of claim 76, wherein R_2 is $-CO_2H$.

78. The compound of any one of claims 59-65, wherein R_1 is $-CO_2$-Me.

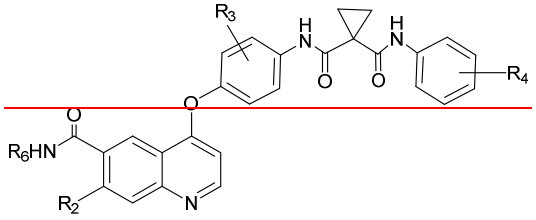
79. The compound of any one of claims 59-650, wherein R_1 is $-CO-NHR_6$.

80. The compound of claim 79, wherein R_1 is $-CO-NH_2$.

81. The compound of any one of claims 59-65, wherein R_1 is $-CO-NMeR_6$.

82. The compound of any one of claims 59-65, wherein R_1 is selected from the group consisting of , and .

83. The compound of claim 64, which is a compound of formula I-A:



I-A

wherein R_6 is (C_1-C_6) alkyl, R_2 is (C_1-C_6) alkoxy, R_3 is -H or halo, and R_4 is halo.

84. The compound of any one of claims 1-83 which is selected from the group consisting of:

Cmpd No	Name
5	methyl 4-[4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]-7-

Cmpd No	Name
6	4-[4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]-7-
7	1-N-[4-(6-carbamoyl-7-methoxyquinolin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
8	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(methylcarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
9	1-N-[4-[6-(ethylcarbamoyl)-7-methoxyquinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
10	1-N-[4-[6-[2-(dimethylamino)ethylcarbamoyl]-7-methoxyquinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
11	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(2-piperidin-1-ylethylcarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-
12	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(2-morpholin-4-ylethylcarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-
13	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(oxetan-3-ylcarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
14	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-[(1-methylazetidin-3-yl)carbamoyl]quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
15	1-N-[4-[6-(azetidine-1-carbonyl)-7-methoxyquinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
16	1-N'-(4-fluorophenyl)-1-N-[4-[6-(3-hydroxyazetidine-1-carbonyl)-7-methoxyquinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
17	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(methoxycarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
21	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-[[(2R)-pyrrolidin-2-yl]methylcarbamoyl]quinolin-4-yl]oxyphenyl]cyclopropane-1,1-
22	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-[[(2S)-pyrrolidin-2-yl]methylcarbamoyl]quinolin-4-yl]oxyphenyl]cyclopropane-1,1-
37	1-N-[4-(6-cyano-7-methoxyquinolin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
45	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(1,3-oxazol-2-yl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
58	1-N-[4-(6-carbamoylquinolin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
59	1-N'-(4-fluorophenyl)-1-N-[4-[6-(methylcarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
60	1-N'-(4-fluorophenyl)-1-N-[4-[6-[(1-methylazetidin-3-yl)carbamoyl]quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
67	1-N-[4-(6-carbamoyl-7-fluoroquinolin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
68	1-N-[4-(6-carbamoyl-7-chloroquinolin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;

Cmpd No	Name
69	1-N-[4-(7-bromo-6-carbamoylquinolin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
70	1-N-[4-[6-carbamoyl-7-(2-methoxyethylamino)quinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
71	1-N-[4-[6-carbamoyl-7-(3-morpholin-4-ylpropylamino)quinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
81	4-[4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]-7-
82	1-N-[4-[6-carbamoyl-7-(methylamino)quinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide
83	1-N'-(4-fluorophenyl)-1-N-[4-[7-(methylamino)-6-(methylcarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-
84	methyl 4-[4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]-7-
87	1-N-[4-(7-amino-6-carbamoylquinolin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
88	1-N-[4-[7-amino-6-(methylcarbamoyl)quinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
89	7-amino-4-[4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]quinoline-
90	methyl 7-amino-4-[4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]quinoline-
92	1-N'-(4-fluorophenyl)-1-N-[4-[(2-methyl-4-oxo-2,3-dihydropyrido[3,2-g][1,3]benzoxazin-6-yl)oxy]phenyl]cyclopropane-1,1-dicarboxamide;
98	1-N-[4-[6-carbamoyl-7-(3-morpholin-4-ylpropoxy)quinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
103	1-N-[4-[6-carbamoyl-7-(2-methoxyethoxy)quinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
106	1-N-[4-[6-carbamoyl-7-(2-hydroxyethoxy)quinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
128	methyl 4-[2-chloro-4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]-7-
130	4-[2-chloro-4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]-7-
132	1-N'-[4-(6-carbamoyl-7-methoxyquinolin-4-yl)oxy-3-chlorophenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
134	1-N'-[3-chloro-4-[7-methoxy-6-(methylcarbamoyl)quinolin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
129	methyl 4-[2-fluoro-4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]-7-
131	4-[2-fluoro-4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]-7-

Cmpd No	Name
133	1-N'-[4-(6-carbamoyl-7-methoxyquinolin-4-yl)oxy-3-fluorophenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
135	1-N'-[3-fluoro-4-[7-methoxy-6-(methylcarbamoyl)quinolin-4-yl]oxyphenyl]-1-N-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
140	methyl 4-[4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]-6-
141	4-[4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]-6-
142	1-N-[4-(7-carbamoyl-6-methylquinolin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
143	1-N'-(4-fluorophenyl)-1-N-[4-[6-methyl-7-(methylcarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
150	methyl 4-[4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]-6-
151	4-[4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]-6-
152	1-N-[4-(7-carbamoyl-6-methoxyquinolin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
153	1-N'-(4-fluorophenyl)-1-N-[4-[6-methoxy-7-(methylcarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
162	methyl 4-[4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]quinoline-
163	4-[4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]quinoline-
164	1-N-[4-(7-carbamoylquinolin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
165	1-N'-(4-fluorophenyl)-1-N-[4-[7-(methylcarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
175	1-N-[4-[6-(3-cyano-2-fluorophenyl)-7-methoxyquinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
176	1-N'-(4-fluorophenyl)-1-N-[4-(7-methoxy-6-pyridin-2-ylquinolin-4-yl)oxyphenyl]cyclopropane-1,1-dicarboxamide;
177	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(1-methylimidazol-4-yl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
180	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(5-methylfuran-2-yl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
181	tert-butyl 2-[4-[4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]-7-
182	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(1-methylpyrazol-4-yl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
183	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(1,2-oxazol-4-yl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;

Cmpd No	Name
184	1-N-[4-[6-(3,5-dimethyl-1,2-oxazol-4-yl)-7-methoxyquinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
185	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(1H-pyrazol-5-yl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
186	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(1H-pyrazol-4-yl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
187	1-N-[4-(6-cyclopropyl-7-methoxyquinolin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
188	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(1H-pyrrol-2-yl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
191	1-N'-(4-fluorophenyl)-1-N-[4-[6-(1H-imidazol-2-yl)-7-methoxyquinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
192	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(1,3-oxazol-5-yl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
195	tert-butyl 3-[4-[4-[[1-[(4-fluorophenyl)carbamoyl]cyclopropanecarbonyl]amino]phenoxy]-7-
196	1-N'-(4-fluorophenyl)-1-N-[4-[6-(3-hydroxyoxetan-3-yl)-7-methoxyquinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
197	1-N'-(4-fluorophenyl)-1-N-[4-[6-(3-hydroxyazetidin-3-yl)-7-methoxyquinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
198	1-N-[4-[6-(azetidin-1-yl)-7-methoxyquinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
199	1-N'-(4-fluorophenyl)-1-N-[4-[6-(3-hydroxyazetidin-1-yl)-7-methoxyquinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
200	1-N-[4-[6-(3,3-difluoroazetidin-1-yl)-7-methoxyquinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
201	1-N'-(4-fluorophenyl)-1-N-[4-(7-methoxy-6-pyridin-3-ylquinolin-4-yl)oxyphenyl]cyclopropane-1,1-dicarboxamide;
202	1-N'-(4-fluorophenyl)-1-N-[4-(7-methoxy-6-pyridin-4-ylquinolin-4-yl)oxyphenyl]cyclopropane-1,1-dicarboxamide;
204	1-N'-(4-fluorophenyl)-1-N-[4-[6-(1H-pyrazol-5-yl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
206	1-N'-(4-fluorophenyl)-1-N-[4-(7-methoxy-6-sulfamoylquinolin-4-yl)oxyphenyl]cyclopropane-1,1-dicarboxamide;
209	1-N'-(4-fluorophenyl)-1-N-[4-(6-sulfamoylquinolin-4-yl)oxyphenyl]cyclopropane-1,1-dicarboxamide;
210	1-N'-(4-fluorophenyl)-1-N-[4-(7-methoxy-6-methylsulfonylquinolin-4-yl)oxyphenyl]cyclopropane-1,1-dicarboxamide;
220	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(1,3,4-oxadiazol-2-yl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
221	1-N'-(4-fluorophenyl)-1-N-[4-[6-(1,3,4-oxadiazol-2-yl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;

or a pharmaceutically acceptable salt thereof.

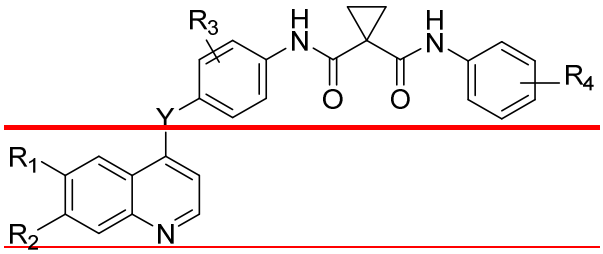
85. The compound of any one of claims 1-83 which is selected from the group consisting of:

Cmpd No	Name
27	1-N'-(4-fluorophenyl)-1-N-[4-[6-(2-hydroxyethoxycarbamoyl)-7-methoxyquinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
20	1-N'-(4-fluorophenyl)-1-N-[4-[6-(hydroxycarbamoyl)-7-methoxyquinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
26	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(oxetan-3-yloxycarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
30	1-N-[4-[6-(2,3-dihydroxypropoxycarbamoyl)-7-methoxyquinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide; *Enantiomer 1*
31	1-N-[4-[6-(2,3-dihydroxypropoxycarbamoyl)-7-methoxyquinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide; *Enantiomer 2*
32	1-N'-(4-fluorophenyl)-1-N-[4-[6-(hydrazinecarbonyl)-7-methoxyquinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
34	1-N-[4-(6-acetyl-7-methoxyquinolin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
35	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-[(E)-N-methoxy-C-methylcarbonimidoyl]quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
36	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-[(Z)-N-methoxy-C-methylcarbonimidoyl]quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
50	1-N'-(4-fluorophenyl)-1-N-[4-[7-(2-hydroxyethoxy)-6-(1,3-oxazol-2-yl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
51	1-N-[4-(6-dimethylphosphoryl-7-methoxyquinolin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
96	1-N-[4-[(2-ethyl-4-oxo-2,3-dihydropyrido[3,2-g][1,3]benzoxazin-6-yl)oxy]phenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
110	1-N'-(4-fluorophenyl)-1-N-[4-[7-(2-hydroxyethoxy)-6-(methylcarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
115	1-N-[4-[6-carbamoyl-7-(2-hydroxypropoxy)quinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
116	1-N'-(4-fluorophenyl)-1-N-[4-[7-(2-hydroxypropoxy)-6-(methylcarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
125	1-N'-(4-fluorophenyl)-1-N-[4-[7-(2-hydroxypropoxy)-6-(1,3-oxazol-2-yl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;

Cmpd No	Name
166	1-N'-(4-fluorophenyl)-1-N-[4-[7-(2-hydroxyethoxycarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
169	1-N-[4-[7-[[(2R)-2,3-dihydroxypropoxy]carbamoyl]quinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
170	1-N-[4-[7-[[(2S)-2,3-dihydroxypropoxy]carbamoyl]quinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
167	1-N'-(4-fluorophenyl)-1-N-[4-[7-(oxetan-3-yloxycarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
193	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-[(E)-methoxyiminomethyl]quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
207	1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(methylsulfamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
208	1-N-[4-[6-(ethylsulfamoyl)-7-methoxyquinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
213	1-N'-(4-fluorophenyl)-1-N-[4-[7-(methoxycarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;
214	1-N-[4-[7-(ethylcarbamoyl)quinolin-4-yl]oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide;
254	1-N'-(4-fluorophenyl)-1-N-[4-(7-sulfamoylquinolin-4-yl)oxyphenyl]cyclopropane-1,1-dicarboxamide;
255	1-N-[4-(7-acetylquinolin-4-yl)oxyphenyl]-1-N'-(4-fluorophenyl)cyclopropane-1,1-dicarboxamide; and
256	1-N'-(4-fluorophenyl)-1-N-[4-[7-[(E)-N-methoxy-C-methylcarbonimidoyl]quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide;

or a pharmaceutically acceptable salt thereof.

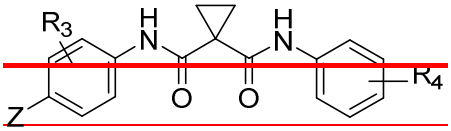
86. A process for making a compound of Formula I:



I

or a pharmaceutically acceptable salt thereof, comprising:

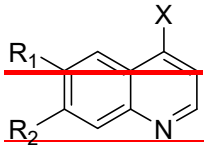
reacting a compound of formula II:



II

wherein Z is selected from the group consisting of NH_2, SH, and OH;

with a compound of formula III:



III

wherein X is a leaving group;

R_1 is selected from the group consisting of -H, -CN, -CO-NR_5R_6, -CO_2R_7, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted (C_1-C_6) alkyl, optionally substituted (C_3-C_8) cycloalkyl, optionally substituted (C_3-C_6) heterocycloalkyl, -$SO_2NR_8R_9$, and -(SO_2)-(C_1-C_6) alkyl;

wherein when R_1 is selected from the group consisting of -CN, -CO-NR_5R_6, -CO_2R_7, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted (C_3-C_8) cycloalkyl, optionally substituted (C_3-C_6) heterocycloalkyl, -$SO_2NR_8R_9$, and -(SO_2)-(C_1-C_6) alkyl, R_2 is -H, halo, -NR_5R_6, or optionally substituted (C_1-C_6) alkoxy;

wherein when R_1 is -H, optionally substituted (C_1-C_6) alkyl, or optionally substituted (C_1-C_6) alkoxy, R_2 is -CO-NR_5R_6 or -CO_2R_7;

or R_1 and R_2 taken together with the atoms to which they are attached to form optionally substituted cycloalkyl or optionally substituted heterocyloalkyl;

R_3 is selected from the group consisting of -H, optionally substituted (C_1-C_6) alkyl; -CN; and halo;

R_4 is -H or halo;

 is optionally substituted with one two, three, or four groups independently selected from the group consisting of halo and (C_1-C_6) alkyl, wherein "~~~~" indicate points of attachment;

R_5 and R_6 are each independently –H, optionally substituted (C_1-C_6) alkyl, or optionally substituted (C_1-C_6) alkoxy;

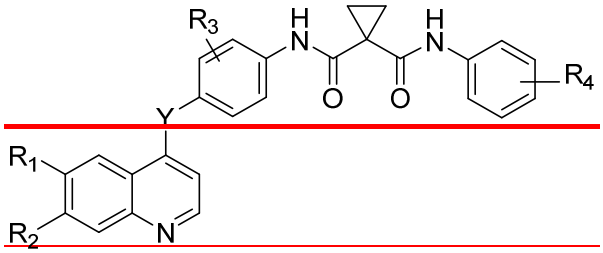
R_7 is –H or optionally substituted (C_1-C_6) alkyl;

R_8 and R_9 are each independently –H and optionally substituted (C_1-C_6) alkyl; or

R_8 and R_9 may connect to form optionally substituted heterocycle; and

Y is selected from the group consisting of O, S, SO, SO_2, NH, and N-((C_1-C_6) alkyl).

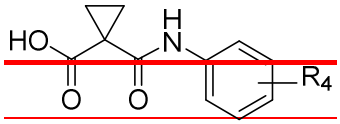
87. A process for making a compound of Formula I:



I

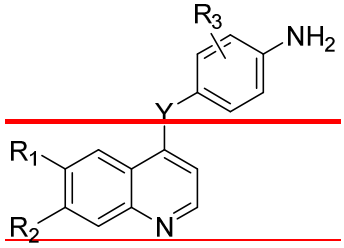
or a pharmaceutically acceptable salt thereof, comprising:

reacting a compound of formula IV:



IV

with a compound of formula V:



V

R_1 is selected from the group consisting of –H, –CN, –CO-NR_5R_6, –CO_2R_7, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted (C_1-C_6) alkyl, optionally substituted (C_3-C_8) cycloalkyl, optionally substituted (C_3-C_6) heterocycloalkyl, –$SO_2NR_8R_9$, and –(SO_2)-(C_1-C_6) alkyl;

wherein when R_1 is selected from the group consisting of -CN, $-CO-NR_5R_6$, $-CO_2R_7$, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted (C_3-C_8) cycloalkyl, optionally substituted (C_3-C_6) heterocycloalkyl, $-SO_2NR_8R_9$, and $-(SO_2)$-(C_1-C_6) alkyl, R_2 is -H, halo, $-NR_5R_6$, or optionally substituted (C_1-C_6) alkoxy;

wherein when R_1 is -H, optionally substituted (C_1-C_6) alkyl, or optionally substituted (C_1-C_6) alkoxy, R_2 is $-CO-NR_5R_6$ or $-CO_2R_7$;

or R_1 and R_2 taken together with the atoms to which they are attached to form optionally substituted cycloalkyl or optionally substituted heterocyloalkyl;

R_3 is selected from the group consisting of -H, optionally substituted (C_1-C_6) alkyl, -CN, and halo;

R_4 is -H or halo;

 is optionally substituted with one, two, three, or four groups independently selected from the group consisting of halo, and (C_1-C_6) alkyl, wherein "~~~~" indicate points of attachment;

R_5 and R_6 are each independently -H, optionally substituted (C_1-C_6) alkyl, or optionally substituted (C_1-C_6) alkoxy;

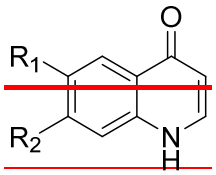
R_7 is -H or optionally substituted (C_1-C_6) alkyl;

R_8 and R_9 are each independently -H and optionally substituted (C_1-C_6 alkyl); or

R_8 and R_9 may connect to form optionally substituted heterocycle; and

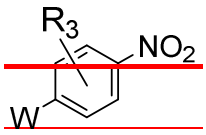
Y is selected from the group consisting of O, S, SO, SO_2, NH, and N-((C_1-C_6) alkyl).

88. The process of claim 87, further comprising reacting a compound of Formula VI:



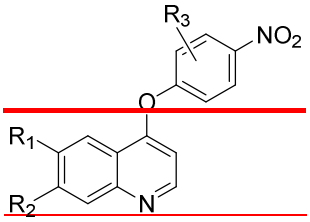
VI

with a compound of Formula VII:



VII

to form a compound of Formula VIII:



VIII

and reducing the compound of Formula VIII to provide a compound of Formula V, wherein:

R_1 is selected from the group consisting of -H, -CN, $-CO-NR_5R_6$, $-CO_2R_7$, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted (C_1-C_6) alkyl, optionally substituted (C_3-C_8) cycloalkyl, optionally substituted (C_3-C_6) heterocycloalkyl, $-SO_2NR_8R_9$, and $-(SO_2)$-(C_1-C_6) alkyl;

wherein when R_1 is selected from the group consisting of -CN, $-CO-NR_5R_6$, $-CO_2R_7$, optionally substituted aryl, optionally substituted heteroaryl, optionally substituted (C_3-C_8) cycloalkyl, optionally substituted (C_3-C_6) heterocycloalkyl, $-SO_2NR_8R_9$, and $-(SO_2)$-(C_1-C_6) alkyl, R_2 is -H, halo, $-NR_5R_6$, or optionally substituted (C_1-C_6) alkoxy;

wherein when R_1 is -H, optionally substituted (C_1-C_6) alkyl, or optionally substituted (C_1-C_6) alkoxy, R_2 is $-CO-NR_5R_6$, or $-CO_2R_7$;

or R_1 and R_2 taken together with the atoms to which they are attached to form optionally substituted cycloalkyl or optionally substituted heterocyloalkyl;

R_3 is selected from the group consisting of -H, optionally substituted (C_1-C_6) alkyl, -CN, and halo; and

W is halo.

89. A pharmaceutical composition comprising a compound of any one of claims 1-85, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

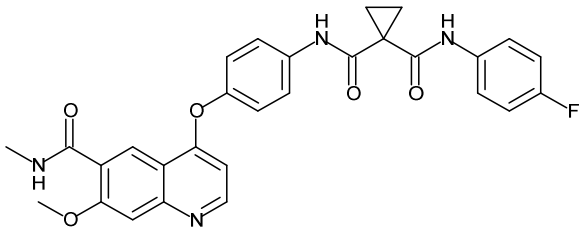
~~90. A method of treating a disease, disorder, or syndrome mediated at least in part by modulating in vivo activity of a protein kinase, comprising administering to a subject in need thereof a compound of any one of claims 1-85 or a pharmaceutical composition of claim 89.~~

~~91. The method of claim 90, wherein the disease, disorder, or syndrome mediated at least in part by modulating in vivo activity of a protein kinase is cancer.~~

~~92. A method for inhibiting a protein kinase, the method comprising contacting the protein kinase with a compound of any one of claims 1-85.~~

~~93. The method of any one of claims 90-92, wherein the protein kinase is Axl, Mer, c-Met, KDR, or a combination thereof.~~

1. A compound which is:



or a pharmaceutically acceptable salt thereof.

2. A compound which is 1-N'-(4-fluorophenyl)-1-N-[4-[7-methoxy-6-(methylcarbamoyl)quinolin-4-yl]oxyphenyl]cyclopropane-1,1-dicarboxamide or a pharmaceutically acceptable salt thereof.