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HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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(54) Title: IRE1 SMALL MOLECULE INHIBITORS

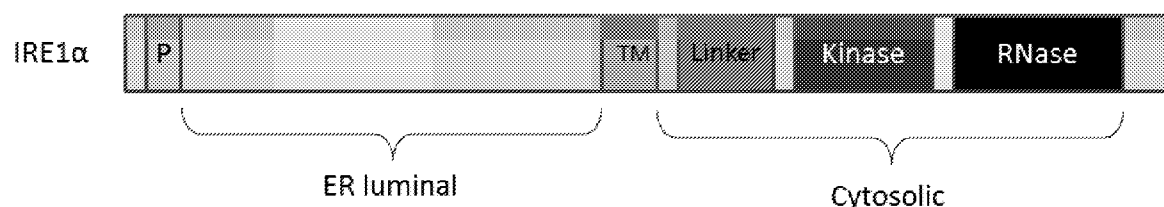


FIG. 1

(57) Abstract: Provided herein are small molecule inhibitors for the targeting of IRE1 protein family members. Binding may be direct or indirect. Further provided herein are methods of using IRE1 small molecule inhibitors for use in treating or ameliorating cancer in a subject. Moreover, IRE1 small molecule inhibitors described herein are for the treatment of cancer, where the cancer is a solid or hematologic cancer.

IRE1 SMALL MOLECULE INHIBITORS

CROSS-REFERENCE

[0001] This application claims benefit of U.S. Provisional Patent Application No. 62/513,929 filed on June 1, 2017, which is incorporated herein by reference in its entirety.

SEQUENCE LISTING

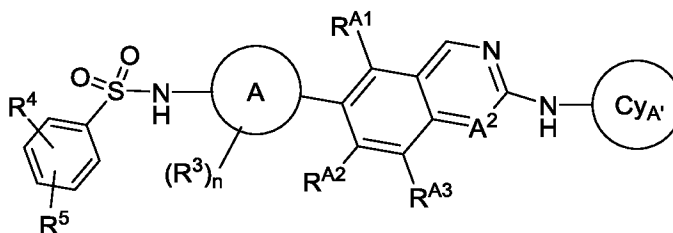
[0001.1] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 23, 2018, is named 51089-711_601_SL.txt and is 23,840 bytes in size.

BACKGROUND

[0002] Aggressive tumors have evolved strategies that enable them to thrive under constant adverse conditions. For example, cancer cells respond to hypoxia, nutrient starvation, oxidative stress, and high metabolic demand by adjusting their protein folding capacity via the endoplasmic reticulum (ER) stress response pathway. There exists a need for improved methods and compositions to target cancer cells and counter their mechanisms of survival.

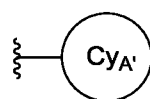
BRIEF SUMMARY

[0003] Provided in one aspect is a compound of Formula (I), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (I)

wherein,



is a substituted C₃-C₁₀ cycloalkyl that is substituted with 1-3R¹ and 0-3R²; each R¹ is independently -OR⁶, -SR⁶, -S(=O)R⁷, -S(=O)₂R⁷, or -N(R⁶)₂; each R² is independently H, halogen, -CN, -OR⁸, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -NR⁸S(=O)₂R⁹, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -OCO₂R⁹, -N(R⁸)₂, -OC(=O)N(R⁸)₂, -NR⁸C(=O)R⁹, -NR⁸C(=O)OR⁹, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₁-C₄heteroalkyl,

optionally substituted C₃-C₆cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R⁶ is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₁-C₄fluoroalkyl, -X-optionally substituted C₁-C₄alkyl, -X-optionally substituted C₁-C₄heteroalkyl, -X-optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; or two R⁶ are taken together with the N atom to which they are attached to form an optionally substituted heterocycle;

X is -(C=O)-;

each R⁷ is independently optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R⁸ is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₁-C₄fluoroalkyl, , optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

or two R⁸ are taken together with the N atom to which they are attached to form an optionally substituted heterocycle;

each R⁹ is independently optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, or optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

A² is N or CR^A;

R^A, R^{A1}, R^{A2}, and R^{A3} are each independently H, halogen, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted aryl, or -OR¹⁰;

R¹⁰ is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

ring A is a monocyclic carbocycle or a monocyclic heterocycle;

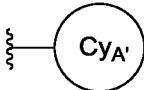
each R³ is independently H, halogen, -CN, -OR¹¹, -SR¹¹, -N(R¹¹)₂, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₁-

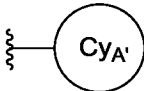
C₄heteroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;
 each R¹¹ is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

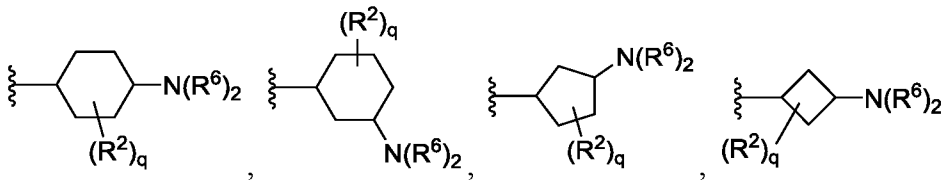
n is 0, 1, 2, 3, or 4;

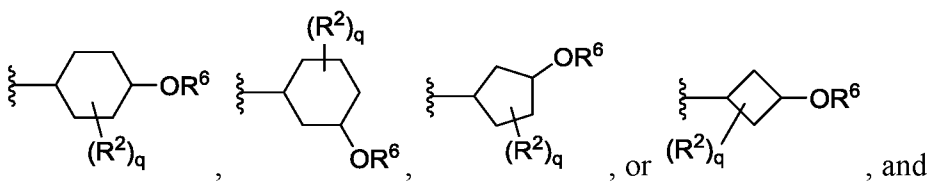
R⁴ and R⁵ are each independently H, halogen, -CN, -OR¹², -SR¹², -N(R¹²)₂, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;
 and

R¹² is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

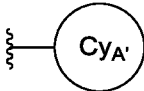
[0004] In some embodiments,  is substituted C₄-C₇ cycloalkyl that is substituted with 1-3R¹ and 0-3R².

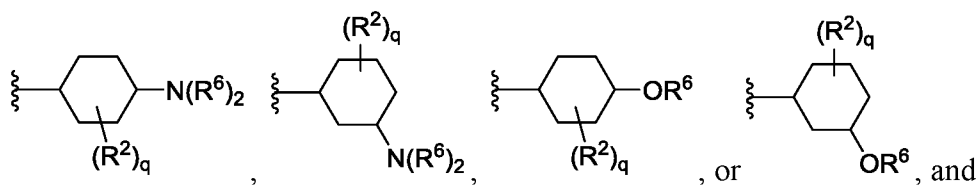
[0005] In some embodiments,  is

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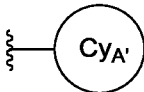
, and

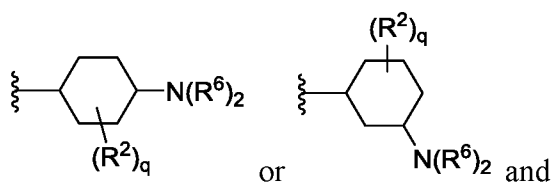
q is 0, 1, 2, or 3.

[0006] In some embodiments,  is



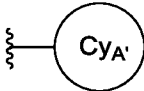
q is 0, 1, 2, or 3.

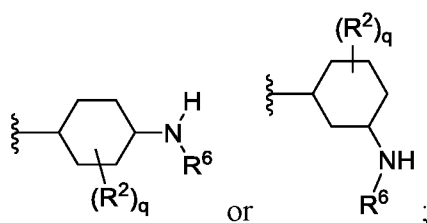
[0007] In some embodiments,  is



q is 0, 1, 2, or 3.

[0008] In some embodiments, q is 0 or 1. In some embodiments, each R^6 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_1 - C_4 fluoroalkyl, -X-optionally substituted C_1 - C_4 alkyl, -X-optionally substituted C_1 - C_4 heteroalkyl, or -X-optionally substituted C_1 - C_4 fluoroalkyl. In some embodiments, each R^6 is independently H. In some embodiments, each R^2 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

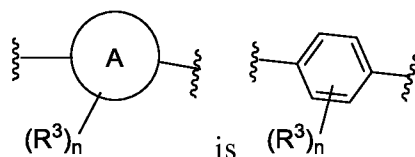
[0009] In some embodiments,  is



R^6 is H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_1 - C_4 fluoroalkyl, -X-optionally substituted C_1 - C_4 alkyl, -X-optionally substituted C_1 - C_4 heteroalkyl, or -X-optionally substituted C_1 - C_4 fluoroalkyl; q is 0 or 1; and R^2 is H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

[0010] In some embodiments, R^6 is H. In some embodiments, A^2 is N. In some embodiments, A^2 is CR^A . In some embodiments, R^A is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl. In some embodiments, R^A is H. In some embodiments, R^{A1} is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl. In some embodiments, R^{A1} is H. In some embodiments, R^{A2} is H, optionally substituted C_1 - C_4 alkyl, or

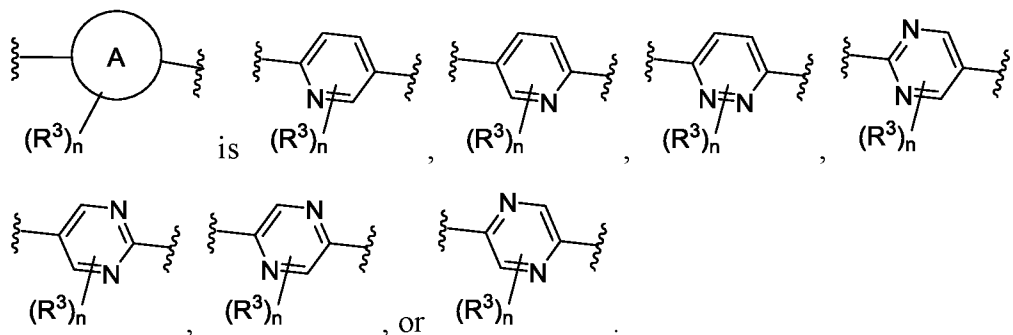
optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^{A2} is H. In some embodiments, R^{A3} is H, halogen, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted aryl, or -OR¹⁰. In some embodiments, R^{A3} is H, halogen, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, or -OR¹⁰. In some embodiments, R^{A3} is optionally substituted C₁-C₄alkyl. In some embodiments, R^{A3} is methyl, ethyl, propyl or butyl. In some embodiments, R^{A3} is -OR¹⁰ and R¹⁰ is methyl, ethyl, propyl or butyl. In some embodiments, ring A is phenylene or a monocyclic C₃-C₈cycloalkylene that is selected from cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene, and cyclooctylene. In some embodiments, ring A is phenylene.



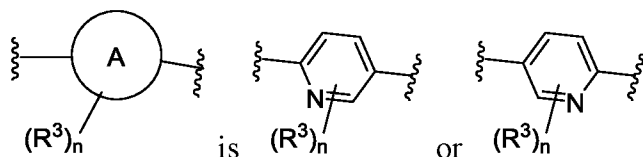
[0011] In some embodiments,

[0012] In some embodiments, ring A is a monocyclic C₁-C₅heteroarylene containing 1-4 N atoms, and 0 or 1 O or S atom, or a monocyclic C₁-C₅heteroarylene containing 0-4 N atoms, and 1 O or S atom. In some embodiments, ring A is a monocyclic 6-membered heteroarylene selected from pyridinylene, pyrimidinylene, pyrazinylene, and pyridazinylene. In some embodiments, ring A is pyridinylene.

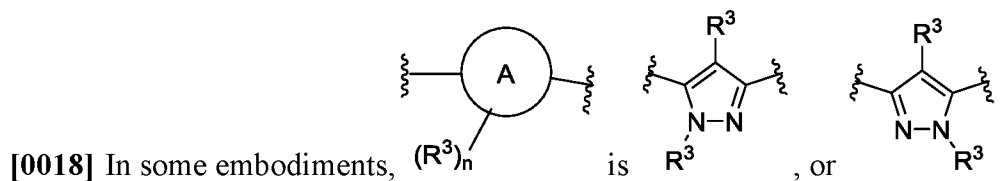
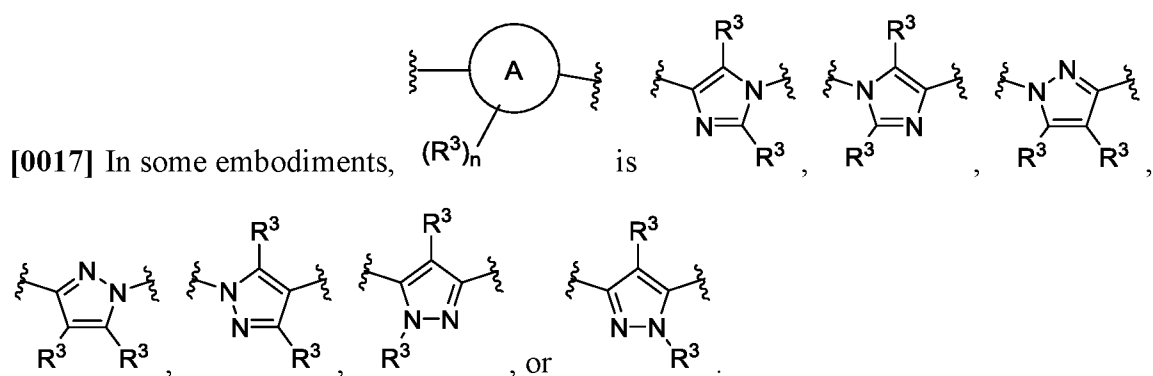
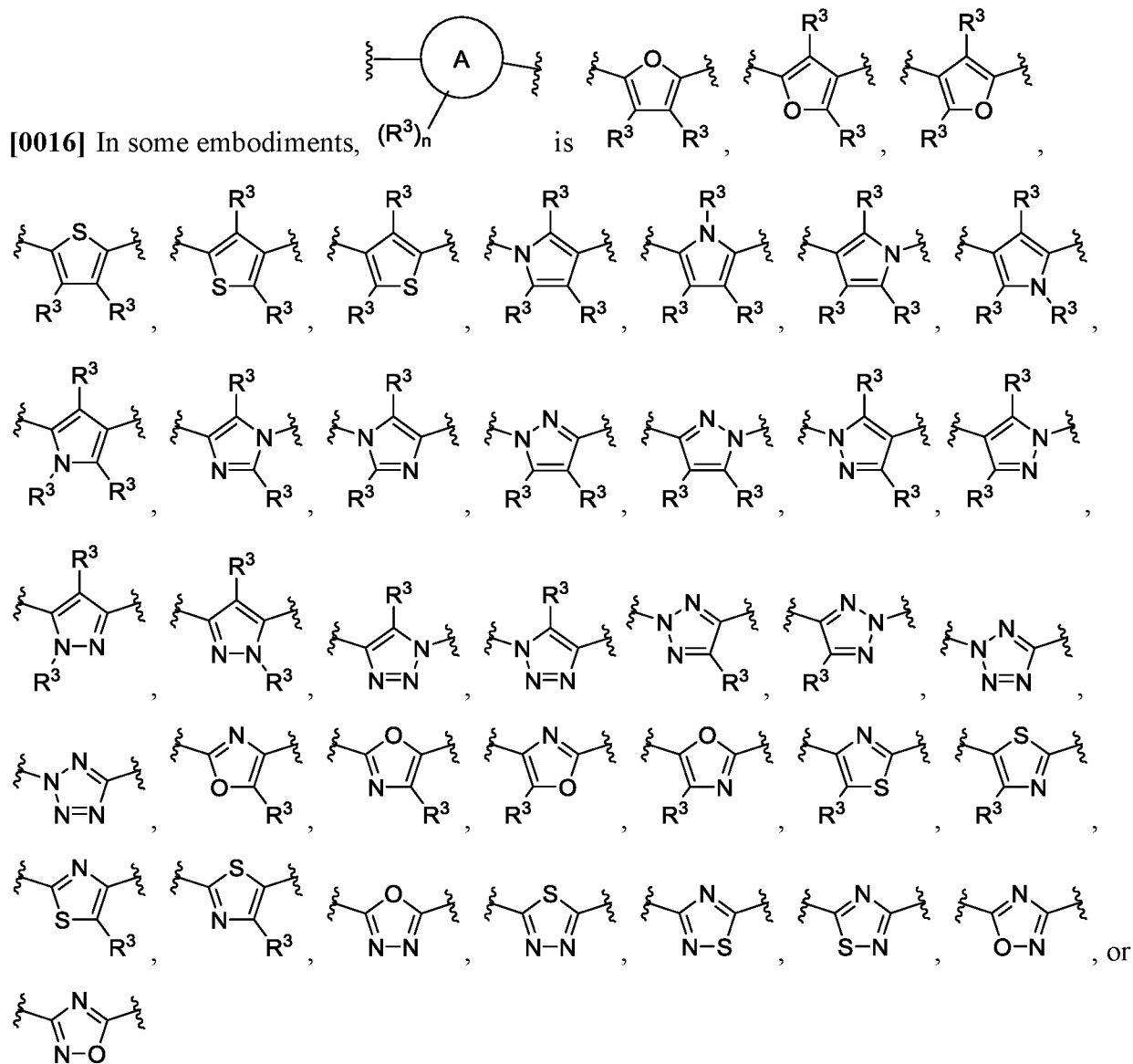
[0013] In some embodiments,



[0014] In some embodiments,



[0015] In some embodiments, ring A is a monocyclic 5-membered heteroarylene selected from furanylene, thienylene, pyrrolylene, oxazolylen, thiazolylen, imidazolylen, pyrazolylen, triazolylen, tetrazolylen, isoxazolylen, isothiazolylen, oxadiazolylen, and thiadiazolylen. In some embodiments, ring A is oxazolylen, thiazolylen, imidazolylen, pyrazolylen, or oxadiazolylen. In some embodiments, ring A is pyrazolylen.

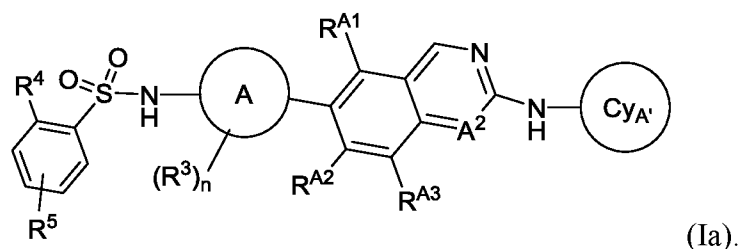


[0019] In some embodiments, ring A is a monocyclic C_2 - C_8 heterocycloalkylene containing at least 1 N atom in the ring that is selected from aziridinylene, azetidinylen,

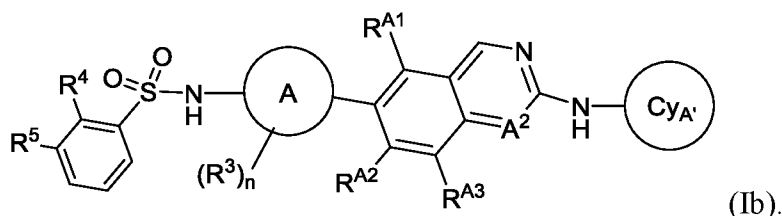
pyrrolidinylene, piperidinylene, piperazinylene, and azepanylene. In some embodiments, each R^3 is independently H, halogen, -CN, -OR¹¹, -SR¹¹, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl; and n is 1, 2, or 3. In some embodiments, R^3 is optionally substituted C₁-C₄alkyl.

[0020] In some embodiments, R^3 is methyl, ethyl, propyl, or butyl. In some embodiments, R^3 is -OR¹¹. In some embodiments, R^{11} is H, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^{11} is methyl, ethyl, propyl, or butyl. In some embodiments, R^{11} is -CF₃ or -CH₂CF₃. In some embodiments, R^4 is H, halogen, -CN, -OR¹², -SR¹², -N(R¹²)₂, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^4 is H. In some embodiments, R^4 is halogen. In some embodiments, R^4 is -Cl, -Br, -F, or -I. In some embodiments, R^4 is -OR¹². In some embodiments, R^{12} is H, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^4 is optionally substituted C₁-C₄alkyl. In some embodiments, R^4 is methyl, ethyl, propyl, or butyl. In some embodiments, R^4 is optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^4 is -CF₃ or -CH₂CF₃. In some embodiments, R^5 is H, halogen, -CN, -OR¹², -SR¹², -N(R¹²)₂, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^5 is H. In some embodiments, R^5 is halogen. In some embodiments, R^5 is -Cl, -Br, -F, or -I. In some embodiments, R^5 is -OR¹². In some embodiments, R^{12} is H, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^5 is optionally substituted C₁-C₄alkyl. In some embodiments, R^5 is methyl, ethyl, propyl, or butyl. In some embodiments, R^5 is optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^5 is -CF₃ or -CH₂CF₃.

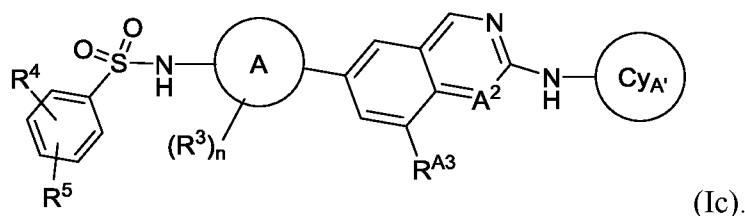
[0021] In some embodiments, the compound has the structure of formula (Ia)



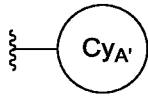
[0022] In some embodiments, the compound has the structure of formula (Ib)

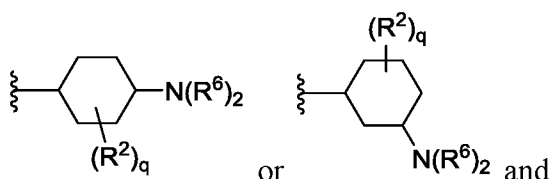


[0023] In some embodiments, the compound has the structure of formula (Ic)



(Ic).

[0024] In some embodiments,  is

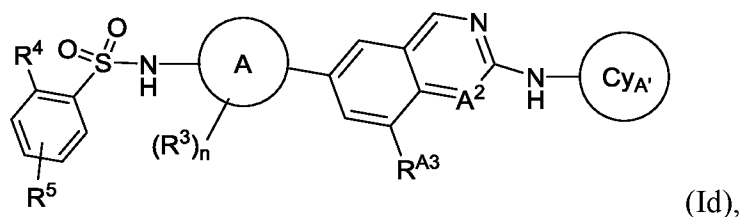


q is 0 or 1.

[0025] In some embodiments, each R⁶ is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₁-C₄fluoroalkyl, -X-optionally substituted C₁-C₄alkyl, -X-optionally substituted C₁-C₄heteroalkyl, or -X-optionally substituted C₁-C₄fluoroalkyl. In some embodiments, each R⁶ is independently H. In some embodiments, each R² is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, A² is N. In some embodiments, A² is CR^A. In some embodiments, R^A is H, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^A is H. In some embodiments, R^{A1} is H, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^{A1} is H. In some embodiments, R^{A2} is H, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^{A2} is H. In some embodiments, R^{A3} is H, halogen, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted aryl, or -OR¹⁰. In some embodiments, R^{A3} is H, halogen, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, or -OR¹⁰. In some embodiments, R^{A3} is optionally substituted C₁-C₄alkyl. In some embodiments, R^{A3} is methyl, ethyl, propyl, or butyl. In some embodiments, R^{A3} is ethyl. In some embodiments, ring A is phenylene. In some embodiments, ring A is a monocyclic 6-membered heteroarylene selected from pyridinylene, pyrimidinylene, pyrazinylene, and pyridazinylene. In some embodiments, ring A is pyridinylene. In some embodiments, ring A is a monocyclic 5-membered heteroarylene selected from furanylene, thienylene, pyrrolylene, oxazolylene, thiazolylene, imidazolylene, pyrazolylene, triazolylene, tetrazolylene, isoxazolylene, isothiazolylene, oxadiazolylene, and thiadiazolylene. In some embodiments, ring A is pyrazolylene. In some embodiments, each R³ is independently H, -OR¹¹, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl; and n is 1, 2, or 3. In some embodiments, R¹¹ is H, optionally substituted C₁-

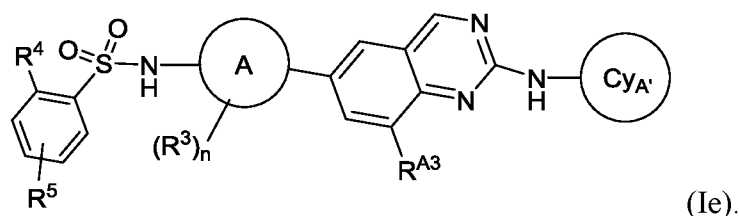
C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R⁴ and R⁵ are each independently H, halogen, -CN, -OR¹², -SR¹², -N(R¹²)₂, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl.

[0026] In some embodiments, the compound has the structure of formula (Id)

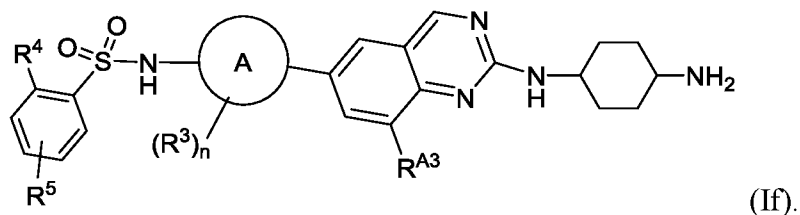


and R^{A3} is optionally substituted C₁-C₄ alkyl.

[0027] In some embodiments, the compound has the structure of formula (Ie)



[0028] In some embodiments, the compound has the structure of formula (If)



[0029] In some embodiments, ring A is phenylene, pyridinylene, pyrazolylene, thiazolylene, imidazolylene, oxazolylene, or oxadiazolylene. In some embodiments, R⁴ and R⁵ are each independently H, halogen, -CN, -OR¹², -SR¹², -N(R¹²)₂, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl.

[0030] In another aspect, provided herein is a compound, or a pharmaceutically acceptable salt, or solvate thereof, selected from:

N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-ethylpyridazin-3-yl)-2-chlorobenzenesulfonamide;

2-chloro-N-(5-(8-ethyl-2-(((1r,4r)-4-hydroxycyclohexyl)amino)quinazolin-6-yl)-6-methoxypyridin-2-yl)benzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-cyanobenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-methylbenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-methylquinazolin-6-yl)-6-ethylpyridin-2-yl)-2-chlorobenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-methylquinazolin-6-yl)-6-methylpyridin-2-yl)-2-chlorobenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-(trifluoromethoxy)pyridin-2-yl)-2-chlorobenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-methoxybenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methylpyridin-2-yl)benzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methylpyridin-2-yl)-2-methylbenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methylpyridin-2-yl)-3-methylbenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-5-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide;

2-chloro-N-(4-(2-(((1r,4r)-4-(dimethylamino)cyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluoro-5-methoxyphenyl)benzenesulfonamide;

2-chloro-N-(4-(8-ethyl-2-(((1r,4r)-4-(methylamino)cyclohexyl)amino)quinazolin-6-yl)-2-fluoro-5-methoxyphenyl)benzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-(1,1-difluoroethyl)quinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-(methoxymethyl)quinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-(trifluoromethyl)quinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide;

2-chloro-N-(5-(2-((4-(dimethylamino)bicyclo[2.2.2]octan-1-yl)amino)-8-ethylquinazolin-6-yl)-6-ethylpyridin-2-yl)benzenesulfonamide;

N-(5-(2-(((1s,4s)-4-aminocyclohexyl)amino)-8-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide;

N-(5-(2-(((1s,4s)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide; and

N-(5-(2-(((1s,4s)-4-aminocyclohexyl)amino)-8-methylquinazolin-6-yl)-3-fluoro-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide.

[0031] In some embodiments, the compound or pharmaceutically acceptable salt, or solvate thereof, selectively binds to IRE1a at one or more binding sites. In some embodiments, the IRE1a comprises an RNase domain, a kinase domain, or any combination thereof. In some embodiments, the kinase domain is an auto-transphosphorylation kinase domain. In some embodiments, the kinase domain comprises an ATP-binding pocket. In some embodiments, the kinase domain comprises an activation loop. In some embodiments, at least one binding site is within the RNase domain. In some embodiments, at least one binding site is within the kinase domain. In some embodiments, the at least one binding site is within the ATP-binding pocket of the kinase domain. In some embodiments, In some embodiments, the at least one binding site is within the activation loop of the kinase domain. In some embodiments, binding occurs at a first binding site. In some embodiments, the first binding site is located within the RNase domain, kinase domain, ATP-binding pocket, or activation loop. In some embodiments, the first binding site comprises at least one amino acid residue of within amino acid residues 465-977 of SEQ ID NO: 1. In some embodiments, the first binding site comprises at least one amino acid residue within amino acid residues 568-833 of SEQ ID NO: 1. In some embodiments, the first binding site comprises at least one amino acid residue within amino acid residues 577-586, 597, 599, 626, 642-643, 645, 648, 688, 692-693, 695, or 711 of SEQ ID NO: 1. In some embodiments, the first binding site comprises at least one amino acid residue within amino acid residues 710-725 or 729-736 of SEQ ID NO: 1. In some embodiments, the first binding site comprises at least one amino acid residue within amino acid residues 835-963 of SEQ ID NO: 1. In some embodiments, binding further occurs at a second binding site. In some embodiments, the second binding site is located within the RNase domain, the kinase domain, the ATP-binding pocket, or the activation loop. In some embodiments, the second binding site comprises at least one amino acid residue of within amino acid residues 465-977 of SEQ ID NO: 1. In some embodiments, the second binding site comprises at least one amino acid residue within amino acid residues 568-833 of SEQ ID NO: 1. In some embodiments, the second binding site comprises at least one amino acid residue within amino acid residues 577-586, 597, 599, 626, 642-643, 645, 648, 688, 692-693, 695, or 711 of SEQ ID NO: 1. In some embodiments, the second binding site comprises at least one amino acid residue within amino acid residues 710-725 or 729-736 of SEQ

ID NO: 1. In some embodiments, the second binding site comprises at least one amino acid residue within amino acid residues 835-963 of SEQ ID NO: 1. In some embodiments, binding occurs when the IRE1a is in a homo-dimerized conformation. In some embodiments, binding occurs when the IRE1a is in an oligomerized conformation. In some embodiments, binding occurs when the IRE1a is in a non-oligomerized or non-dimerized conformation. In some embodiments, binding occurs when the IRE1a is in an ATP-bound state. In some embodiments, binding occurs when the IRE1a is in a non-ATP-bound state. In some embodiments, the compound selectively binds to a first IRE1a. In some embodiments, selectively binding to the first IRE1a blocks dimerization of the first IRE1a to a second IRE1a. In some embodiments, selectively binding to the first IRE1a blocks auto-transphosphorylation of the first IRE1a. In some embodiments, selectively binding to the first IRE1a blocks auto-transphosphorylation of a second IRE1a to which the first IRE1a is dimerized. In some embodiments, selectively binding to the first IRE1a blocks activation of the first IRE1a. In some embodiments, selectively binding to the first IRE1a blocks activation a second IRE1a to which the first IRE1a is dimerized. In some embodiments, selectively binding to the first IRE1a blocks kinase activity of the first IRE1a. In some embodiments, selectively binding to the first IRE1a blocks kinase activity of a second IRE1a to which the first IRE1a is dimerized. In some embodiments, selectively binding to the first IRE1a blocks RNase activity of the first IRE1a. In some embodiments, selectively binding to the first IRE1a blocks RNase activity of a second IRE1a to which the first IRE1a is dimerized.

[0032] In another aspect, provided herein is a compound that selectively binds a first IRE1a at two or more sites, wherein when the compound is bound to the first IRE1a protein, the compound binds to an ATP-binding pocket of the first IRE1a and blocks the binding of ATP to the first IRE1a. In some embodiments, the ATP binding pocket is comprised within a kinase domain. In some embodiments, the ATP binding pocket is comprised within amino acid residues 465-977 of SEQ ID NO: 1. In some embodiments, the ATP binding pocket is comprised within amino acid residues 568-833 of SEQ ID NO: 1. In some embodiments, the ATP binding pocket comprises one or more of amino acid residues 577-586, 597, 599, 626, 642-643, 645, 648, 688, 692-693, 695, or 711 of SEQ ID NO: 1.

[0033] In another aspect, provided herein is a pharmaceutical composition comprising any one of the compounds described herein, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

[0034] In another aspect, provided herein is a method for treating or ameliorating the effects of a disease associated with altered IRE1 signaling, the method comprising administering to a subject

in need thereof a pharmaceutical composition, wherein the pharmaceutical composition comprises the compound of any one of the compounds described herein. In some embodiments, the disease is cancer. In some embodiments, the cancer is a solid cancer or a hematologic cancer. In some embodiments, the cancer is ovarian cancer, breast cancer, or triple negative breast cancer (TNBC).

[0035] In another aspect, provided herein is a method for treating or ameliorating a cell proliferative disorder, the method comprising administering a pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt, or solvate thereof, that selectively binds to at least one amino acid residue of a IRE1 family protein comprising an RNase domain and kinase domain. In some embodiments, the IRE1 family protein is IRE1a. In some embodiments, the compound binds to an ATP-binding site of IRE1a. In some embodiments, the cell proliferative disorder is cancer. In some embodiments, the cancer is a solid cancer or a hematologic cancer, lung cancer, or bladder cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0036] The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

[0037] **Figure 1** shows an example diagram of the domain structure of IRE1a. A signal peptide (P) and transmembrane (TM) region are indicated.

[0038] **Figure 2** shows an example alignment of the C-terminal half IRE1 orthologues from yeast (ScIre1) (SEQ ID NO: 4), human (HsIre1) (SEQ ID NO: 5), mouse (MmIre1) (SEQ ID NO: 6), and rat (RnIRE1) (SEQ ID NO: 7). Stars indicate kinase domain dimer interface residues. Circles indicate Kinase extension nuclease (KEN) domain dimer interface residues. Triangles indicate putative nuclease active site residues. Yellow highlighted residues are highly conserved in Ire1 orthologues. Green highlighted residues are invariant in all analyzed Ire1 orthologues. Blue highlighted residues are invariant in analyzed RNaseL and Ire1 orthologues.

[0039] **Figure 3** depicts the bioavailability of Compound 3 and Compound 37 *in vivo*. Mice were dosed with Compound 3 or Compound 37 intravenously, orally, and intraperitoneally.

[0040] **Figure 4** shows suppression of IRE1a-dependent splicing of X-box binding protein 1 (XBP1). The bottom left panel shows the unspliced (XBP1u) and spliced XBP1(s) protein with varying combinations of Compound 3 and TM, where mpk is mg/kg.

[0041] **Figure 5** shows that Compound 3 can inhibit IRE1a-dependent signaling in various cell types in the tumor microenvironment.

DETAILED DESCRIPTION

Certain Terminology

[0042] Unless otherwise stated, the following terms used in this application have the definitions given below. The use of the term “including” as well as other forms, such as “include”, “includes,” and “included,” is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0043] As used herein and in the appended claims, the singular forms “a,” “and,” and “the” include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to “an agent” includes a plurality of such agents, and reference to “the cell” includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range may vary between 1% and 15% of the stated number or numerical range. The term “comprising” (and related terms such as “comprise” or “comprises” or “having” or “including”) is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, may “consist of” or “consist essentially of” the described features.

Definitions

[0044] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0045] “Amino” refers to the -NH_2 radical.

[0046] “Cyano” refers to the -CN radical.

[0047] “Nitro” refers to the -NO_2 radical.

[0048] “Oxa” refers to the -O- radical.

[0049] “Oxo” refers to the =O radical.

[0050] “Thioxo” refers to the =S radical.

[0051] “Imino” refers to the =N-H radical.

[0052] “Oximo” refers to the =N-OH radical.

[0053] As used herein, $\text{C}_1\text{-C}_x$ includes $\text{C}_1\text{-C}_2$, $\text{C}_1\text{-C}_3$. . . $\text{C}_1\text{-C}_x$. By way of example only, a group designated as “ $\text{C}_1\text{-C}_4$ ” indicates that there are one to four carbon atoms in the moiety, i.e. groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms. Thus, by way of

example only, “C₁-C₄ alkyl” indicates that there are one to four carbon atoms in the alkyl group, *i.e.*, the alkyl group is selected from among methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl.

[0054] An “alkyl” group refers to an aliphatic hydrocarbon group. The alkyl group is branched or straight chain. In some embodiments, the “alkyl” group has 1 to 10 carbon atoms, *i.e.* a C₁-C₁₀alkyl. Whenever it appears herein, a numerical range such as “1 to 10” refers to each integer in the given range; *e.g.*, “1 to 10 carbon atoms” means that the alkyl group consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, 6 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, an alkyl is a C₁-C₆alkyl. In one aspect the alkyl is methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, or *t*-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, tertiary butyl, pentyl, neopentyl, or hexyl.

[0055] An “alkylene” group refers refers to a divalent alkyl radical. Any of the above mentioned monovalent alkyl groups may be an alkylene by abstraction of a second hydrogen atom from the alkyl. In some embodiments, an alkylene is a C₁-C₆alkylene. In other embodiments, an alkylene is a C₁-C₄alkylene. In certain embodiments, an alkylene comprises one to four carbon atoms (*e.g.*, C₁-C₄ alkylene). In other embodiments, an alkylene comprises one to three carbon atoms (*e.g.*, C₁-C₃ alkylene). In other embodiments, an alkylene comprises one to two carbon atoms (*e.g.*, C₁-C₂ alkylene). In other embodiments, an alkylene comprises one carbon atom (*e.g.*, C₁ alkylene). In other embodiments, an alkylene comprises two carbon atoms (*e.g.*, C₂ alkylene). In other embodiments, an alkylene comprises two to four carbon atoms (*e.g.*, C₂-C₄ alkylene). Typical alkylene groups include, but are not limited to, -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -CH₂CH₂-, -CH₂CH(CH₃)-, -CH₂C(CH₃)₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, and the like.

[0056] The term “alkenyl” refers to a type of alkyl group in which at least one carbon-carbon double bond is present. In one embodiment, an alkenyl group has the formula -C(R)=CR₂, wherein R refers to the remaining portions of the alkenyl group, which may be the same or different. In some embodiments, R is H or an alkyl. In some embodiments, an alkenyl is selected from ethenyl (*i.e.*, vinyl), propenyl (*i.e.*, allyl), butenyl, pentenyl, pentadienyl, and the like. Non-limiting examples of an alkenyl group include -CH=CH₂, -C(CH₃)=CH₂, -CH=CHCH₃, -C(CH₃)=CHCH₃, and -CH₂CH=CH₂.

[0057] The term “alkynyl” refers to a type of alkyl group in which at least one carbon-carbon triple bond is present. In one embodiment, an alkenyl group has the formula -C≡C-R, wherein R refers to the remaining portions of the alkynyl group. In some embodiments, R is H or an alkyl. In some embodiments, an alkynyl is selected from ethynyl, propynyl, butynyl, pentynyl, hexynyl,

and the like. Non-limiting examples of an alkynyl group include $\text{-C}\equiv\text{CH}$, $\text{-C}\equiv\text{CCH}_3$, $\text{C}\equiv\text{CCH}_2\text{CH}_3$, $\text{-CH}_2\text{C}\equiv\text{CH}$.

[0058] An “alkoxy” group refers to a (alkyl)O- group, where alkyl is as defined herein.

[0059] The term “alkylamine” refers to the $\text{-N(alkyl)}_x\text{H}_y$ group, where x is 0 and y is 2, or where x is 1 and y is 1, or where x is 2 and y is 0.

[0060] The term “aromatic” refers to a planar ring having a delocalized π -electron system containing $4n+2$ π electrons, where n is an integer. The term “aromatic” includes both carbocyclic aryl (“aryl”, *e.g.*, phenyl) and heterocyclic aryl (or “heteroaryl” or “heteroaromatic”) groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon atoms) groups.

[0061] The term “carbocyclic” or “carbocycle” refers to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from “heterocyclic” rings or “heterocycles” in which the ring backbone contains at least one atom which is different from carbon. In some embodiments, at least one of the two rings of a bicyclic carbocycle is aromatic. In some embodiments, both rings of a bicyclic carbocycle are aromatic. Carbocycle includes cycloalkyl and aryl.

[0062] As used herein, the term “aryl” refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. In one aspect, aryl is phenyl or a naphthyl. In some embodiments, an aryl is a phenyl. In some embodiments, an aryl is a $\text{C}_6\text{-C}_{10}$ aryl. Depending on the structure, an aryl group is a monoradical or a diradical (*i.e.*, an arylene group).

[0063] The term “cycloalkyl” refers to a monocyclic or polycyclic aliphatic, non-aromatic radical, wherein each of the atoms forming the ring (*i.e.* skeletal atoms) is a carbon atom. In some embodiments, cycloalkyls are spirocyclic or bridged compounds. In some embodiments, cycloalkyls are optionally fused with an aromatic ring, and the point of attachment is at a carbon that is not an aromatic ring carbon atom. In some embodiments, cycloalkyl groups include groups having from 3 to 10 ring atoms. In some embodiments, cycloalkyl groups include groups having from 3 to 6 ring atoms. In some embodiments, cycloalkyl groups are selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, spiro[2.2]pentyl, norbornyl and bicycle[1.1.1]pentyl. In some embodiments, a cycloalkyl is a $\text{C}_3\text{-C}_6$ cycloalkyl. In some embodiments, a cycloalkyl is a monocyclic cycloalkyl. Monocyclic cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like.

[0064] The term “cycloalkylene” refers to a monocyclic or polycyclic aliphatic, non-aromatic divalent radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. In some embodiments, cycloalkylene are spirocyclic or bridged compounds. In some embodiments, cycloalkylenes are optionally fused with an aromatic ring, and the point of attachment is at a carbon that is not an aromatic ring carbon atom. In some embodiments, cycloalkylene groups include groups having from 3 to 10 ring atoms. In some embodiments, cycloalkylene groups include groups having from 3 to 6 ring atoms.

[0065] The term “halo” or, alternatively, “halogen” or “halide” means fluoro, chloro, bromo or iodo. In some embodiments, halo is fluoro, chloro, or bromo.

[0066] The term “haloalkyl” refers to an alkyl in which one or more hydrogen atoms are replaced by a halogen atom. In one aspect, a fluoroalkyl is a C₁-C₆fluoroalkyl.

[0067] The term “fluoroalkyl” refers to an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoroalkyl is a C₁-C₆fluoroalkyl. In some embodiments, a fluoroalkyl is selected from trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like.

[0068] The term “heteroalkyl” refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (*e.g.* -NH-, -N(alkyl)-, sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C₁-C₆heteroalkyl.

[0069] The term “heteroalkylene” refers to an alkylene group in which one or more skeletal atoms of the alkylene are selected from an atom other than carbon, *e.g.*, oxygen, nitrogen (*e.g.* -NH-, -N(alkyl)-, sulfur, or combinations thereof. In some embodiments, a heteroalkylene is attached to the rest of the molecule at a carbon atom of the heteroalkylene. In one aspect, a heteroalkylene is a C₁-C₆heteroalkylene.

[0070] As used herein, the term “heteroatom” refers to an atom of any element other than carbon or hydrogen. In some embodiments, the heteroatom is nitrogen, oxygen, or sulfur. In some embodiments, the heteroatom is nitrogen or oxygen. In some embodiments, the heteroatom is nitrogen.

[0071] The term “heterocycle” or “heterocyclic” refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings (also known as heteroalicyclic groups) containing one to four heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S and N, wherein each heterocyclic group has from 3 to 10 atoms in its ring system, and with the proviso that any ring does not contain two adjacent O or S atoms. In some embodiments, heterocycles are monocyclic, bicyclic, polycyclic, spirocyclic or bridged compounds. Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include rings having 3 to 10 atoms in its

ring system and aromatic heterocyclic groups include rings having 5 to 10 atoms in its ring system. The heterocyclic groups include benzo-fused ring systems. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinoliziny. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, and furopyridinyl. The foregoing groups are either C-attached (or C-linked) or *N*-attached where such is possible. For instance, a group derived from pyrrole includes both pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole includes imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems. Non-aromatic heterocycles are optionally substituted with one or two oxo (=O) moieties, such as pyrrolidin-2-one. In some embodiments, at least one of the two rings of a bicyclic heterocycle is aromatic. In some embodiments, both rings of a bicyclic heterocycle are aromatic.

[0072] The terms “heteroaryl” or, alternatively, “heteroaromatic” refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. Illustrative examples of heteroaryl groups include monocyclic heteroaryls and bicyclic heteroaryls. Monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Bicyclic heteroaryls include indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. In some embodiments, a heteroaryl contains 0-4 N atoms in the ring. In some

embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 0-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, heteroaryl is a C₁-C₉heteroaryl. In some embodiments, monocyclic heteroaryl is a C₁-C₅heteroaryl. In some embodiments, monocyclic heteroaryl is a 5-membered or 6-membered heteroaryl. In some embodiments, bicyclic heteroaryl is a C₆-C₉heteroaryl.

[0073] A “heterocycloalkyl” or “heteroalicyclic” group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. In some embodiments, a heterocycloalkyl is a spirocyclic or bridged compound. In some embodiments, a heterocycloalkyl is fused with an aryl or heteroaryl. In some embodiments, the heterocycloalkyl is oxazolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidin-2-onyl, pyrrolidine-2,5-dithionyl, pyrrolidine-2,5-dionyl, pyrrolidinonyl, imidazolidinyl, imidazolidin-2-onyl, or thiazolidin-2-onyl. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In one aspect, a heterocycloalkyl is a C₂-C₁₀heterocycloalkyl. In another aspect, a heterocycloalkyl is a C₄-C₁₀heterocycloalkyl. In some embodiments, a heterocycloalkyl contains 0-2 N atoms in the ring. In some embodiments, a heterocycloalkyl contains 0-2 N atoms, 0-2 O atoms and 0-1 S atoms in the ring.

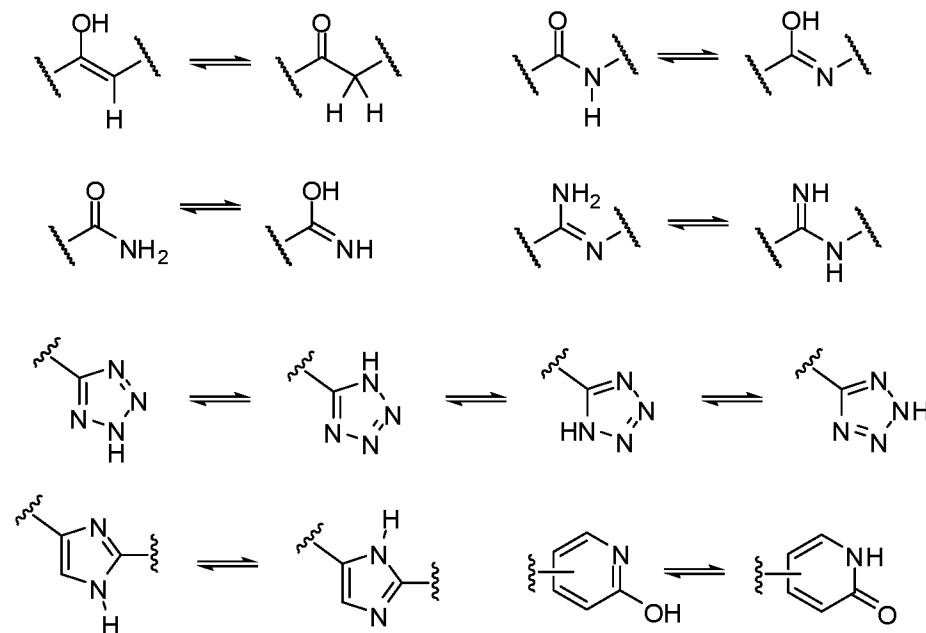
[0074] The term “bond” or “single bond” refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. In one aspect, when a group described herein is a bond, the referenced group is absent thereby allowing a bond to be formed between the remaining identified groups.

[0075] The term “moiety” refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[0076] The term “optionally substituted” or “substituted” means that the referenced group is optionally substituted with one or more additional group(s) individually and independently selected from D, halogen, -CN, -NH₂, -NH(alkyl), -CH₂N(alkyl)₂, -N(alkyl)₂, -OH, -CO₂H, -CO₂alkyl, -CH₂NH₂, -C(=O)NH₂, -C(=O)NH(alkyl), -C(=O)N(alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(alkyl), -S(=O)₂N(alkyl)₂, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from D, halogen, -CN, -NH₂, -NH(CH₃), -N(CH₃)₂, -OH, -CO₂H, -CO₂(C₁-C₄alkyl), -CH₂NH₂, -C(=O)NH₂, -C(=O)NH(C₁-C₄alkyl), -C(=O)N(C₁-C₄alkyl)₂, -

$\text{S(=O)}_2\text{NH}_2$, $-\text{S(=O)}_2\text{NH}(\text{C}_1\text{-C}_4\text{alkyl})$, $-\text{S(=O)}_2\text{N}(\text{C}_1\text{-C}_4\text{alkyl})_2$, $\text{C}_1\text{-C}_4\text{alkyl}$, $\text{C}_3\text{-C}_6\text{cycloalkyl}$, $\text{C}_1\text{-C}_4\text{fluoroalkyl}$, $\text{C}_1\text{-C}_4\text{heteroalkyl}$, $\text{C}_1\text{-C}_4\text{alkoxy}$, $\text{C}_1\text{-C}_4\text{fluoroalkoxy}$, $-\text{SC}_1\text{-C}_4\text{alkyl}$, $-\text{S(=O)}\text{C}_1\text{-C}_4\text{alkyl}$, and $-\text{S(=O)}_2\text{C}_1\text{-C}_4\text{alkyl}$. In some embodiments, optional substituents are independently selected from D, halogen, $-\text{CN}$, $-\text{NH}_2$, $-\text{OH}$, $-\text{NH}(\text{CH}_3)$, $-\text{N}(\text{CH}_3)_2$, $-\text{CH}_3$, $-\text{CH}_2\text{CH}_3$, $-\text{CH}_2\text{NH}_2$, $-\text{CF}_3$, $-\text{OCH}_3$, and $-\text{OCF}_3$. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic) includes oxo ($=\text{O}$).

[0077] A “tautomer” refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. The compounds presented herein may, in certain embodiments, exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. Some examples of tautomeric equilibrium include:



[0078] “Optional” or “optionally” means that a subsequently described event or circumstance may or may not occur and that the description includes instances when the event or circumstance occurs and instances in which it does not. For example, “optionally substituted aryl” means that the aryl radical may or may not be substituted and that the description includes both substituted aryl radicals and aryl radicals having no substitution.

[0079] “Pharmaceutically acceptable salt” includes both acid and base addition salts. A pharmaceutically acceptable salt of any one of the pyrazole compounds described herein is intended to encompass any and all pharmaceutically suitable salt forms. Preferred pharmaceutically acceptable salts of the compounds described herein are pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

[0080] “Pharmaceutically acceptable acid addition salt” refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrate, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., “Pharmaceutical Salts,” *Journal of Pharmaceutical Science*, 66:1-19 (1997)). Acid addition salts of basic compounds may be prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

[0081] “Pharmaceutically acceptable base addition salt” refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Pharmaceutically acceptable base addition salts may be formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chlorprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-

methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, *N*-ethylpiperidine, polyamine resins and the like. See Berge et al., *supra*.

[0082] “Prodrug” is meant to indicate a compound that may be converted under physiological conditions or by solvolysis to a biologically active compound described herein. Thus, the term “prodrug” refers to a precursor of a biologically active compound that is pharmaceutically acceptable. A prodrug may be inactive when administered to a subject, but is converted *in vivo* to an active compound, for example, by hydrolysis. The prodrug compound often offers advantages of solubility, tissue compatibility or delayed release in a mammalian organism (*see, e.g.,* Bundgard, H., Design of Prodrugs (1985), pp. 7-9, 21-24 (Elsevier, Amsterdam).

[0083] A discussion of prodrugs is provided in Higuchi, T., et al., “Pro-drugs as Novel Delivery Systems,” A.C.S. Symposium Series, Vol. 14, and in Bioreversible Carriers in Drug Design, ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

[0084] The term “prodrug” is also meant to include any covalently bonded carriers, which release the active compound *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of an active compound, as described herein, may be prepared by modifying functional groups present in the active compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent active compound. Prodrugs include compounds wherein a hydroxy, amino or mercapto group is bonded to any group that, when the prodrug of the active compound is administered to a mammalian subject, cleaves to form a free hydroxy, free amino or free mercapto group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol or amine functional groups in the active compounds and the like.

[0085] The term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[0086] The term “modulate” as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[0087] The term “modulator” as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of an agonist, partial agonist, an inverse agonist, antagonist, degrader, or combinations thereof. In some embodiments, a modulator is an agonist.

[0088] The terms “administer,” “administering,” “administration,” and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the

desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical and rectal administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein. In some embodiments, the compounds and compositions described herein are administered orally.

[0089] The terms “co-administration” or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient, and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[0090] The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of an agent or a compound being administered, which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate “effective” amount in any individual case is optionally determined using techniques, such as a dose escalation study.

[0091] The terms “enhance” or “enhancing,” as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term “enhancing” refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An “enhancing-effective amount,” as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[0092] The term “pharmaceutical combination” as used herein, means a product that results from the mixing or combining of more than one active ingredient and includes both fixed and non-fixed combinations of the active ingredients. The term “fixed combination” means that the active ingredients, e.g. a compound described herein, or a pharmaceutically acceptable salt thereof, and a co-agent, are both administered to a patient simultaneously in the form of a single entity or dosage. The term “non-fixed combination” means that the active ingredients, e.g. a compound described herein, or a pharmaceutically acceptable salt thereof, and a co-agent, are administered to a patient as separate entities either simultaneously, concurrently or sequentially with no specific intervening time limits, wherein such administration provides effective levels of the two compounds in the body of the patient. The latter also applies to cocktail therapy, e.g. the administration of three or more active ingredients.

[0093] The terms “kit” and “article of manufacture” are used as synonyms.

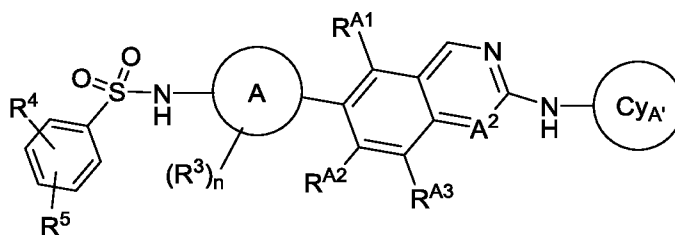
[0094] The term “subject” or “patient” encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[0095] As used herein, “treatment” or “treating” or “palliating” or “ameliorating” are used interchangeably herein. These terms refers to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By “therapeutic benefit” is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient may still be afflicted with the underlying disorder. For prophylactic benefit, the compositions may be administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease may not have been made.

Compounds

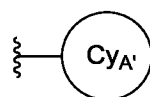
[0096] Compounds described herein, including pharmaceutically acceptable salts, and pharmaceutically acceptable solvates thereof, that modulate IRE1 mediated signaling, directly or indirectly.

[0097] Provided in one aspect is a compound of Formula (I), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (I)

wherein,



is a substituted C₃-C₁₀ cycloalkyl that is substituted with 1-3R¹ and 0-3R²; each R¹ is independently -OR⁶, -SR⁶, -S(=O)R⁷, -S(=O)₂R⁷, or -N(R⁶)₂;

each R^2 is independently H, halogen, -CN, -OR⁸, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -NR⁸S(=O)₂R⁹, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -OCO₂R⁹, -N(R⁸)₂, -OC(=O)N(R⁸)₂, -NR⁸C(=O)R⁹, -NR⁸C(=O)OR⁹, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R⁶ is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₁-C₄fluoroalkyl, -X-optionally substituted C₁-C₄alkyl, -X-optionally substituted C₁-C₄heteroalkyl, -X-optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; or two R⁶ are taken together with the N atom to which they are attached to form an optionally substituted heterocycle;

X is -(C=O)-;

each R⁷ is independently optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R⁸ is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₁-C₄fluoroalkyl, , optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

or two R⁸ are taken together with the N atom to which they are attached to form an optionally substituted heterocycle;

each R⁹ is independently optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, or optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

A² is N or CR^A;

R^A, R^{A1}, R^{A2}, and R^{A3} are each independently H, halogen, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted aryl, or -OR¹⁰;

R¹⁰ is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

ring A is a monocyclic carbocycle or a monocyclic heterocycle;

each R^3 is independently H, halogen, -CN, -OR¹¹, -SR¹¹, -N(R¹¹)₂, optionally substituted

C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₁-

C₄heteroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-

C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R¹¹ is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-

C₄fluoroalkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₃-

C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted

aryl, or optionally substituted heteroaryl;

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

R⁴ and R⁵ are each independently H, halogen, -CN, -OR¹², -SR¹², -N(R¹²)₂, optionally

substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted

C₁-C₄heteroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-

C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

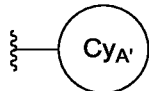
and

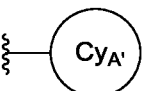
R¹² is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-

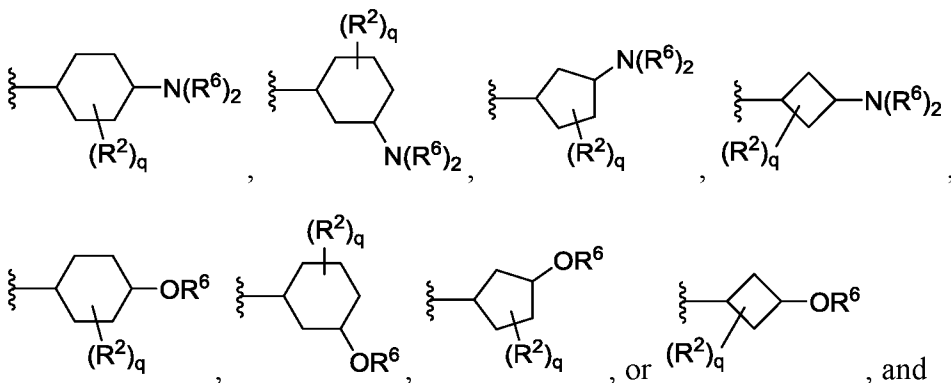
C₄fluoroalkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₃-

C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted

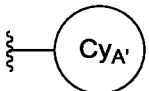
aryl, or optionally substituted heteroaryl.

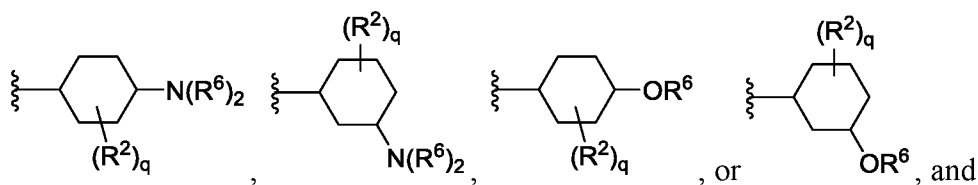
[0098] In some embodiments,  is substituted C₄-C₇ cycloalkyl that is substituted with 1-3R¹ and 0-3R².

[0099] In some embodiments,  is

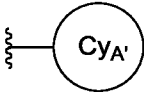


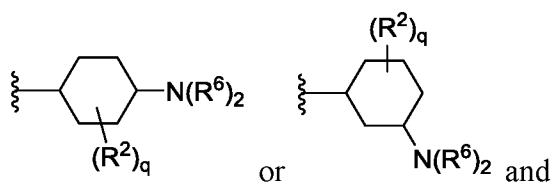
q is 0, 1, 2, or 3.

[00100] In some embodiments,  is



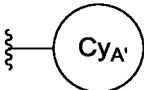
q is 0, 1, 2, or 3.

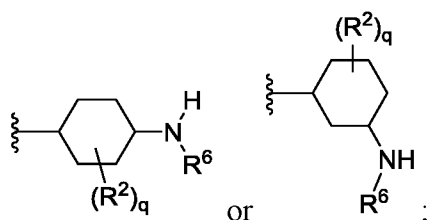
[00101] In some embodiments,  is



q is 0, 1, 2, or 3.

[00102] In some embodiments, q is 0 or 1. In some embodiments, each R^6 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_1 - C_4 fluoroalkyl, -X-optionally substituted C_1 - C_4 alkyl, -X-optionally substituted C_1 - C_4 heteroalkyl, or -X-optionally substituted C_1 - C_4 fluoroalkyl. In some embodiments, each R^6 is independently H. In some embodiments, each R^2 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

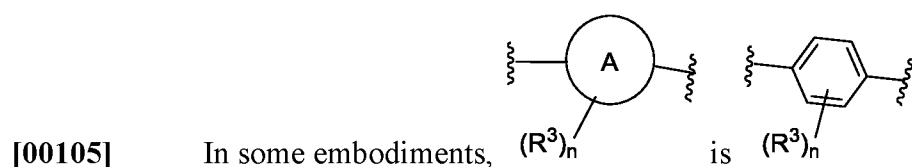
[00103] In some embodiments,  is



R^6 is H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_1 - C_4 fluoroalkyl, -X-optionally substituted C_1 - C_4 alkyl, -X-optionally substituted C_1 - C_4 heteroalkyl, or -X-optionally substituted C_1 - C_4 fluoroalkyl; q is 0 or 1; and R^2 is H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

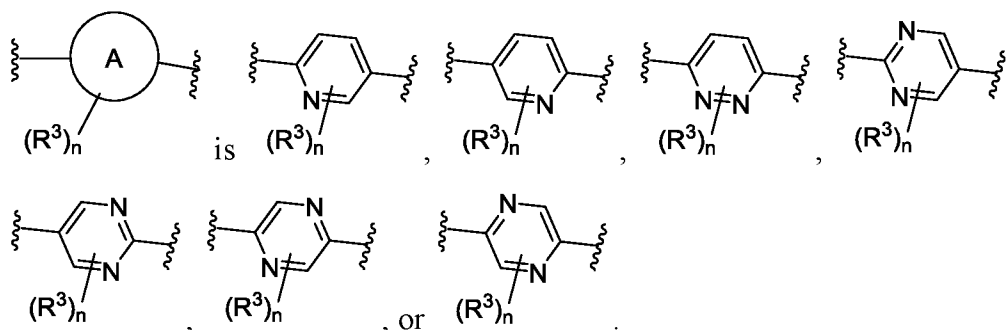
[00104] In some embodiments, R^6 is H. In some embodiments, A^2 is N. In some embodiments, A^2 is CR^A . In some embodiments, R^A is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl. In some embodiments, R^A is H. In some embodiments, R^{A1} is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl. In some

embodiments, R^{A1} is H. In some embodiments, R^{A2} is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl. In some embodiments, R^{A2} is H. In some embodiments, R^{A3} is H, halogen, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, optionally substituted aryl, or $-OR^{10}$. In some embodiments, R^{A3} is H, halogen, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, or $-OR^{10}$. In some embodiments, R^{A3} is optionally substituted C_1 - C_4 alkyl. In some embodiments, R^{A3} is methyl, ethyl, propyl or butyl. In some embodiments, R^{A3} is $-OR^{10}$ and R^{10} is methyl, ethyl, propyl or butyl. In some embodiments, ring A is phenylene or a monocyclic C_3 - C_8 cycloalkylene that is selected from cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene, and cyclooctylene. In some embodiments, ring A is phenylene.

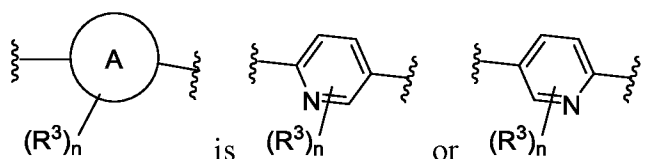


[00106] In some embodiments, ring A is a monocyclic C_1 - C_5 heteroarylene containing 1-4 N atoms, and 0 or 1 O or S atom, or a monocyclic C_1 - C_5 heteroarylene containing 0-4 N atoms, and 1 O or S atom. In some embodiments, ring A is a monocyclic 6-membered heteroarylene selected from pyridinylene, pyrimidinylene, pyrazinylene, and pyridazinylene. In some embodiments, ring A is pyridinylene.

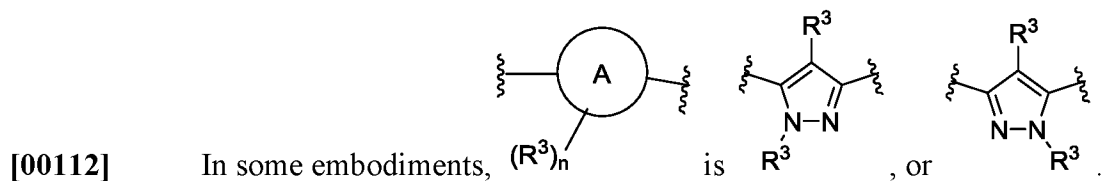
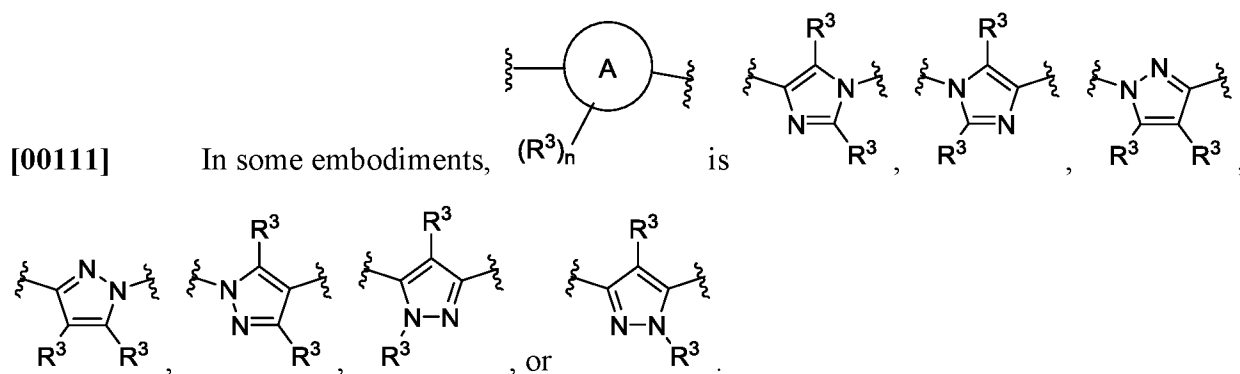
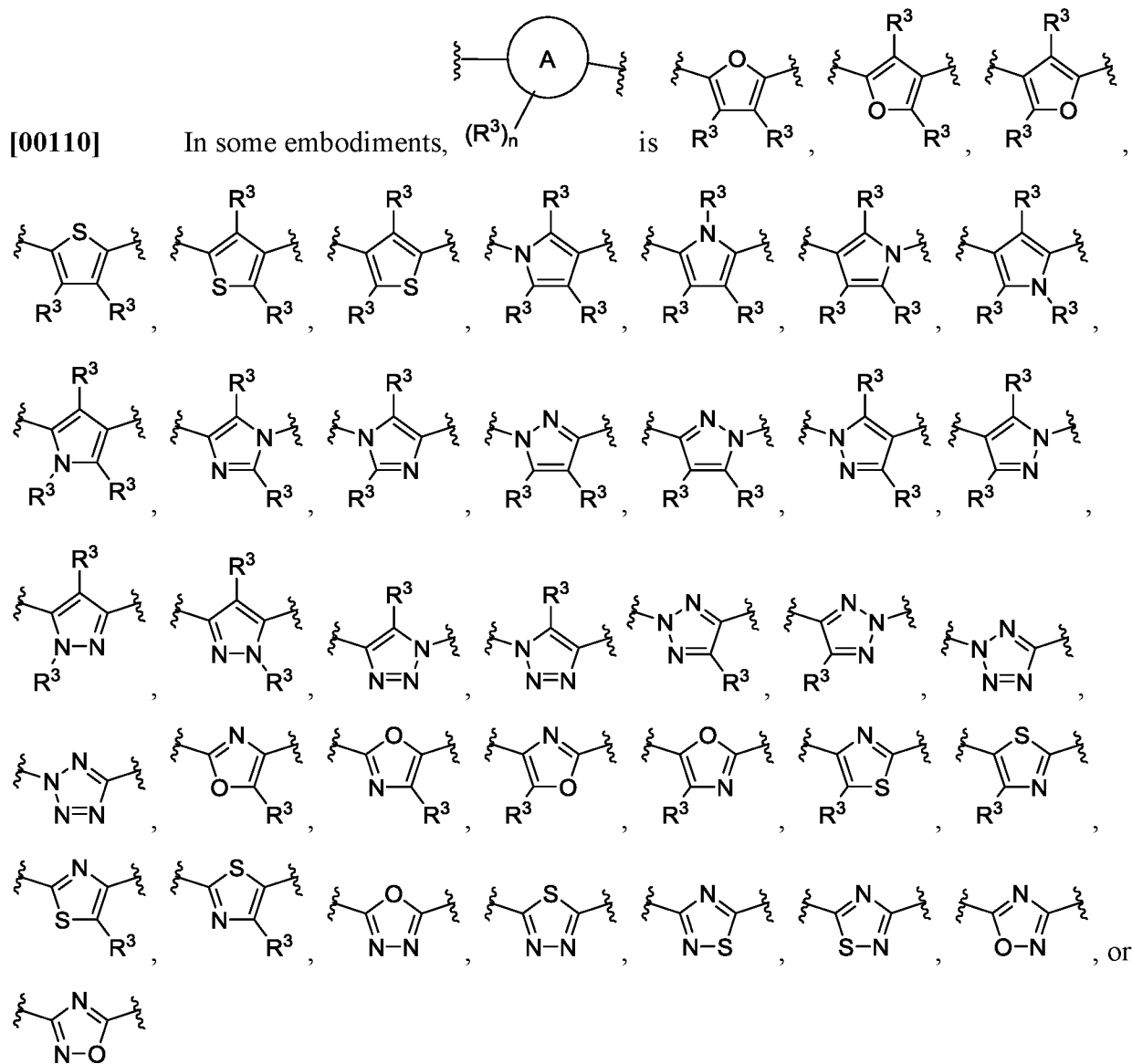
[00107] In some embodiments,



[00108] In some embodiments,



[00109] In some embodiments, ring A is a monocyclic 5-membered heteroarylene selected from furanylene, thienylene, pyrrolylene, oxazolylen, thiazolylen, imidazolylen, pyrazolylen, triazolylen, tetrazolylen, isoxazolylen, isothiazolylen, oxadiazolylen, and thiadiazolylen. In some embodiments, ring A is oxazolylen, thiazolylen, imidazolylen, pyrazolylen, or oxadiazolylen. In some embodiments, ring A is pyrazolylen.

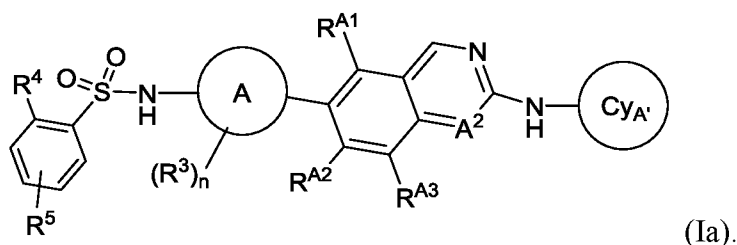


[00113] In some embodiments, ring A is a monocyclic C_2 - C_8 heterocycloalkylene containing at least 1 N atom in the ring that is selected from aziridinylene,

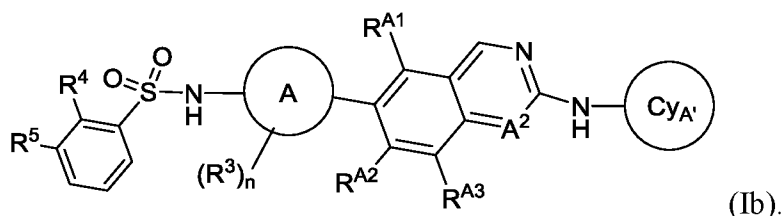
azetidinylene, pyrrolidinylene, piperidinylene, piperazinylene, and azepanylene. In some embodiments, each R^3 is independently H, halogen, -CN, -OR¹¹, -SR¹¹, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl; and n is 1, 2, or 3. In some embodiments, R^3 is optionally substituted C₁-C₄alkyl.

[00114] In some embodiments, R^3 is methyl, ethyl, propyl, or butyl. In some embodiments, R^3 is -OR¹¹. In some embodiments, R^{11} is H, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^{11} is methyl, ethyl, propyl, or butyl. In some embodiments, R^{11} is -CF₃ or -CH₂CF₃. In some embodiments, R^4 is H, halogen, -CN, -OR¹², -SR¹², -N(R¹²)₂, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^4 is H. In some embodiments, R^4 is halogen. In some embodiments, R^4 is -Cl, -Br, -F, or -I. In some embodiments, R^4 is -OR¹². In some embodiments, R^{12} is H, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^4 is optionally substituted C₁-C₄alkyl. In some embodiments, R^4 is methyl, ethyl, propyl, or butyl. In some embodiments, R^4 is optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^4 is -CF₃ or -CH₂CF₃. In some embodiments, R^5 is H, halogen, -CN, -OR¹², -SR¹², -N(R¹²)₂, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^5 is H. In some embodiments, R^5 is halogen. In some embodiments, R^5 is -Cl, -Br, -F, or -I. In some embodiments, R^5 is -OR¹². In some embodiments, R^{12} is H, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^5 is optionally substituted C₁-C₄alkyl. In some embodiments, R^5 is methyl, ethyl, propyl, or butyl. In some embodiments, R^5 is optionally substituted C₁-C₄fluoroalkyl. In some embodiments, R^5 is -CF₃ or -CH₂CF₃.

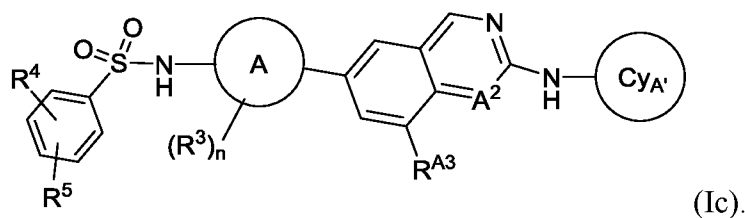
[00115] In some embodiments, the compound has the structure of formula (Ia)

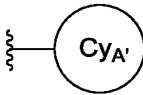


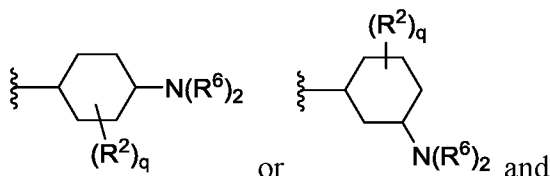
[00116] In some embodiments, the compound has the structure of formula (Ib)



[00117] In some embodiments, the compound has the structure of formula (Ic)



[00118] In some embodiments,  is

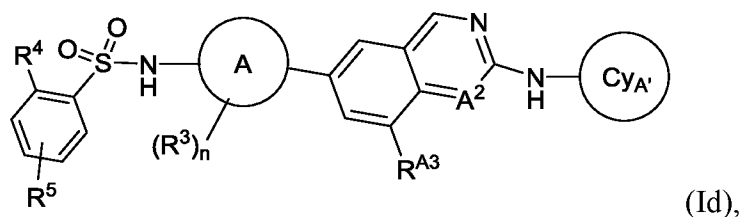


q is 0 or 1.

[00119] In some embodiments, each R^6 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_1 - C_4 fluoroalkyl, -X- optionally substituted C_1 - C_4 alkyl, -X- optionally substituted C_1 - C_4 heteroalkyl, or -X- optionally substituted C_1 - C_4 fluoroalkyl. In some embodiments, each R^6 is independently H. In some embodiments, each R^2 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, or optionally substituted C_1 - C_4 fluoroalkyl. In some embodiments, A^2 is N. In some embodiments, A^2 is CR^A . In some embodiments, R^A is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl. In some embodiments, R^A is H. In some embodiments, R^{A1} is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl. In some embodiments, R^{A1} is H. In some embodiments, R^{A2} is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl. In some embodiments, R^{A2} is H. In some embodiments, R^{A3} is H, halogen, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, optionally substituted aryl, or $-OR^{10}$. In some embodiments, R^{A3} is H, halogen, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, or $-OR^{10}$. In some embodiments, R^{A3} is optionally substituted C_1 - C_4 alkyl. In some embodiments, R^{A3} is methyl, ethyl, propyl, or butyl. In some embodiments, R^{A3} is ethyl. In some embodiments, ring A is phenylene. In some embodiments, ring A is a monocyclic 6-membered heteroarylene selected from pyridinylene, pyrimidinylene, pyrazinylene, and pyridazinylene. In some embodiments, ring A is pyridinylene. In some embodiments, ring A is a monocyclic 5-membered heteroarylene selected from furanylene, thienylene, pyrrolylene, oxazolylen, thiazolylen, imidazolylen, pyrazolylen, triazolylen, tetrazolylen, isoxazolylen, isothiazolylen, oxadiazolylen, and thiadiazolylen. In some embodiments, ring A is pyrazolylen. In some embodiments, each R^3 is independently H, $-OR^{11}$, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl; and n is 1, 2, or 3. In some embodiments,

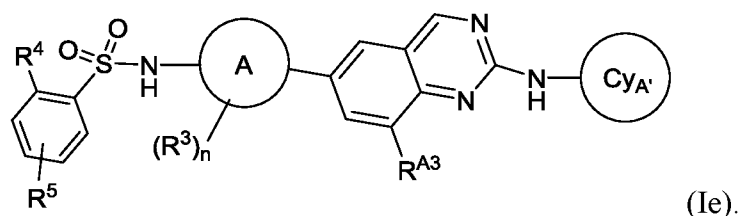
R^{11} is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl. In some embodiments, R^4 and R^5 are each independently H, halogen, -CN, -OR¹², -SR¹², -N(R¹²)₂, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

[00120] In some embodiments, the compound has the structure of formula (Id)

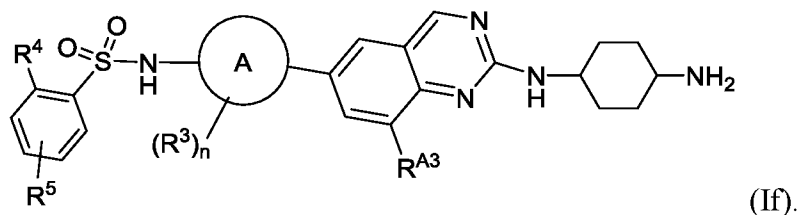


and R^{A3} is optionally substituted C_1 - C_4 alkyl.

[00121] In some embodiments, the compound has the structure of formula (Ie)

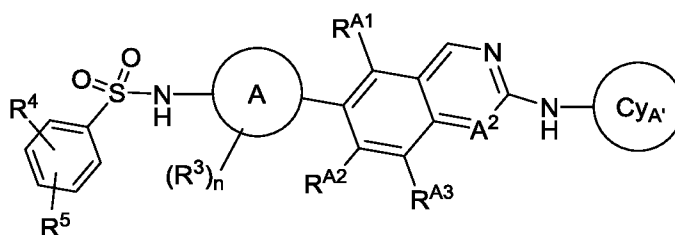


[00122] In some embodiments, the compound has the structure of formula (If)



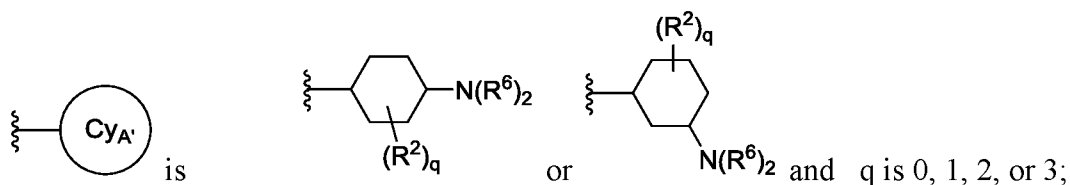
[00123] In some embodiments, ring A is phenylene, pyridinylene, pyrazolylene, thiazolylene, imidazolylene, oxazolylene, or oxadiazolylene. In some embodiments, R^4 and R^5 are each independently H, halogen, -CN, -OR¹², -SR¹², -N(R¹²)₂, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

[00124] In exemplary embodiments, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (I)

wherein,



each R^6 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_1 - C_4 fluoroalkyl, -X-optionally substituted C_1 - C_4 alkyl, -X-optionally substituted C_1 - C_4 heteroalkyl, or -X-optionally substituted C_1 - C_4 fluoroalkyl;

each R^2 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, or optionally substituted C_1 - C_4 fluoroalkyl;

A^2 is N;

R^{A1} is H;

R^{A2} is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl;

R^{A3} is methyl, ethyl, propyl or butyl;

ring A is a monocyclic 6-membered heteroarylene selected from pyridinylene, pyrimidinylene, pyrazinylene, and pyridazinylene.;

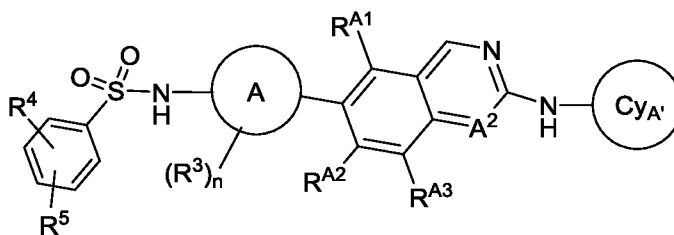
R^3 is independently H, halogen, -CN, -OR¹¹, -SR¹¹, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl; and n is 1, 2, or 3;

R^{11} is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted C_2 - C_{10} heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl

R^4 is -Cl, -Br, -F, or -I;

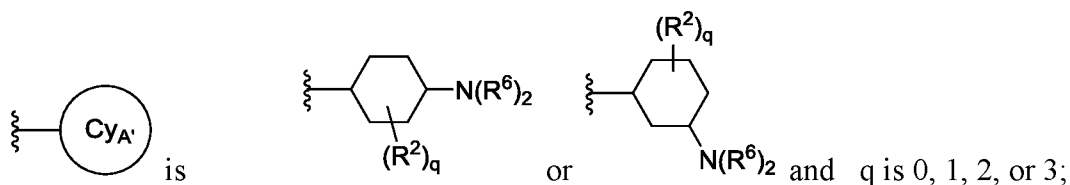
and R^5 is hydrogen.

[00125] In exemplary embodiments, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (I)

wherein,



each R^6 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_1 - C_4 fluoroalkyl, -X-optionally substituted C_1 - C_4 alkyl, -X-optionally substituted C_1 - C_4 heteroalkyl, or -X-optionally substituted C_1 - C_4 fluoroalkyl;

each R^2 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, or optionally substituted C_1 - C_4 fluoroalkyl;

A^2 is N;

R^{A1} is H;

R^{A2} is H;

R^{A3} is methyl, ethyl, propyl or butyl;

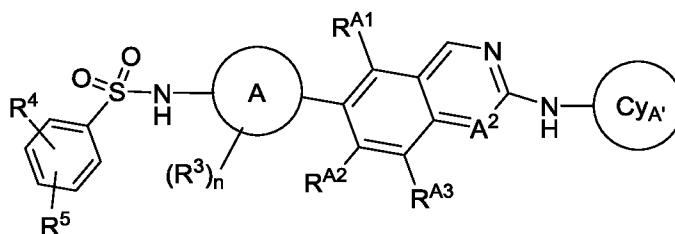
ring A is pyridinylene;

R^3 is methyl, ethyl, propyl, or butyl and n is 1, 2 or 3;

R^4 is -Cl, -Br, -F, or -I;

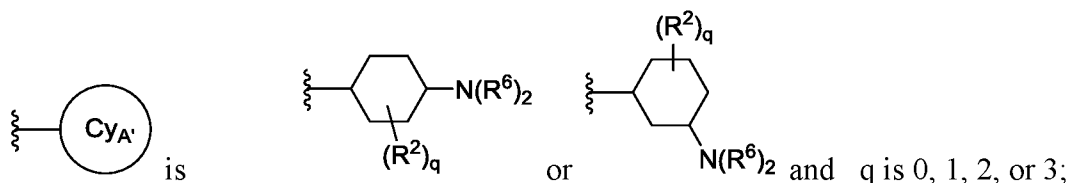
and R^5 is hydrogen.

[00126] In exemplary embodiments, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (I)

wherein,



each R^6 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_1 - C_4 fluoroalkyl, -X-optionally substituted C_1 - C_4 alkyl, -X-optionally substituted C_1 - C_4 heteroalkyl, or -X-optionally substituted C_1 - C_4 fluoroalkyl;

each R^2 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, or optionally substituted C_1 - C_4 fluoroalkyl;

A^2 is N;

R^{A1} is H;

R^{A2} is H;

R^{A3} is methyl, ethyl, propyl or butyl;

wherein ring A is pyridinylene;

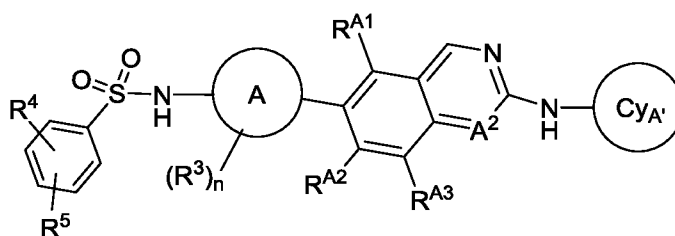
R^3 is $-OR^{11}$ and n is 1, 2 or 3;

R^{11} is methyl, ethyl, propyl, or butyl

R^4 is $-Cl$, $-Br$, $-F$, or $-I$;

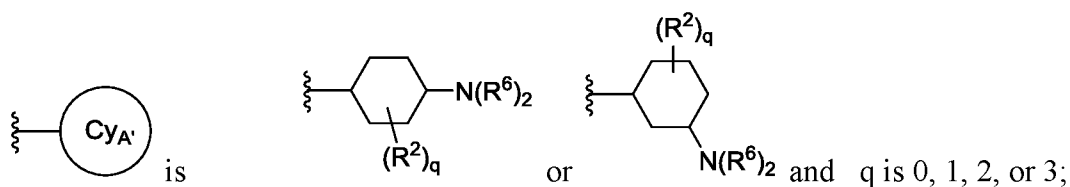
and R^5 is hydrogen.

[00127] In exemplary embodiments, provided herein is a compound of Formula (I), or a pharmaceutically acceptable salt, or solvate thereof:



Formula (I)

wherein,



each R^6 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_1 - C_4 fluoroalkyl, $-X$ -optionally substituted C_1 - C_4 alkyl, $-X$ -optionally substituted C_1 - C_4 heteroalkyl, or $-X$ -optionally substituted C_1 - C_4 fluoroalkyl;

each R^2 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, or optionally substituted C_1 - C_4 fluoroalkyl;

A^2 is N;

R^{A1} is H;

R^{A2} is H;

R^{A3} is methyl, ethyl, propyl or butyl;

wherein ring A is pyridinylene;

R^3 is $-OR^{11}$ and n is 1, 2 or 3;

R^{11} is CF_3 or $-CH_2CF_3$;

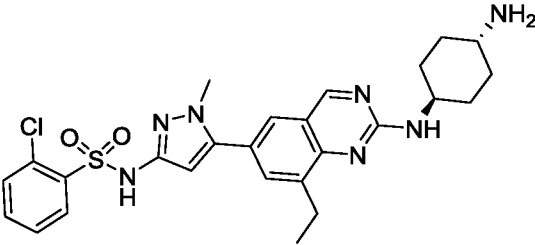
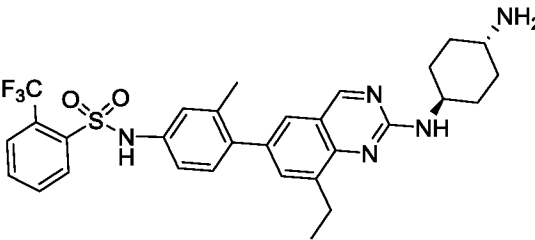
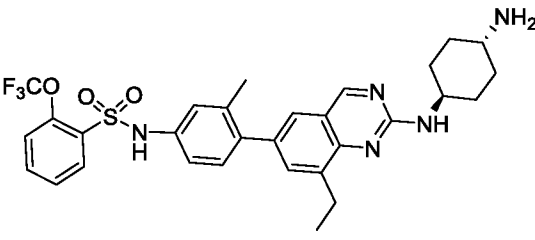
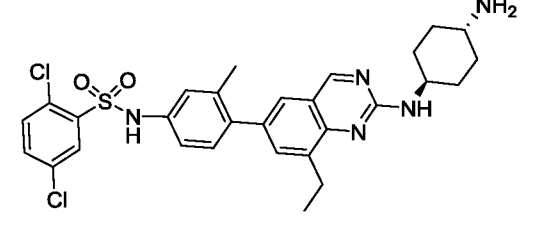
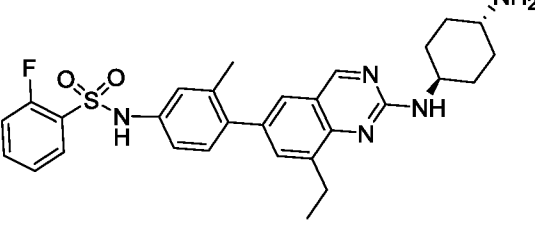
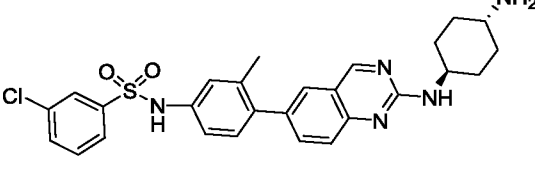
R⁴ is -Cl, -Br, -F, or -I;

and R⁵ is hydrogen.

[00128] In some embodiments, a compound described herein is selected from any one of the compounds from Table 1.

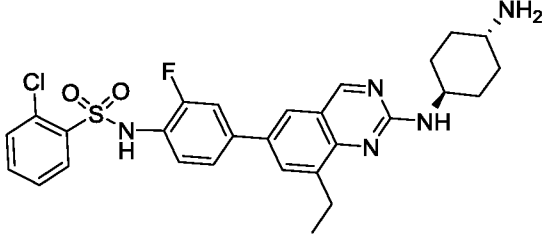
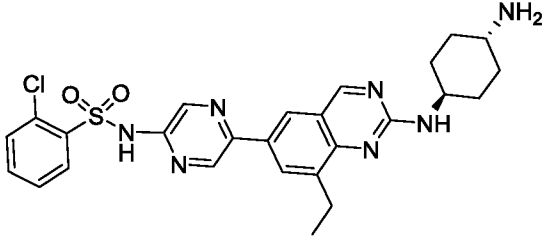
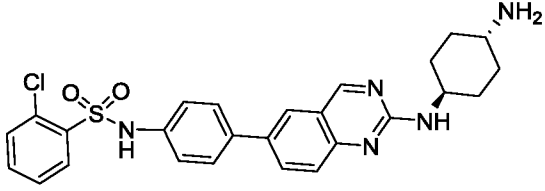
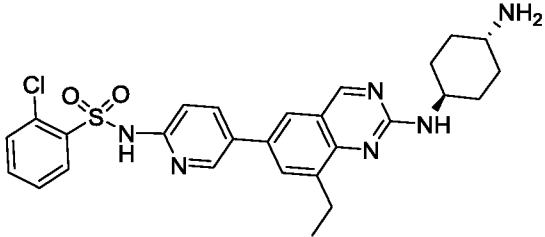
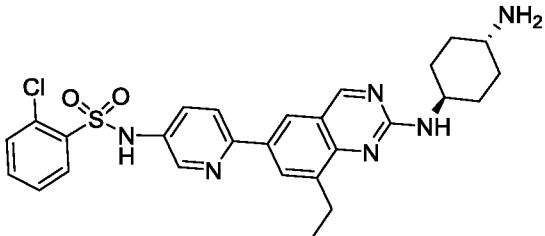
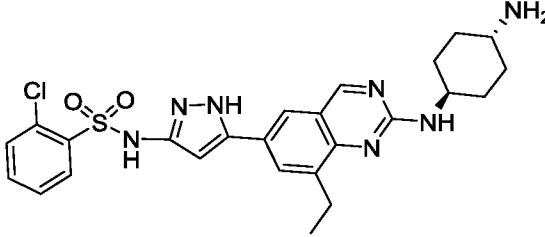
Table 1

Compound No.	Structure	Name
1		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-1-methyl-1H-pyrazol-3-yl)-2-chlorobenzenesulfonamide
2		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-3-methylphenyl)-2-chlorobenzenesulfonamide
3		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-chlorobenzenesulfonamide
4		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-methylpyridin-2-yl)-2-chlorobenzenesulfonamide
5		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-4-methylpyridin-2-yl)-2-chlorobenzenesulfonamide

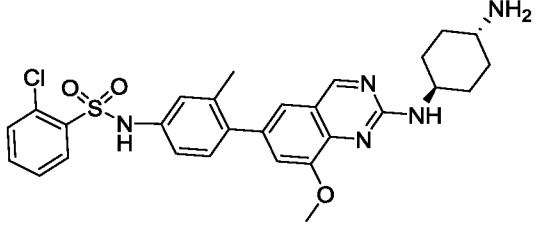
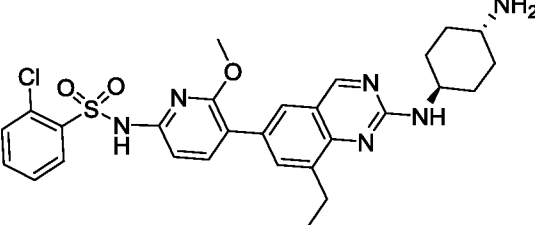
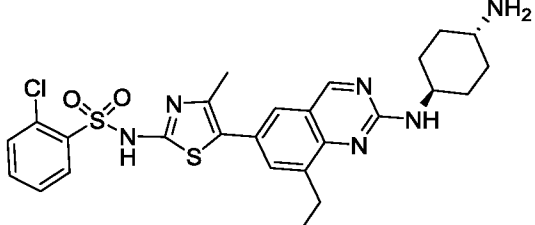
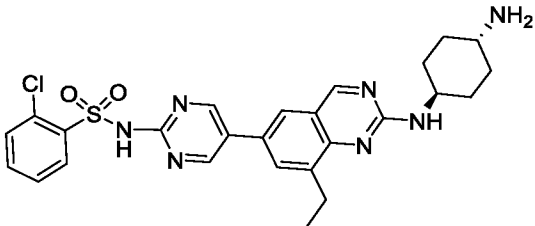
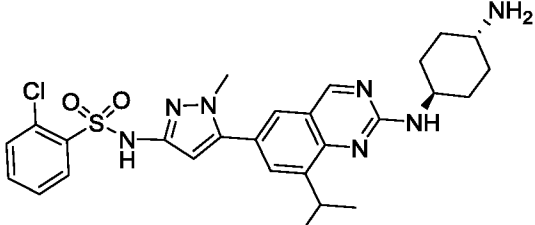
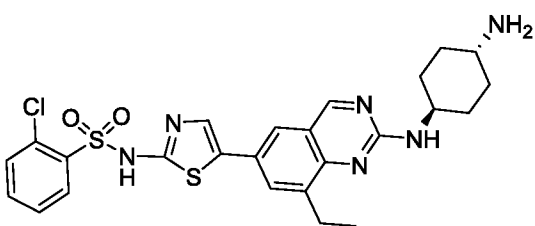
Compound No.	Structure	Name
6		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-1-methyl-1H-pyrazol-3-yl)-2-chlorobenzenesulfonamide
7		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-(trifluoromethyl)benzenesulfonamide
8		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-(trifluoromethoxy)benzenesulfonamide
9		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2,5-dichlorobenzenesulfonamide
10		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-fluorobenzenesulfonamide
11		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-3-methylphenyl)-3-chlorobenzenesulfonamide

Compound No.	Structure	Name
12		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-4-chlorobenzenesulfonamide
13		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-methoxybenzenesulfonamide
14		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-(trifluoromethyl)phenyl)-2-chlorobenzenesulfonamide
15		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)benzenesulfonamide
16		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methylpyridin-2-yl)-2-chlorobenzenesulfonamide
17		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-chlorophenyl)-2-chlorobenzenesulfonamide

Compound No.	Structure	Name
18		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)phenyl)-2-chlorobenzenesulfonamide
19		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methoxyphenyl)-2-chlorobenzenesulfonamide
20		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-methylpyridin-3-yl)-2-chlorobenzenesulfonamide
21		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluoro-5-methylphenyl)-2-chlorobenzenesulfonamide
22		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-2,3-dimethylphenyl)-2-chlorobenzenesulfonamide
23		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-methylpyrimidin-2-yl)-2-chlorobenzenesulfonamide

Compound No.	Structure	Name
24		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
25		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)pyrazin-2-yl)-2-chlorobenzenesulfonamide
26		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)phenyl)-2-chlorobenzenesulfonamide
27		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)pyridin-2-yl)-2-chlorobenzenesulfonamide
28		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)pyridin-3-yl)-2-chlorobenzenesulfonamide
29		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-1H-pyrazol-3-yl)-2-chlorobenzenesulfonamide

Compound No.	Structure	Name
30		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-hydroxyquinazolin-6-yl)-3-methylphenyl)-2-chloro-N-methylbenzenesulfonamide
31		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-chloro-N-methylbenzenesulfonamide
32		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)pyridazin-3-yl)-2-chlorobenzenesulfonamide
33		N-(2-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)pyrimidin-5-yl)-2-chlorobenzenesulfonamide
34		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-ethylphenyl)-2-chlorobenzenesulfonamide
35		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-fluorophenyl)-2-chlorobenzenesulfonamide

Compound No.	Structure	Name
36		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-methoxyquinazolin-6-yl)-3-methylphenyl)-2-chlorobenzenesulfonamide
37		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide
38		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-methylthiazol-2-yl)-2-chlorobenzenesulfonamide
39		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)pyrimidin-2-yl)-2-chlorobenzenesulfonamide
40		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-isopropylquinazolin-6-yl)-1-methyl-1H-pyrazol-3-yl)-2-chlorobenzenesulfonamide
41		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)thiazol-2-yl)-2-chlorobenzenesulfonamide

Compound No.	Structure	Name
42		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluoro-5-methoxyphenyl)-2-chlorobenzenesulfonamide
43		N-(1-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-1H-pyrazol-4-yl)-2-chlorobenzenesulfonamide
44		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)isoxazol-3-yl)-2-chlorobenzenesulfonamide
45		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-methoxyquinazolin-6-yl)-1-methyl-1H-pyrazol-3-yl)-2-chlorobenzenesulfonamide
46		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-methoxypyrimidin-2-yl)-2-chlorobenzenesulfonamide
47		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-propylquinazolin-6-yl)-1-methyl-1H-pyrazol-3-yl)-2-chlorobenzenesulfonamide

Compound No.	Structure	Name
48		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-3-fluorophenyl)-2-chlorobenzenesulfonamide
49		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)pyridazin-3-yl)-2-chlorobenzenesulfonamide
50		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
51		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-5-fluoropyridin-3-yl)-2-chlorobenzenesulfonamide
52		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-fluoropyridin-3-yl)-2-chlorobenzenesulfonamide
53		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-2,5-difluorophenyl)-2-chlorobenzenesulfonamide
54		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-3-fluoropyridin-2-yl)-2-chlorobenzenesulfonamide

Compound No.	Structure	Name
		chlorobenzenesulfonamide
55		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-fluoropyridin-2-yl)-2-chlorobenzenesulfonamide
56		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-2,3-difluorophenyl)-2-chlorobenzenesulfonamide
57		N-(4-(3-(((1r,4r)-4-aminocyclohexyl)amino)isoquinolin-7-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
58		(S)-2-amino-N-(((1r,4S)-4-((6-(4-((2-chlorophenyl)sulfonamido)-3-fluorophenyl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)-3-methylbutanamide
59		N-(((1r,4r)-4-((6-(4-((2-chlorophenyl)sulfonamido)-3-fluorophenyl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)acetamide

Compound No.	Structure	Name
60		2-chloro-N-(4-(8-ethyl-2-(((1r,4r)-4-(methylamino)cyclohexyl)amino)quinazolin-6-yl)-2-fluorophenyl)benzenesulfonamide
62		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-3,5-difluorophenyl)-2-chlorobenzenesulfonamide
63		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-2,6-difluorophenyl)-2-chlorobenzenesulfonamide
65		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-methoxypyridazin-3-yl)-2-chlorobenzenesulfonamide
66		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-methoxypyridazin-3-yl)-2-chlorobenzenesulfonamide
67		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-methylpyridazin-3-yl)-2-chlorobenzenesulfonamide

Compound No.	Structure	Name
68		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-4-methylpyrimidin-2-yl)-2-chlorobenzenesulfonamide
69		2-chloro-N-(4-(2-(((1r,4r)-4-(dimethylamino)cyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)benzenesulfonamide
70		N-(4-(2-(((1R,3R,4S)-4-amino-3-methylcyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
71		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluoro-3-methylphenyl)-2-chlorobenzenesulfonamide
72		N-(4-(2-(((1R,3S)-3-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
73		(S)-2-chloro-N-(4-(8-ethyl-2-(piperidin-3-ylamino)quinazolin-6-yl)-2-fluorophenyl)benzenesulfonamide

Compound No.	Structure	Name
		ide
74		N-(4-(2-(((1R,3R,4R)-4-amino-3-methylcyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
75		N-(4-(2-(((1R,3S)-3-aminocyclohexyl)amino)quinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
76		(S)-2-chloro-N-(2-fluoro-4-(2-(piperidin-3-ylamino)quinazolin-6-yl)phenyl)benzenesulfonamide
77		N-(4-(2-(((1R,3R)-3-aminocyclopentyl)amino)quinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
78		N-(4-(2-(((1R,3R)-3-aminocyclopentyl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
79		N-(4-(2-(((1R,3S)-3-aminocyclopentyl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide

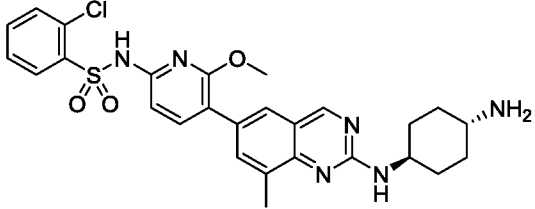
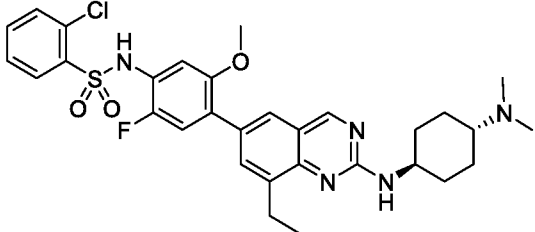
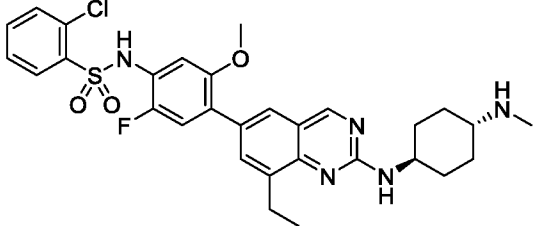
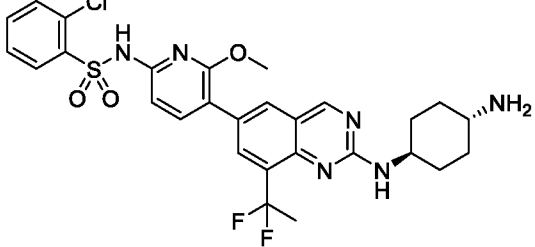
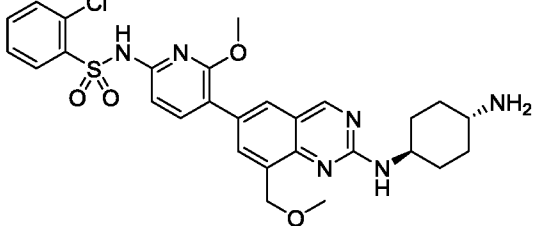
Compound No.	Structure	Name
80		N-(4-(2-(((1R,3S)-3-aminocyclopentyl)amino)quinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
81		N-(4-(2-((4-aminobicyclo[2.2.2]octan-1-yl)amino)quinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
82		N-(4-(2-(((2r,5r)-5-amino-octahydropentalen-2-yl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
83		N-(4-(2-(((2r,5r)-5-amino-octahydropentalen-2-yl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
84		N-(4-(2-(((2s,5s)-5-amino-octahydropentalen-2-yl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
85		N-(4-(2-(((2s,5s)-5-amino-octahydropentalen-2-yl)amino)quinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide

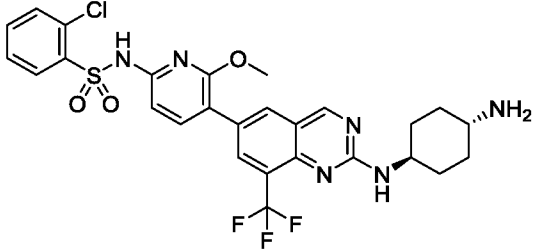
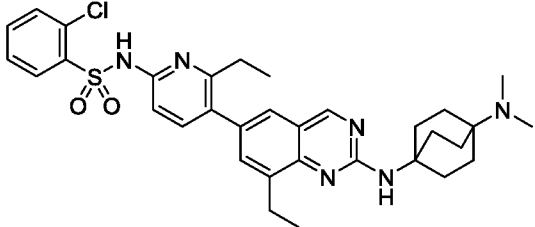
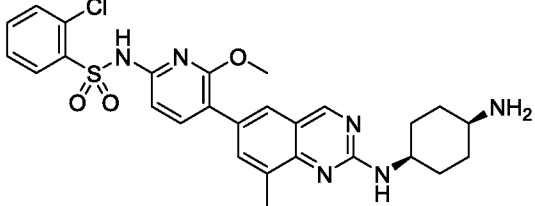
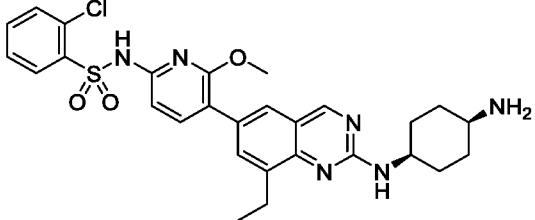
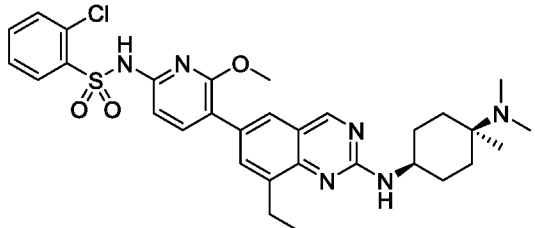
Compound No.	Structure	Name
86		N-(4-(2-((4-aminobicyclo[2.2.1]heptan-1-yl)amino)quinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
87		N-(4-(2-((4-aminobicyclo[2.2.2]octan-1-yl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
88		2-chloro-N-(4-(8-ethyl-2-(((1r,4r)-4-(pyrrolidin-1-yl)cyclohexyl)amino)quinazolin-6-yl)-2-fluorophenyl)benzenesulfonamide
89		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-1,3,4-thiadiazol-2-yl)-2-chlorobenzenesulfonamide
90		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-methylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide
92		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide

Compound No.	Structure	Name
93		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-methoxypyridin-3-yl)-2-chlorobenzenesulfonamide
94		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methylpyrazin-2-yl)-2-chlorobenzenesulfonamide
96		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-ethylpyridazin-3-yl)-2-chlorobenzenesulfonamide
98		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyrazin-2-yl)-2-chlorobenzenesulfonamide
100		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-ethylpyridazin-3-yl)-2-chlorobenzenesulfonamide
101		2-chloro-N-(5-(8-ethyl-2-(((1r,4r)-4-hydroxycyclohexyl)amino)quinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide

Compound No.	Structure	Name
		yl)benzenesulfonamide
102		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-cyanobenzenesulfonamide
103		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-methylbenzenesulfonamide
104		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide
105		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-methylquinazolin-6-yl)-6-ethylpyridin-2-yl)-2-chlorobenzenesulfonamide
106		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-methylquinazolin-6-yl)-6-methylpyridin-2-yl)-2-chlorobenzenesulfonamide
107		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-(trifluoromethoxy)pyridin-2-yl)-2-methylbenzenesulfonamide

Compound No.	Structure	Name
		chlorobenzenesulfonamide
109		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-methoxybenzenesulfonamide
110		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide
111		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methylpyridin-2-yl)benzenesulfonamide
112		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methylpyridin-2-yl)-2-methylbenzenesulfonamide
113		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methylpyridin-2-yl)-3-methylbenzenesulfonamide
114		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-5-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide

Compound No.	Structure	Name
115		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide
120		2-chloro-N-(4-(2-(((1r,4r)-4-(dimethylamino)cyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluoro-5-methoxyphenyl)benzenesulfonamide
121		2-chloro-N-(4-(8-ethyl-2-(((1r,4r)-4-(methylamino)cyclohexyl)amino)quinazolin-6-yl)-2-fluoro-5-methoxyphenyl)benzenesulfonamide
123		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-(1,1-difluoroethyl)quinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide
129		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-(methoxymethyl)quinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide

Compound No.	Structure	Name
134		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-(trifluoromethyl)quinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide
136		2-chloro-N-(5-(2-(((4-(dimethylamino)bicyclo[2.2.2]octan-1-yl)amino)-8-ethylquinazolin-6-yl)-6-ethylpyridin-2-yl)benzenesulfonamide
138		N-(5-(2-(((1s,4s)-4-methylcyclohexyl)amino)-8-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide
140		N-(5-(2-(((1s,4s)-4-ethylcyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide
143		2-chloro-N-(5-(2-(((1s,4s)-4-methylcyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)benzenesulfonamide

Compound No.	Structure	Name
144		2-chloro-N-(5-(2-(((1s,4s)-4-(dimethylamino)-4-methylcyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-fluoro-6-methoxypyridin-2-yl)benzenesulfonamide
146		N-(5-(2-(((1s,4s)-4-aminocyclohexyl)amino)-8-methylquinazolin-6-yl)-3-fluoro-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide

IRE1-like Family of Proteins

[00129] In some embodiments, a compound disclosed herein selectively binds to a protein of the serine/threonine-protein kinase/endoribonuclease inositol-requiring enzyme 1 (IRE1) family of proteins. In humans, IRE1 is encoded by the ERN1 gene. Exemplary IRE1 family proteins include isoforms IRE1 and IRE1a. Other exemplary IRE1 family proteins include IRE1 homologues or orthologues in other organisms. Exemplary organisms include human, non-human primate, mouse, rat, chicken, fruit fly, yeast, and others listed in **Table 2**. In some embodiments, the IRE1 protein is human IRE1a.

Table 2.

Organism	Accession #
<i>Homo sapiens</i>	NP_001424.3
<i>Mus musculus</i>	NP_076402.1
<i>Rattus norvegicus</i>	XP_006247696.1

[00130] In some embodiments, a compound disclosed herein selectively binds to an IRE1 family protein comprising a kinase domain and/or an RNase domain. In some embodiments, the kinase domain is a trans-autophosphorylation kinase domain. In some embodiments, the IRE1 family protein is IRE1a. An example arrangement of domains within an IRE1a protein is depicted in **Figure 1**. An example alignment of IRE1 family protein orthologues is depicted in **Figure 2**.

[00131] In some embodiments, a compound disclosed herein selectively binds to a trans-autophosphorylation kinase domain region of IRE1a. In some embodiments, a compound disclosed herein selectively binds to a trans-autophosphorylation kinase domain region of IRE1a, for example within amino acid residues 568-833 of SEQ ID NO: 1, or equivalent amino acid residues thereof.

[00132] In some embodiments, a compound disclosed herein selectively binds to an ATP-binding pocket within a trans-autophosphorylation kinase domain region of IRE1a. In some embodiments, a compound disclosed herein selectively binds to an ATP-binding pocket within a trans-autophosphorylation kinase domain region of IRE1a, for example, one or more of amino acid residues 577-711, 577-586, 597, 599, 626, 642-643, 645, 648, 688, 692-693, 695, or 711 of SEQ ID NO: 1, or equivalent amino acid residues thereof.

[00133] In some embodiments, a compound disclosed herein selectively binds to an activation loop within a trans-autophosphorylation kinase domain region of IRE1a. In some embodiments, a compound disclosed herein selectively binds to an activation loop within a trans-autophosphorylation kinase domain region of IRE1a, for example, one or more of amino acid residues 710-736, 710-725, or 729-736 of SEQ ID NO: 1, or equivalent amino acid residues thereof.

[00134] In some embodiments, a compound disclosed herein selectively binds to an RNase domain region of IRE1a. In some embodiments, a compound disclosed herein selectively binds to an RNase domain region of IRE1a, for example within amino acid residues 835-963 of SEQ ID NO: 1, or equivalent amino acid residues thereof.

[00135] In some embodiments, a compound disclosed herein selectively binds to a kinase domain dimer interface amino acid residue. In some embodiments, a compound disclosed herein selectively binds to a kinase domain dimer interface amino acid residue, such as one or more of amino acid residues 569-701, 569, 591, 592, 594, 617, 620, 627, 628, 631, 674, 678, or 701 of SEQ ID NO: 1.

[00136] In some embodiments, a compound disclosed herein selectively binds to a first IRE1a and blocks dimerization between kinase domain dimer interface amino acid residues of the first IRE1a and a second IRE1a. In some embodiments, a compound disclosed herein selectively binds to a first IRE1a, and inhibit dimerization at one or more of amino acid residues 569-701, 569, 591, 592, 594, 617, 620, 627, 628, 631, 674, 678, or 701 of SEQ ID NO: 1.

[00137] In some embodiments, a compound disclosed herein selectively binds to a kinase-extension nuclease (KEN) domain dimer interface amino acid residue of an IRE1a. In some embodiments, a compound disclosed herein selectively binds to a KEN domain dimer interface

amino acid residue, such as one or more of amino acid residues 840-925, 840, 844, 851, 908, 912, or 925 of SEQ ID NO: 1.

[00138] In some embodiments, a compound disclosed herein selectively binds to amino acid residues of a nuclease active site. In some embodiments, a compound disclosed herein selectively binds to amino acid residues of a nuclease active site, such as one or more of amino acid residues 847-910, 847, 850, 886, 888, 889, 890, 892, 902, 905, 906, or 910 of SEQ ID NO: 1.

[00139] In some embodiments, a compound disclosed herein selectively binds to an RNase domain and a trans-autophosphorylation kinase domain region of IRE1a. In some embodiments, a compound disclosed herein selectively binds to an RNase domain and an ATP-binding pocket within a trans-autophosphorylation kinase domain region of IRE1a. In some embodiments, a compound disclosed herein selectively binds to an RNase domain and an activation loop within a trans autophosphorylation kinase domain region of IRE1a.

[00140] In some embodiments, a compound disclosed herein selectively binds to IRE1a at two sites located in an RNase domain, trans-autophosphorylation kinase domain region, ATP-binding pocket, activation loop, or any combination thereof. In some embodiments, a compound disclosed herein selectively binds to IRE1a at two or more sites. In some embodiments, a compound disclosed herein selectively binds to IRE1a at two or more sites located in an RNase domain, trans-autophosphorylation kinase domain region, ATP-binding pocket, activation loop, or any combination thereof. In some embodiments, a compound disclosed herein selectively binds to IRE1a at three sites located in an RNase domain, trans-autophosphorylation kinase domain region, ATP-binding pocket, activation loop, or any combination thereof.

[00141] In some embodiments, a compound disclosed herein selectively binds to IRE1a at a first site located in an RNase domain, trans-autophosphorylation kinase domain region, ATP-binding pocket, or activation loop. In some embodiments, a first site comprises one or more of any amino acid residue within amino acid residues 465-977 of SEQ ID NO: 1. In some embodiments, a compound disclosed herein selectively binds to IRE1a at a second site located in an RNase domain, trans-autophosphorylation kinase domain region, ATP-binding pocket, or activation loop. In some examples, the first site is located within the same domain or region as the second site. In some examples, the first site is located within a different domain or region as the second site.

[00142] In some embodiments, a compound disclosed herein selectively binds to first IRE1a, thereby blocking dimerization of the first IRE1a to a second IRE1a. In some embodiments, a compound disclosed herein selectively binds to first IRE1a, thereby blocking auto-transphosphorylation of the first IRE1a or a second IRE1a to which the first IRE1a is

dimerized. In some embodiments, a compound disclosed herein selectively binds to a first IRE1a, thereby blocking activation of the first IRE1a or a second IRE1a to which the first IRE1a is dimerized. In some embodiments, a compound disclosed herein selectively binds to a first IRE1a, thereby blocking kinase activity of the first IRE1a or a second IRE1a to which the first IRE1a is dimerized. In some embodiments, a compound disclosed herein selectively binds to a first IRE1a, thereby blocking RNase activity of the first IRE1a or a second IRE1a to which the first IRE1a is dimerized.

[00143] In some embodiments, a compound disclosed herein selectively binds to IRE1a when in a homo-dimerized conformation. In some embodiments, a compound disclosed herein selectively binds to IRE1a when in an oligomerized conformation. In some embodiments, a compound disclosed herein selectively binds to IRE1a when in a non-oligomerized or non-dimerized conformation. In some embodiments, a compound disclosed herein selectively binds to IRE1a when in an ATP-bound state. In some embodiments, a compound disclosed herein selectively binds to a IRE1 family protein when in a non-ATP-bound state. In some embodiments, the compound is a pharmaceutically acceptable salt, or solvate thereof.

IRE1 Signaling Pathway

[00144] In some embodiments, a compound disclosed herein selectively binds to an IRE1 family protein and alters a downstream signaling pathway. In some embodiments, a compound disclosed herein selectively binds to an IRE1 family protein and alters signaling of immunoglobulin heavy-chain binding protein (BIP), protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), glucose regulate protein 78 (Grp78), eukaryotic translation initiation factor 2 α (eIF2 α), X-box binding protein 1 (XBP1), activating transcription factor 6 α (ATF6 α), C/EBP homologous protein (CHOP), growth arrest and DNA damage-inducible protein 34 (GADD34), tumor necrosis factor receptor-associated factor 2 (TRAF2), JUN N-terminal kinase (JNK), regulated IRE1-dependent decay (RIDD), transcriptionally active XBP1 (XBP1s), or unspliced XBP1 (XBP1u). In some embodiments, a compound disclosed herein selectively binds to an IRE1 family protein and alters a downstream cellular process. In some embodiments, an IRE1 family protein is IRE1, IRE1a, or ERN1.

[00145] In some embodiments, a compound disclosed herein selectively binds to an IRE1 family protein and decreases or blocks a downstream signaling pathway. In some embodiments, a compound disclosed herein selectively binds to an IRE1 family protein and decreases or blocks activity or signaling of TXNIP, Caspase 1, Interleukin 1-beta, JNK, Bim, cytochrome C, Caspase 3, Caspase 8, mRNA degradation, miRNA degradation, apoptosis-inducing proteins, or inflammation-inducing proteins. In some embodiments, a compound disclosed herein selectively

binds to an IRE1 family protein and decreases XBP1 mRNA levels. In some embodiments, a compound disclosed herein selectively binds to an IRE1 family protein and decreases transcriptionally active XBP1 (XBP1s) mRNA levels. In some embodiments, a compound disclosed herein selectively binds to an IRE1 family protein and decreases spliced XBP1 mRNA levels. In some embodiments, an IRE1 family protein is IRE1, IRE1a, or ERN1.

[00146] In some embodiments, a compound disclosed herein selectively binds to an IRE1 family protein and increases, activates, or removes a block of a downstream signaling pathway. In some embodiments, a compound disclosed herein selectively binds to an IRE1 family protein and increases, activates, or removes a block of activity or signaling of Bcl2, Bcl-XL, Mcl-1, Bax, Bak, other anti-apoptotic proteins, or an mRNA translocon proteins. In some embodiments, an IRE1 family protein is IRE1, IRE1a, or ERN1.

[00147] In some embodiments, a compound disclosed herein selectively binds to an IRE1 family protein and disrupts binding with an effector protein. In some cases, the effector protein binds to the IRE1 family protein when in a dimerized or oligomerized state. In some cases, the effector protein binds to the IRE1 family protein when in a non-dimerized or non-oligomerized state. In some cases, the effector protein is immunoglobulin heavy-chain binding protein (BIP), protein kinase R (PKR)-like endoplasmic reticulum kinase (PERK), glucose regulate protein 78 (Grp78), tumor necrosis factor receptor-associated factor 2 (TRAF2), JUN N-terminal kinase (JNK), transcriptionally active XBP1 (XBP1s), unspliced XBP1 (XBP1u), regulated IRE1-dependent decay (RIDD), Heat shock protein 90 kDa alpha (HSP 90-alpha), or misfolded protein. In some embodiments, an IRE1 family protein is IRE1, IRE1a, or ERN1.

[00148] In some embodiments, a compound disclosed herein selectively binds to an IRE1 family protein and alters activity of a cellular process or cellular function, such as regulated IRE1-dependent decay (RIDD), RNA decay, translation, autophagy, cell survival, ER protein folding, ERAD, reactive oxygen species generation, transport, ER-associated protein degradation (ERAD), protein synthesis, or apoptosis. In some embodiments, where an altered or lack of a cellular process or cellular function is associated with a disease state, selective binding of a compound disclosed herein results in inhibiting or alleviating the disease state, or inhibiting a deleterious activity associated with the disease state. In some embodiments, an IRE1 family protein is IRE1, IRE1a, or ERN1.

Diseases Associated with Altered IRE1 Pathway Signaling

[00149] In some cases, a compound disclosed herein is used to treat or ameliorate a disease associated with altered IRE1a pathway signaling when administered to a subject in need thereof. In some cases, a compound disclosed herein is used to treat or ameliorate the effects of a

disease associated with altered IRE1a pathway signaling when administered to a subject in need thereof. Exemplary disease associated with altered IRE1a signaling include cancer. In some cases, a compound disclosed herein is used to treat or ameliorate a cancer when administered to a subject in need thereof. Exemplary cancers include tumors, solid and hematologic cancers. In some cases, a compound disclosed herein is used to treat or ameliorate a cell proliferative disorder when administered to a subject in need thereof. In some cases, the cell proliferative disorder is a cancer. In some cases, the cancer is ovarian cancer, lung cancer, bladder cancer, breast cancer, or triple negative breast cancer (TNBC).

[00150] An IRE1a pathway can be involved in a variety of pathological conditions, including neurodegenerative diseases, inflammation, metabolic disorders, liver dysfunction, brain ischemia, heart ischemia, autoimmune diseases, and cancer. In some cases, modulation of this pathway provides therapeutic methods useful for treatment of such diseases.

[00151] In some instances, a compound disclosed herein is used to reinforce anti-tumor mechanisms. In some cases, an anti-tumor mechanism comprises direct inhibition of tumor growth. In some cases, an anti-tumor mechanism comprises induction of anti-tumor immunity. In some cases, anti-tumor mechanisms comprise direct inhibition of tumor growth and simultaneous induction of anti-tumor immunity. In some cases, a compound disclosed herein can prevent lipid accumulation in myeloid cells exposed to ovarian cancer-derived ascites supernatants. In some cases, a compound disclosed herein can block myeloid cell immunosuppression mediated by tumor-associated factors. In some cases, a compound disclosed herein can be employed as therapeutic compound that enhances dendritic cell and T cell anti-tumor activity in mammals. For example, the compounds disclosed herein can be used to treat murine and human ovarian cancers.

Methods of Dosing and Treatment Regimens

[00152] In one embodiment, the compounds described herein, or a pharmaceutically acceptable salt thereof, are used in the preparation of medicaments for the treatment of diseases or conditions in a mammal that would benefit from administration of any one of the compounds disclosed. Methods for treating any of the diseases or conditions described herein in a mammal in need of such treatment, involves administration of pharmaceutical compositions that include at least one compound described herein or a pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said mammal.

[00153] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic

applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[00154] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a “prophylactically effective amount or dose.” In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in patients, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. In one aspect, prophylactic treatments include administering to a mammal, who previously experienced at least one symptom of the disease being treated and is currently in remission, a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition.

[00155] In certain embodiments wherein the patient's condition does not improve, upon the doctor's discretion the administration of the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00156] In certain embodiments wherein a patient's status does improve, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (*e.g.*, a “drug holiday”). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, or more than 28 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%), 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00157] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the improved disease, disorder or condition is retained. In certain embodiments, however, the patient requires intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00158] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (e.g., weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[00159] In general, however, doses employed for adult human treatment are typically in the range of 0.01 mg to 5000 mg per day. In one aspect, doses employed for adult human treatment are from about 1 mg to about 1000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00160] In one embodiment, the daily dosages appropriate for the compound described herein, or a pharmaceutically acceptable salt thereof, are from about 0.01 mg/kg to about 50 mg/kg per body weight. In some embodiments, the daily dosage or the amount of active in the dosage form are lower or higher than the ranges indicated herein, based on a number of variables in regard to an individual treatment regime. In various embodiments, the daily and unit dosages are altered depending on a number of variables including, but not limited to, the activity of the compound used, the disease or condition to be treated, the mode of administration, the requirements of the individual subject, the severity of the disease or condition being treated, and the judgment of the practitioner.

[00161] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD50 and the ED50. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD50 and ED50. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the ED50 with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

[00162] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound described herein, or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by

injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) administered non-systemically or locally to the mammal.

[00163] In any of the aforementioned aspects are further embodiments comprising single administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered once a day; or (ii) the compound is administered to the mammal multiple times over the span of one day, e.g., two, three, four or more times daily.

[00164] In any of the aforementioned aspects are further embodiments comprising multiple administrations of the effective amount of the compound, including further embodiments in which (i) the compound is administered continuously or intermittently: as in a single dose; (ii) the time between multiple administrations is every 6 hours; (iii) the compound is administered to the mammal every 8 hours; (iv) the compound is administered to the mammal every 12 hours; (v) the compound is administered to the mammal every 24 hours. In further or alternative embodiments, the method comprises a drug holiday, wherein the administration of the compound is temporarily suspended or the dose of the compound being administered is temporarily reduced; at the end of the drug holiday, dosing of the compound is resumed. In one embodiment, the length of the drug holiday varies from 2 days to 1 year.

[00165] In certain instances, it is appropriate to administer at least one compound described herein, or a pharmaceutically acceptable salt thereof, in combination with one or more other therapeutic agents. In one embodiment, the therapeutic effectiveness of one of the compounds described herein is enhanced by administration of an adjuvant (*i.e.*, by itself the adjuvant has minimal therapeutic benefit, but in combination with another therapeutic agent, the overall therapeutic benefit to the patient is enhanced). Or, in some embodiments, the benefit experienced by a patient is increased by administering one of the compounds described herein with another agent (which also includes a therapeutic regimen) that also has therapeutic benefit.

[00166] It is understood that the dosage regimen to treat, prevent, or ameliorate the condition(s) for which relief is sought, is modified in accordance with a variety of factors (e.g. the disease, disorder or condition from which the subject suffers; the age, weight, sex, diet, and medical condition of the subject). Thus, in some instances, the dosage regimen actually employed varies and, in some embodiments, deviates from the dosage regimens set forth herein.

[00167] For combination therapies described herein, dosages of the co-administered compounds vary depending on the type of co-drug employed, on the specific drug employed, on the disease or condition being treated and so forth. In additional embodiments, when co-administered with one or more other therapeutic agents, the compound provided herein is administered either simultaneously with the one or more other therapeutic agents, or sequentially.

[00168] In combination therapies, the multiple therapeutic agents (one of which is one of the compounds described herein) are administered in any order or even simultaneously. If administration is simultaneous, the multiple therapeutic agents are, by way of example only, provided in a single, unified form, or in multiple forms (e.g., as a single pill or as two separate pills).

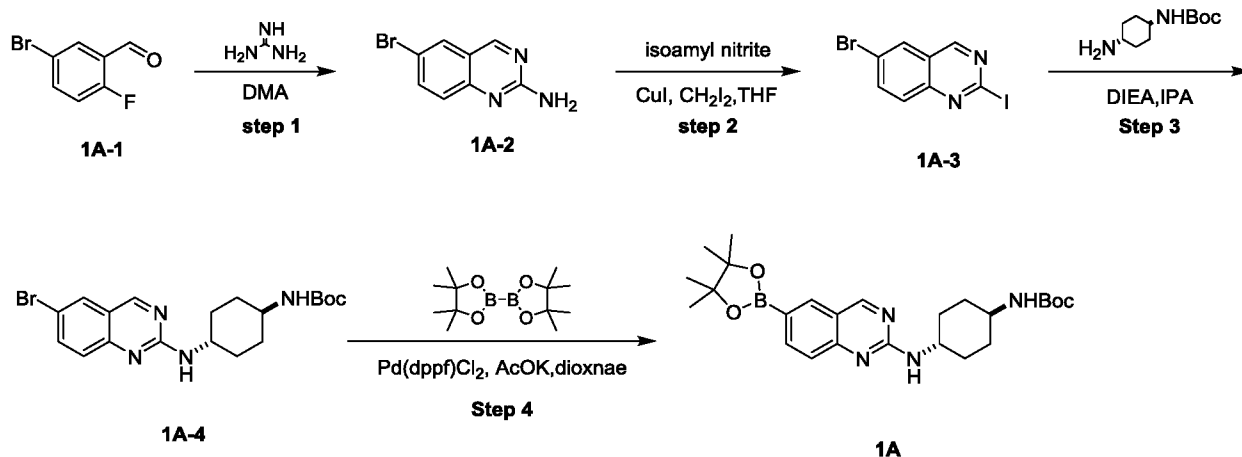
[00169] The compounds described herein, or a pharmaceutically acceptable salt thereof, as well as combination therapies, are administered before, during or after the occurrence of a disease or condition, and the timing of administering the composition containing a compound varies. Thus, in one embodiment, the compounds described herein are used as a prophylactic and are administered continuously to subjects with a propensity to develop conditions or diseases in order to prevent the occurrence of the disease or condition. In another embodiment, the compounds and compositions are administered to a subject during or as soon as possible after the onset of the symptoms. In specific embodiments, a compound described herein is administered as soon as is practicable after the onset of a disease or condition is detected or suspected, and for a length of time necessary for the treatment of the disease. In some embodiments, the length required for treatment varies, and the treatment length is adjusted to suit the specific needs of each subject. For example, in specific embodiments, a compound described herein or a formulation containing the compound is administered for at least 2 weeks, about 1 month to about 5 years.

EXAMPLES

I. Chemical Synthesis

[00170] In some embodiments, the compounds that modulate IRE1 mediated signaling disclosed herein are synthesized according to the following examples. The examples are intended to illustrate but not limit the disclosed embodiments.

Example 1A: Synthesis of tert-butyl ((1r,4r)-4-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (1A)



Step 1: 6-bromoquinazolin-2-amine (1A-2)

[00171] To a solution of 5-bromo-2-fluorobenzaldehyde (20.0 g, 98.5 mmol) in DMA (700 mL) was added guanidine-carbonic acid (26.6 g, 147.7 mmol). The mixture was stirred at 160°C for 0.5 h, cooled to rt and concentrated. The residue was diluted with H_2O (300 mL) and extracted with ethyl acetate (200 mL \times 3). The combined organic layers were washed with brine (100 mL \times 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was washed with DCM (300 mL) to get compound **1A-2** (4.0 g, crude).

Step 2: 6-bromo-2-iodoquinazoline (1A-3)

[00172] To a solution of compound **1A-2** (2.0 g, 8.9 mmol) in THF (20.0 mL) under N_2 were added of isoamyl nitrite (3.1 g, 26.8 mmol, 3.6 mL), diiodomethane (11.9 g, 44.7 mmol, 3.6 mL) and CuI (1.7 g, 8.9 mmol). The mixture was stirred at 80°C for 2 h, cooled to rt, quenched by addition of ice water (100 mL), and extracted with ethyl acetate (100 mL \times 3). The combined organic layers were washed with brine (100 mL \times 3), dried over anhydrous Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (SiO_2) to afford compound **1A-3** (2.1 g, crude).

Step 3: 1-tert-butyl ((1r, 4r)-4-((6-bromoquinazolin-2-yl)amino)cyclohexyl)carbamate (1A-4)

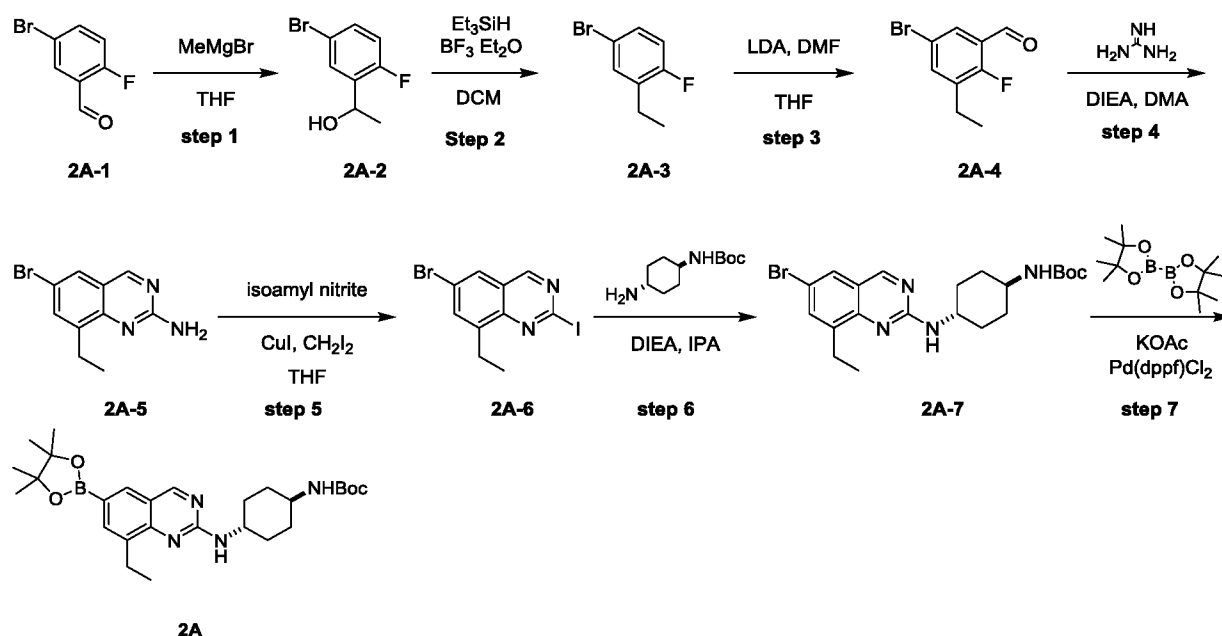
[00173] To a solution of compound **1A-3** (4.0 g, 11.9 mmol) in IPA (120.0 mL) was added DIEA (4.6 g, 35.8 mmol, 6.2 mL) and tert-butyl ((1r, 4r)-4-aminocyclohexyl)carbamate (7.6 g, 35.8 mmol). The mixture was stirred at 80°C for 12 h, cooled to rt and filtered. The collected solid was washed with Dichloromethane / Methanol (10/1, 60 mL). The combined filtrate was concentrated to give a residue which was purified by column chromatography (SiO_2) to afford compound **1A-4** (3.6 g, 6.8 mmol, 57.2% yield). $\text{M}+\text{H}^+ = 421.1$ (LCMS); ^1H NMR (CHLOROFORM-*d*, 400MHz) δ 8.87 (s, 1H), 7.78 (d, $J = 1.8$ Hz, 1H), 7.71 (dd, $J = 2.0, 9.0$ Hz,

1H), 7.44 (d, $J = 9.2$ Hz, 1H), 5.19 (br d, $J = 7.9$ Hz, 1H), 4.43 (br s, 1H), 3.93 (br d, $J = 7.5$ Hz, 1H), 3.49 (br s, 1H), 2.27 - 2.00 (m, 4H), 1.46 (s, 9H), 1.40 - 1.29 (m, 4H)

Step 4: tert-butyl ((1r,4r)-4-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (1A)

[00174] A mixture of compound **1A-4** (2.0 g, 4.7 mmol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (1.3 g, 5.2 mmol), AcOK (1.4 g, 14.2 mmol) and Pd(dppf)Cl₂ (347 mg, 474.6 μ mol) in dioxane (50 mL) was degassed and purged with N₂ three times, and heated at 90°C for 12 h under N₂. The reaction was cooled to rt and concentrated to give a residue. The residue was purified by column chromatography (SiO₂) to afford compound **1A** (2.7 g, crude). $M+H^+ = 469.2$ (LCMS).

Example 2A: Synthesis of tert-butyl ((1r,4r)-4-((8-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (2A)



Step 1: 1-(5-bromo-2-fluorophenyl)ethan-1-ol (2A-2)

[00175] A solution of 5-bromo-2-fluorobenzaldehyde (55.0 g, 270.9 mmol) in THF (500.0 mL) was cooled to 0°C. Then MeMgBr (3 M, 94.8 mL) was added. The mixture was stirred at 0°C for 0.5 h, quenched with NH₄Cl (500 mL) and extracted with ethyl acetate (500 mL \times 3). The combined organic layers were washed with brine (500 mL \times 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂) to afford compound **2A-2** (46.0 g, crude).

Step 2: 4-bromo-2-ethyl-1-fluorobenzene (2A-3)

[00176] To a solution of compound **2A-2** (46.0 g, 210.0 mmol) and triethylsilane (48.8 g, 420.0 mmol, 66.9 mL) in DCM (500.0 mL) was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (59.6 g, 420.0 mmol, 51.8 mL) at 0°C. The mixture was stirred at 25°C for 2 h, concentrated, quenched by addition of Sat. NaHCO_3 (200 mL) at 0°C, and extracted with ethyl acetate (200 mL \times 3). The combined organic layers were washed with brine (200 mL \times 3), dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography (SiO_2) to afford compound **2A-3** (24.0 g, crude). ^1H NMR (CHCl_3 , 400MHz) δ 7.31 (dd, J = 2.2, 6.6 Hz, 1H), 7.27 - 7.21 (m, 1H), 6.87 (t, J = 9.2 Hz, 1H), 2.62 (q, J = 7.5 Hz, 2H), 1.20 (t, J = 7.6 Hz, 3H).

Step 3: 5-bromo-3-ethyl-2-fluorobenzaldehyde (2A-4)

[00177] To a solution of compound **2A-3** (24.0 g, 82.7 mmol) in THF (500 mL) was added LDA (2 M, 49.6 mL) at -78°C. The mixture was stirred at -78°C for 1 h. Then dimethyl formamide (7.8 g, 107.5 mmol, 8.3 mL) was added and stirred for 1 h at -78°C. The reaction mixture was quenched by addition of NH_4Cl (100 mL) and the resulting mixture was extracted with ethyl acetate (200 mL \times 3). The combined organic layers were washed with brine (100 mL \times 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2) to afford compound **2A-4** (13.0 g, crude). ^1H NMR (CDCl_3 , 400MHz) δ 10.30 (s, 1H), 7.81 (dd, J = 2.6, 5.7 Hz, 1H), 7.58 (dd, J = 2.6, 6.4 Hz, 1H), 2.73 (q, J = 7.6 Hz, 2H), 1.30 - 1.25 (m, 3H).

Step 4: 6-bromo-8-ethylquinazolin-2-amine (2A-5)

[00178] To a solution of carbonic acid-guanidine (3.5 g, 19.4 mmol) and DIEA (5.0 g, 38.9 mmol, 6.8 mL) in DMA (20 mL) was added a solution of compound **2A-4** (3.0 g, 12.98 mmol) in DMA (5 mL). The mixture was stirred at 160°C for 1 h, poured into ice water (30 mL) and extracted with ethyl acetate (40 mL \times 3). The combined organic layers were washed with brine (30 mL \times 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2) to afford compound **2A-5** (1.2 g, crude). ^1H NMR ($\text{DMSO}-d_6$, 400MHz) δ 9.03 (s, 1H), 7.85 (d, J = 2.4 Hz, 1H), 7.60 (d, J = 2.4 Hz, 1H), 6.94 (s, 2H), 2.98 - 2.88 (m, 2H), 1.22 - 1.17 (m, 3H).

Step 5: 6-bromo-8-ethyl-2-iodoquinazoline (2A-6)

[00179] To a mixture of compound **2A-5** (1.2 g, 4.76 mmol) and CH_2I_2 (6.3 g, 23.8 mmol, 1.92 mL) in tetrahydrofuran (24.0 mL) were added CuI (906 mg, 4.7 mmol) and isoamyl nitrite (1.6 g, 14.3 mmol, 2.0 mL). After the mixture was stirred at 80°C for 2 h under N_2 , $\text{NH}_3 \cdot \text{H}_2\text{O}$ (30 mL) was added. The resulting mixture was extracted with ethyl acetate (50 mL \times 3) and the combined organic layers were washed with brine (50 mL \times 3), dried over Na_2SO_4 , filtered and

concentrated. The residue was purified by column chromatography (SiO₂) to afford compound **2A-6** (400 mg, crude).

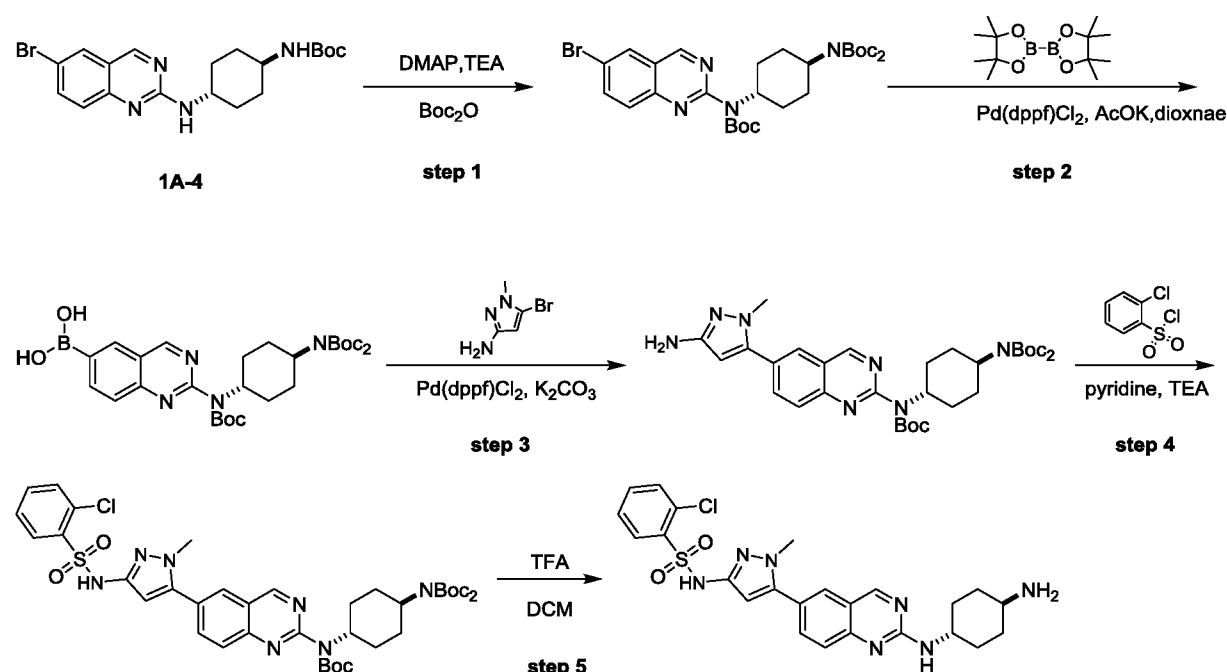
Step 6: tert-butyl ((1r,4r)-4-((6-bromo-8-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (2A-7)

[00180] To a mixture of compound **2A-6** (350 mg, 964.2 μ mol) and DIEA (373 mg, 2.8 mmol, 505.2 μ L) in isopropanol (10 mL) was added tert-butyl ((1r,4r)-4-aminocyclohexyl)carbamate (413 mg, 1.9 mmol). The mixture was stirred at 80°C for 12 h, cooled to rt and concentrated. The residue was purified by prep-TLC (SiO₂) to afford compound **2A-7** (350 mg, crude).

Step 7: tert-butyl ((1r,4r)-4-((8-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (2A)

[00181] To a mixture of compound **2A-7** (150 mg, 333.7 μ mol) and KOAc (98 mg, 1.0 mmol) in dioxane (2 mL) were added 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (101 mg, 400.5 μ mol) and Pd(dppf)Cl₂ (24 mg, 33.3 μ mol). The mixture was stirred at 90°C for 12 h under N₂, cooled to rt and concentrated. The residue was purified by prep-TLC (SiO₂) to afford compound **2A** (100 mg, crude).

Example 1: Synthesis of N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-1-methyl-1H-pyrazol-3-yl)-2-chlorobenzenesulfonamide (1)



Step 1:

[00182] To a solution of tert-butyl ((1r,4r)-4-((6-bromoquinazolin-2-yl)amino)cyclohexyl)carbamate (700 mg, 1.6 mmol) in Boc₂O (46.0 mL) was added TEA (505

mg, 5.0 mmol, 690.9 uL) and DMAP (406 mg, 3.3 mmol). The mixture was stirred at 100°C for 12h, cooled to rt and diluted with DCM (50 mL). Silica gel was added and the resulting suspension was concentrated to give residue which was purified by column chromatography (SiO₂) to afford tert-butyl ((1r,4r)-4-(bis(tert-butoxycarbonyl)amino)cyclohexyl)(6-bromoquinazolin-2-yl)carbamate (340 mg, 437.6 umol, 43.9% yield). ¹H NMR (CHLOROFORM-d, 400MHz): δ 9.25 (s, 1H), 8.06 (d, J = 1.8 Hz, 1H), 7.96 - 7.91 (m, 1H), 7.86 - 7.81 (m, 1H), 4.25 (br t, J = 11.6 Hz, 1H), 3.89 (br t, J = 11.8 Hz, 1H), 2.08 - 1.93 (m, 4H), 1.87 - 1.73 (m, 4H), 1.46 (s, 18H), 1.41 (s, 9H).

Step 2:

[00183] A mixture of tert-butyl ((1r,4r)-4-(bis(tert-butoxycarbonyl)amino)cyclohexyl)(6-bromoquinazolin-2-yl)carbamate (340 mg, 547.0 umol), 4,4,5,5-tetramethyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3,2-dioxaborolane (153 mg, 601.7 umol), AcOK (161 mg, 1.6 mmol) and Pd(dppf)Cl₂ (40 mg, 54.7 umol) in dioxane (5.0 mL) was degassed and purged with N₂ three times, and then the mixture was stirred at 90°C for 12 h under N₂. The reaction was cooled to rt and concentrated to give a residue which was purified by column chromatography (SiO₂) to afford (2-(((1r,4r)-4-(bis(tert-butoxycarbonyl)amino)cyclohexyl)(tert-butoxycarbonyl) amino)quinazolin-6-yl)boronic acid (400 mg, 504.7 umol, 92.2% yield).

Step 3:

[00184] A mixture of (2-(((1r,4r)-4-(bis(tert-butoxycarbonyl)amino)cyclohexyl)(tert-butoxycarbonyl) amino)quinazolin-6-yl)boronic acid (330 mg, 562.6 umol), 5-bromo-1-methyl-1H-pyrazol-3-amine (119 mg, 675.2 umol), K₂CO₃ (233 mg, 1.6 mmol) and Pd(dppf)Cl₂ (41mg, 56.2 umol) in dioxane (15.0 mL) and H₂O (1.5 mL) was degassed and purged with N₂ three times, and the mixture was stirred at 90°C for 12 h under N₂. The reaction was concentrated and the residue was purified by column chromatography (SiO₂) to afford tert-butyl (6-(3-amino-1-methyl-1H-pyrazol-5-yl)quinazolin-2-yl)((1r,4r)-4-(bis(tert-butoxycarbonyl)amino)cyclohexyl)carbamate (120 mg, crude).

Step 4:

[00185] To a solution of tert-butyl (6-(3-amino-1-methyl-1H-pyrazol-5-yl)quinazolin-2-yl)((1r,4r)-4-(bis(tert-butoxycarbonyl)amino)cyclohexyl)carbamate (60 mg, 94.0 umol) in pyridine (2.0 mL) was added TEA (29 mg, 282.2 umol, 39.1 uL) and 2-chlorobenzenesulfonyl chloride (50 mg, 235.2 umol, 32.0 uL). The mixture was stirred at 25°C for 12 h and concentrated. The residue was purified by prep-TLC (SiO₂) to afford tert-butyl ((1r,4r)-4-(bis(tert-butoxycarbonyl)amino)cyclohexyl)(6-(3-((2-chloro phenyl)sulfonamido)-1-methyl-1H-pyrazol-5-yl)quinazolin-2-yl)carbamate (80 mg, crude).

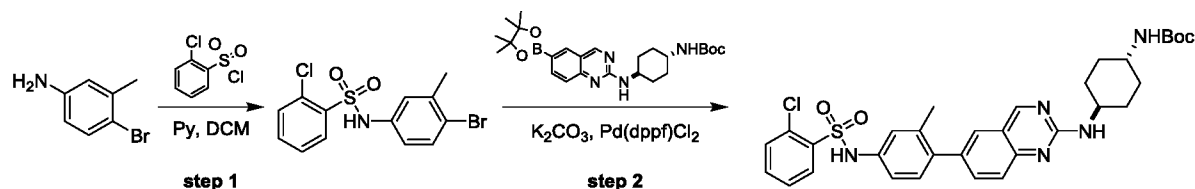
Step 5:

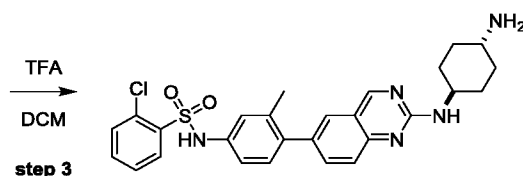
[00186] To a solution of tert-butyl (((1*r*,4*r*)-4-(bis(tert-butoxycarbonyl)amino)cyclohexyl)(6-(3-((2-chloro phenyl)sulfonamido)-1-methyl-1*H*-pyrazol-5-yl)quinazolin-2-yl)carbamate (80 mg, 98.4 μ mol) in DCM (2.0 mL) was added TFA (1.0 mL). The mixture was stirred at 25°C for 15 min and concentrated to give a residue. The residue was dissolved in MeOH (2.0 mL), basified with $\text{NH}_3 \cdot \text{H}_2\text{O}$ (0.02 mL, 25% solution) and concentrated to give a residue. The residue was purified by prep-HPLC to afford N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)quinazolin-6-yl)-1-methyl-1*H*-pyrazol-3-yl)-2-chlorobenzenesulfonamide (36.1 mg, 61.5 μ mol, 62.4% yield, FA). $\text{M}+\text{H}^+ = 512.3$ (LCMS). ^1H NMR (METHANOL- d_4 , 400MHz): δ 9.05 (s, 1H), 8.33 (br s, 1H), 8.07 (dd, $J = 1.1, 7.9$ Hz, 1H), 7.77 (d, $J = 1.8$ Hz, 1H), 7.68 (dd, $J = 2.0, 8.8$ Hz, 1H), 7.60 - 7.50 (m, 3H), 7.42 (ddd, $J = 1.9, 6.6, 8.1$ Hz, 1H), 6.11 (s, 1H), 4.01 - 3.88 (m, 1H), 3.70 (s, 3H), 3.13 (tdd, $J = 4.0, 7.8, 11.6$ Hz, 1H), 2.26 - 2.05 (m, 4H), 1.66 - 1.39 (m, 4H).

[00187] The following compound was synthesized according to procedures described in example 1 above for the preparation of compound 1.

Comp ID	Structure	Chemical Name	Mass ($\text{M}+\text{H}^+$)	^1H NMR (MeOD, 400 MHz)
6		N-(5-(2-(((1 <i>r</i> ,4 <i>r</i>)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-1-methyl-1 <i>H</i> -pyrazol-3-yl)-2-chlorobenzenesulfonamide, formate salt	Calc'd for $\text{C}_{26}\text{H}_{31}\text{Cl}$ $\text{N}_7\text{O}_2\text{S}$: 540.2; Found: 540.2	δ 9.01 (s, 1H), 8.48 (br s, 1H), 8.09 (dd, $J = 1.1, 7.9$ Hz, 1H), 7.63 - 7.49 (m, 4H), 7.43 (dt, $J = 1.9, 7.3$ Hz, 1H), 6.10 (s, 1H), 4.04 - 3.91 (m, 1H), 3.71 (s, 3H), 3.16 (tt, $J = 3.6, 11.4$ Hz, 1H), 3.05 (q, $J = 7.5$ Hz, 2H), 2.30 (br d, $J = 11.2$ Hz, 2H), 2.14 (br d, $J = 11.7$ Hz, 2H), 1.69 - 1.41 (m, 4H), 1.31 (t, $J = 7.5$ Hz, 3H)

Example 2: Synthesis of N-(4-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)quinazolin-6-yl)-3-methylphenyl)-2-chlorobenzenesulfonamide (2)



**Step 1:**

[00188] To a solution of 2-chlorobenzenesulfonyl chloride (170 mg, 806.2 μmol , 109.7 μL) in DCM (2.0 mL) was added pyridine (63 mg, 806.2 μmol , 65.0 μL) and 4-bromo-3-methylaniline (100 mg, 537.4 μmol). The mixture was stirred at 45°C for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (SiO_2) to afford N-(4-bromo-3-methylphenyl)-2-chlorobenzenesulfonamide (190 mg, 447.8 μmol , 83.3% yield).

Step 2:

[00189] A mixture of N-(4-bromo-3-methylphenyl)-2-chlorobenzenesulfonamide (50 mg, 138.6 μmol), tert-butyl ((1r,4r)-4-((6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (64 mg, 138.6 μmol), K_2CO_3 (57 mg, 415.9 μmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (10 mg, 13.8 μmol) in dioxane (2.0 mL) and H_2O (0.2 mL) was degassed and purged with N_2 three times, and then the mixture was stirred at 90°C for 12 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (SiO_2) to afford tert-butyl ((1r,4r)-4-((6-(4-(2-chlorophenylsulfonamido)-2-methylphenyl)quinazolin-2-yl)amino)cyclohexyl)carbamate (30 mg, crude). $\text{M}+\text{H}^+ = 622.2$ (LCMS).

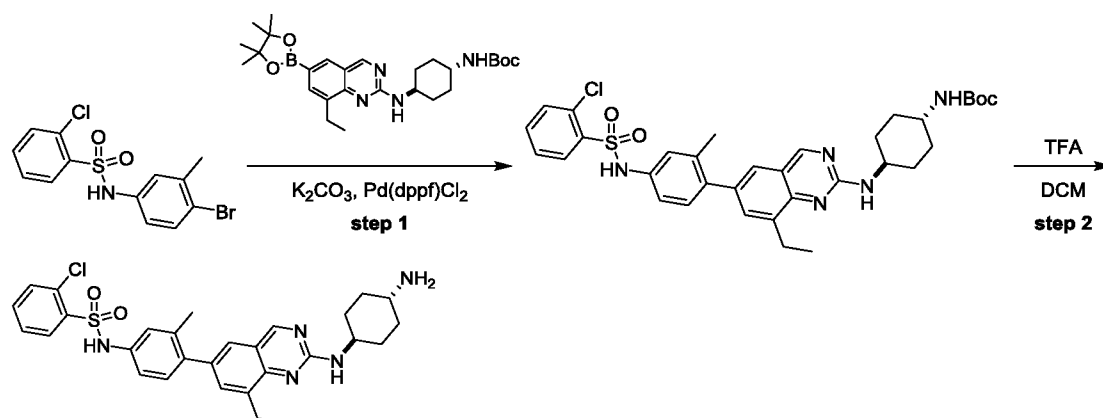
Step 3:

[00190] To a solution of tert-butyl ((1r,4r)-4-((6-(4-(2-chlorophenylsulfonamido)-2-methylphenyl)quinazolin-2-yl)amino)cyclohexyl)carbamate (30 mg, 48.2 μmol) in DCM (2.0 mL) was added TFA (1.0 mL). The mixture was stirred at 25°C for 0.5 h. The reaction mixture was concentrated under reduced pressure. The residue was added dichloromethane (2.0 mL) and $\text{NH}_3 \cdot \text{H}_2\text{O}$ (25% solution) to pH 7, concentrated under reduced pressure again. The residue was purified by prep-HPLC to give N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-3-methylphenyl)-2-chlorobenzenesulfonamide (6.9 mg, 12.1 μmol , 25.2% yield, FA). $\text{M}+\text{H}^+ = 522.0$ (LCMS); ^1H NMR (400MHz, $\text{METHANOL}-d_4$) δ 9.04 (s, 1H), 8.57 (s, 1H), 8.23 - 8.04 (m, 1H), 7.66 - 7.53 (m, 5H), 7.50 - 7.43 (m, 1H), 7.14 - 7.04 (m, 3H), 4.10 - 3.87 (m, 1H), 3.16 (tt, $J = 3.9, 11.6$ Hz, 1H), 2.25 (br d, $J = 10.5$ Hz, 2H), 2.20 (s, 3H), 2.14 (br d, $J = 12.1$ Hz, 2H), 1.70 - 1.39 (m, 4H).

[00191] The following compound was synthesized according to procedures described in example 2 above for the preparation of compound 2.

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
5		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-4-methylpyridin-2-yl)-2-chlorobenzenesulfonamide, formate salt	Calc'd for C ₂₆ H ₂₈ Cl N ₆ O ₂ S: 523.2; Found: 523.2	δ 9.05 (s, 1H), 8.52 (br s, 1H), 8.22 (d, J = 7.5 Hz, 1H), 7.82 (s, 1H), 7.69 (d, J = 1.8 Hz, 1H), 7.67 - 7.62 (m, 1H), 7.61 - 7.55 (m, 1H), 7.55 - 7.52 (m, 1H), 7.50 - 7.45 (m, 1H), 7.38 - 7.30 (m, 1H), 7.15 (s, 1H), 4.06 - 3.90 (m, 1H), 3.24 - 3.05 (m, 1H), 2.31 - 2.20 (m, 5H), 2.12 (br d, J = 12.3 Hz, 2H), 1.69 - 1.40 (m, 4H)

Example 3: Synthesis of N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-chlorobenzenesulfonamide (3)



Step 1:

[00192] A mixture of N-(4-bromo-3-methylphenyl)-2-chlorobenzenesulfonamide (29 mg, 80.5 μmol), tert-butyl ((1r,4r)-4-((8-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (40 mg, 80.5 μmol), K₂CO₃ (16 mg, 120.8 μmol), Pd(dppf)Cl₂ (5 mg, 8.0 μmol) in dioxane (2.0 mL) and water (0.2 mL) was degassed and purged with N₂ three times. The mixture was stirred at 90°C for 12 h under N₂, cooled to rt, and concentrated. The residue was purified by prep-TLC (SiO₂) to give tert-butyl ((1r,4r)-4-((6-(4-(2-chlorophenylsulfonamido)-2-methylphenyl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (47 mg, 58.6 μmol, 72.7% yield). M+H⁺ = 650.3 (LCMS).

Step 2:

[00193] To a solution of tert-butyl ((1r,4r)-4-((6-(4-(2-chlorophenylsulfonamido)-2-methylphenyl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (47 mg, 72.2 μmol) in

DCM (2.0 mL) was added TFA (1.0 mL). The resulting mixture was stirred at 15°C for 0.5 h and concentrated. The residue was dissolved in MeOH (2.0 mL), basified pH to 8 with $\text{NH}_3 \cdot \text{H}_2\text{O}$ (25% solution) and purified by prep-HPLC to give N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-chlorobenzenesulfonamide (10.2 mg, 17.2 μmol , 23.8% yield, FA). $\text{M}+\text{H}^+ = 550.2$ (LCMS); ^1H NMR (400MHz, $\text{METHANOL}-d_4$): δ 8.95 (d, $J = 4.2$ Hz, 1H), 8.39 (br s, 1H), 8.09 (d, $J = 7.7$ Hz, 1H), 7.60 - 7.51 (m, 2H), 7.47 - 7.37 (m, 3H), 7.11 - 7.01 (m, 3H), 4.01 - 3.91 (m, 1H), 3.17 (tt, $J = 3.7, 11.4$ Hz, 1H), 3.04 (q, $J = 7.5$ Hz, 2H), 2.31 (br d, $J = 11.9$ Hz, 2H), 2.19 - 2.10 (m, 5H), 1.66 - 1.54 (m, 2H), 1.54 - 1.43 (m, 2H), 1.34 - 1.27 (m, 3H).

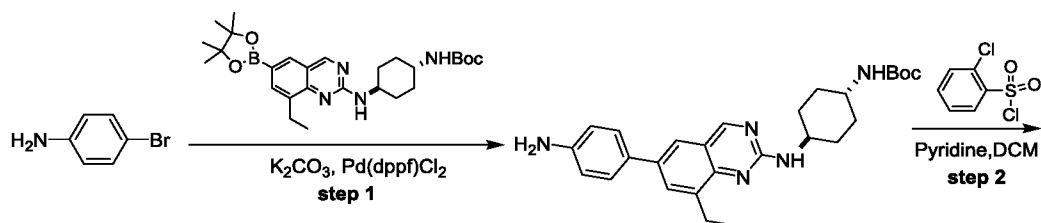
[00194] The following compounds were synthesized according to procedures described in example 3 above for the preparation of compound 3.

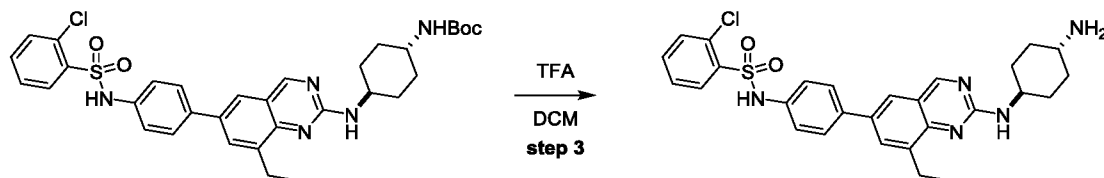
Comp ID	Structure	Chemical Name	Mass ($\text{M}+\text{H}^+$)	^1H NMR (MeOD, 400 MHz)
4		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-methylpyridin-2-yl)-2-chlorobenzenesulfonamide, formate salt	Calc'd for $\text{C}_{28}\text{H}_{32}\text{ClN}_6\text{O}_2\text{S}$: 551.2; Found: 551.2	δ 9.00 (s, 1 H), 8.49 (br s, 1 H), 8.22 (d, $J = 7.34$ Hz, 1 H), 7.80 (s, 1 H), 7.45 - 7.58 (m, 5 H), 7.14 (s, 1 H), 3.91 - 4.03 (m, 1 H), 3.10 - 3.21 (m, 1 H), 3.06 (q, $J = 7.66$ Hz, 2 H), 2.31 (br d, $J = 13.20$ Hz, 2 H), 2.25 (s, 3 H), 2.13 (br d, $J = 12.23$ Hz, 2 H), 1.44 - 1.64 (m, 4 H), 1.31 (t, $J = 7.58$ Hz, 3 H)
14		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-(trifluoromethyl)phenyl)-2-chlorobenzenesulfonamide, formate salt	Calc'd for $\text{C}_{29}\text{H}_{30}\text{ClF}_3\text{N}_5\text{O}_2\text{S}$: 604.2; Found: 604.2	δ 8.95 (br s, 1H), 8.55 (br s, 1H), 8.15 (d, $J = 7.7$ Hz, 1H), 7.63 - 7.53 (m, 3H), 7.48 (br dd, $J = 4.3, 7.2$ Hz, 1H), 7.41 (br d, $J = 7.9$ Hz, 3H), 7.26 (br d, $J = 8.4$ Hz, 1H), 4.02 - 3.92 (m, 1H), 3.21 - 3.11 (m, 1H), 3.03 (q, $J = 7.3$ Hz, 2H), 2.31 (br d, $J = 11.7$ Hz, 2H), 2.14 (br d, $J = 11.5$ Hz, 2H), 1.65 - 1.55 (m, 2H), 1.54 - 1.43 (m, 2H), 1.29 (t, $J = 7.5$ Hz, 3H).
16		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-methylpyridin-2-yl)-2-chlorobenzenesulfonamide, formate salt	Calc'd for $\text{C}_{28}\text{H}_{32}\text{ClN}_6\text{O}_2\text{S}$: 551.2;	δ 9.02 (s, 1H), 8.56 (br s, 1H), 8.33 - 8.19 (m, 1H), 7.69 (d, $J = 8.9$ Hz, 1H), 7.61 - 7.44 (m,

		yl)-6-methylpyridin-2-yl)-2-chlorobenzenesulfonamide, formate salt	Found: 551.1	5H), 7.22 (br d, $J = 8.8$ Hz, 1H), 4.08 - 3.89 (m, 1H), 3.25 - 3.15 (m, 1H), 3.09 (q, $J = 7.5$ Hz, 2H), 2.40 (s, 3H), 2.33 (br d, $J = 11.5$ Hz, 2H), 2.17 (br d, $J = 11.5$ Hz, 2H), 1.70 - 1.46 (m, 4H), 1.34 (t, $J = 7.5$ Hz, 3H).
17		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-chlorophenyl)-2-chlorobenzenesulfonamide, formate salt	Calc'd for $C_{28}H_{30}Cl_2N_5O_2S$: 570.1; Found: 570.1	δ 8.97 (s, 1H), 8.56 (br s, 1H), 8.14 (d, $J = 8.4$ Hz, 1H), 7.63 - 7.56 (m, 2H), 7.56 - 7.52 (m, 2H), 7.48 (ddd, $J = 3.3, 5.3, 8.2$ Hz, 1H), 7.33 - 7.23 (m, 2H), 7.17 (dd, $J = 2.2, 8.4$ Hz, 1H), 4.05 - 3.90 (m, 1H), 3.20 - 3.10 (m, 1H), 3.04 (q, $J = 7.4$ Hz, 2H), 2.31 (br d, $J = 11.7$ Hz, 2H), 2.13 (br d, $J = 11.9$ Hz, 2H), 1.65 - 1.54 (m, 2H), 1.54 - 1.43 (m, 2H), 1.31 (t, $J = 7.5$ Hz, 3H)
19		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methoxyphenyl)-2-chlorobenzenesulfonamide, formate salt	Calc'd for $C_{29}H_{33}ClN_5O_3S$: 566.2; Found: 566.2	δ 8.94 (s, 1 H), 8.51 (br s, 1 H), 8.10 - 8.18 (m, 1 H), 7.63 (d, $J = 1.76$ Hz, 1 H), 7.54 - 7.60 (m, 3 H), 7.46 (ddd, $J = 8.16, 5.84, 2.76$ Hz, 1 H), 7.18 (d, $J = 8.16$ Hz, 1 H), 6.90 (d, $J = 1.98$ Hz, 1 H), 6.81 (dd, $J = 8.16, 1.98$ Hz, 1 H), 3.91 - 4.04 (m, 1 H), 3.73 (s, 3 H), 3.12 - 3.23 (m, 1 H), 3.03 (q, $J = 7.57$ Hz, 2 H), 2.31 (br d, $J = 11.03$ Hz, 2 H), 2.14 (br d, $J = 12.13$ Hz, 2 H), 1.43 - 1.67 (m, 4 H), 1.30 (t, $J = 7.39$ Hz, 3 H)
20		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-methylpyridin-3-yl)-2-chlorobenzenesulfonamide, formate salt	Calc'd for $C_{28}H_{32}ClN_6O_2S$: 551.2; Found: 551.2	δ 9.00 (s, 1 H), 8.53 (br s, 1 H), 8.23 (s, 1 H), 8.14 (d, $J = 7.94$ Hz, 1 H), 7.57 - 7.64 (m, 4 H), 7.55 (s, 1 H), 7.45 - 7.51 (m, 1 H), 3.90 - 4.05 (m, 1 H), 3.16 (br t, $J =$

		chlorobenzenesulfo namide, formate salt		11.36 Hz, 1 H), 3.07 (q, $J = 7.64$ Hz, 2 H), 2.26 - 2.36 (m, 5 H), 2.14 (br d, $J = 10.80$ Hz, 2 H), 1.44 - 1.68 (m, 4 H), 1.32 (t, $J = 7.50$ Hz, 3 H)
21		N-(4-(2-(((1r,4r)-4- aminocyclohexyl)a mino)-8- ethylquinazolin-6- yl)-2-f-luoro-5- methylphenyl)-2- chlorobenzenesulfo namide, formate salt	Calc'd for $C_{29}H_{33}ClF$ N_5O_3S : 568.2; Found: 568.2	δ 8.96 (s, 1H), 8.51 (br s, 1H), 8.01 (d, $J = 7.7$ Hz, 1H), 7.66 - 7.50 (m, 2H), 7.49 - 7.37 (m, 3H), 7.30 (d, $J = 7.9$ Hz, 1H), 6.99 - 6.88 (m, 1H), 4.03 - 3.90 (m, 1H), 3.17 (br t, $J = 11.5$ Hz, 1H), 3.04 (q, $J = 7.4$ Hz, 2H), 2.31 (br d, $J =$ 11.5 Hz, 2H), 2.15 (沒, 5H), 1.67 - 1.55 (m, 2H), 1.54 - 1.43 (m, 2H), 1.30 (t, $J = 7.4$ Hz, 3H)
22		N-(4-(2-(((1r,4r)-4- aminocyclohexyl)a mino)-8- ethylquinazolin -6- yl)-2,3- dimethylphenyl)-2- chlorobenzenesulfo namide, formate salt	Calc'd for $C_{30}H_{35}Cl$ N_5O_2S : 564.2; Found: 564.2	δ 8.97 (s, 1 H), 8.55 (br s, 1 H), 7.88 (dd, $J =$ 8.31, 1.47 Hz, 1 H), 7.64 - 7.68 (m, 1 H), 7.56 - 7.61 (m, 1 H), 7.38 - 7.44 (m, 3 H), 6.90 - 6.93 (m, 1 H), 6.82 - 6.88 (m, 1 H), 3.93 - 4.02 (m, 1 H), 3.12 - 3.21 (m, 1 H), 3.06 (q, $J = 7.34$ Hz, 2 H), 2.32 (br d, $J = 11.74$ Hz, 2 H), 2.26 (s, 3 H), 2.14 (m, 5 H), 1.44 - 1.67 (m, 4 H), 1.31 (t, J $= 7.34$ Hz, 3 H)

**Example 4: Synthesis of N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylq-uinazolin-6-y
l)phenyl)-2-chlorobenzenesulfonamide (18)**



**Step 1:**

[00195] A mixture of 4-bromoaniline (33 mg, 193.3 μmol), tert-butyl ((1r,4r)-4-((8-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (80 mg, 161.1 μmol), K_2CO_3 (33 mg, 241.7 μmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (11 mg, 16.1 μmol) in dioxane (2.0 mL) and water (0.2 mL) was degassed and purged with N_2 . The resulting mixture was stirred at 90°C for 12 h under N_2 . Additional 4-bromoaniline (13 mg) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (10 mg) were added, and the mixture was stirred at 90°C for 4 h, cooled to rt and concentrated. The residue was purified by prep-TLC (SiO_2) to give tert-butyl ((1r,4r)-4-((6-(4-aminophenyl)-8-ethylquinazolin-2-yl)amino)-cyclohexyl)carbamate (40 mg, 65.2 μmol , 40% yield). $\text{M}+\text{H}^+ = 462.3$ (LCMS).

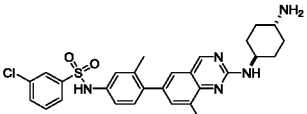
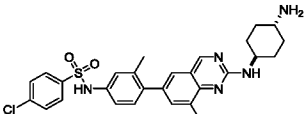
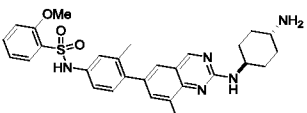
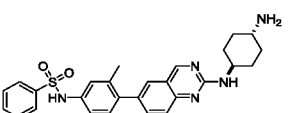
Step 2:

[00196] To a solution of tert-butyl ((1r,4r)-4-((6-(4-aminophenyl)-8-ethylquinazolin-2-yl)amino)-cyclohexyl)carbamate (40 mg, 86.6 μmol) in DCM (2.0 mL) was added pyridine (20 mg, 259.9 μmol , 20.9 μL) and 2-chlorobenzenesulfonyl chloride (18 mg, 86.6 μmol , 11.8 μL). The mixture was stirred at 45°C for 12 h, cooled to rt and concentrated to give tert-butyl ((1r,4r)-4-((6-(4-(2-chlorophenylsulfonamido)phenyl)-8-ethylquinazolin-2-yl)amino)-cyclohexyl)carbamate (50 mg, crude).

Step 3:

[00197] To a solution of tert-butyl ((1r,4r)-4-((6-(4-(2-chlorophenylsulfonamido)phenyl)-8-ethylquinazolin-2-yl)amino)-cyclohexyl)carbamate (50 mg, 78.5 μmol) in DCM (2.0 mL) was added TFA (1.0 mL). The mixture was stirred at 15°C for 0.5 h and concentrated. The residue was dissolved in MeOH (2.0 mL), basified pH to 8 with $\text{NH}_3\cdot\text{H}_2\text{O}$ (25% solution) and purified by prep-HPLC to give N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)phenyl)-2-chlorobenzenesulfonamide (8.7 mg, 14.9 μmol , 18.9% yield, FA). $\text{M}+\text{H}^+ = 536.2$ (LCMS); ^1H NMR (400MHz, $\text{METHANOL}-d_4$) δ 9.00 (s, 1H), 8.50 (br s, 1H), 8.12 - 8.03 (m, 1H), 7.74 (dd, $J = 1.9, 16.2$ Hz, 2H), 7.60 - 7.48 (m, 4H), 7.47 - 7.38 (m, 1H), 7.24 (d, $J = 8.6$ Hz, 2H), 4.02 - 3.92 (m, 1H), 3.17 (tt, $J = 3.9, 11.5$ Hz, 1H), 3.07 (q, $J = 7.4$ Hz, 2H), 2.31 (br d, $J = 11.9$ Hz, 2H), 2.14 (br d, $J = 11.7$ Hz, 2H), 1.67 - 1.55 (m, 2H), 1.54 - 1.42 (m, 2H), 1.33 (t, $J = 7.5$ Hz, 3H). The following compounds were synthesized according to procedures described in example 4 above for the preparation of compound 18.

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
7		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-(trifluoromethyl)benzenesulfonamide, formate salt	Calc'd for C ₃₀ H ₃₃ F ₃ N ₅ O ₂ S: 584.2; Found: 584.2	δ 8.96 (s, 1H), 8.53 (br s, 1H), 8.18 - 8.11 (m, 1H), 7.97 - 7.90 (m, 1H), 7.80 - 7.68 (m, 2H), 7.43 (d, <i>J</i> = 6.2 Hz, 2H), 7.15 - 7.08 (m, 1H), 7.07 - 6.97 (m, 2H), 4.05 - 3.90 (m, 1H), 3.16 (tt, <i>J</i> = 3.8, 11.5 Hz, 1H), 3.05 (q, <i>J</i> = 7.5 Hz, 2H), 2.31 (br d, <i>J</i> = 11.7 Hz, 2H), 2.21 - 2.08 (m, 5H), 1.68 - 1.40 (m, 4H), 1.30 (t, <i>J</i> = 7.5 Hz, 3H)
8		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-(trifluoromethoxy)benzenesulfonamide, formate salt	Calc'd for C ₃₀ H ₃₃ F ₃ N ₅ O ₃ S: 600.2; Found: 600.2	δ 8.95 (s, 1H), 8.57 (br s, 1H), 8.02 (dd, <i>J</i> = 1.7, 7.8 Hz, 1H), 7.73 - 7.62 (m, 1H), 7.52 - 7.34 (m, 4H), 7.12 - 6.95 (m, 3H), 4.03 - 3.88 (m, 1H), 3.20 - 3.09 (m, 1H), 3.04 (q, <i>J</i> = 7.5 Hz, 2H), 2.30 (br d, <i>J</i> = 11.7 Hz, 2H), 2.19 - 2.06 (m, 5H), 1.65 - 1.40 (m, 4H), 1.30 (t, <i>J</i> = 7.4 Hz, 3H)
9		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2,5-dichlorobenzenesulfonamide, formate salt	Calc'd for C ₂₉ H ₃₂ Cl ₂ N ₅ O ₃ S: 584.2; Found: 584.1	δ 8.95 (s, 1H), 8.56 (br s, 1H), 8.07 - 8.00 (m, 1H), 7.59 - 7.53 (m, 2H), 7.47 - 7.39 (m, 2H), 7.14 - 7.00 (m, 3H), 4.02 - 3.89 (m, 1H), 3.18 - 3.08 (m, 1H), 3.04 (q, <i>J</i> = 7.5 Hz, 2H), 2.35 - 2.25 (m, 2H), 2.19 (s, 3H), 2.12 (br d, <i>J</i> = 11.9 Hz, 2H), 1.64 - 1.40 (m, 4H), 1.30 (t, <i>J</i> = 7.5 Hz, 3H)
10		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-fluorobenzenesulfonamide, formate salt	Calc'd for C ₂₉ H ₃₃ FN ₅ O ₃ S: 534.2; Found: 534.1	δ 8.96 (s, 1 H), 8.57 (br s, 1 H), 7.88 (td, <i>J</i> = 7.55, 1.65 Hz, 1 H), 7.46 - 7.72 (m, 2 H), 7.43 (dd, <i>J</i> = 8.71, 1.87 Hz, 2 H), 7.25 - 7.33 (m, 2 H), 7.03 - 7.10 (m, 2 H), 3.91 - 4.05 (m, 1 H), 3.10 - 3.20 (m, 1 H),

				2.98 - 3.09 (m, 2 H), 2.28 - 2.34 (m, 2 H), 2.07 - 2.22 (m, 5 H), 1.42 - 1.65 (m, 4 H), 1.28 - 1.37 (m, 3 H)
11		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-3-chlorobenzenesulfonamide, formate salt	Calc'd for $C_{29}H_{33}Cl$ N_5O_3S : 550.2; Found: 550.2	δ 8.98 (s, 1H), 8.56 (br s, 1H), 7.81 - 7.77 (m, 1H), 7.73 (d, $J = 7.9$ Hz, 1H), 7.60 (br d, $J = 7.9$ Hz, 1H), 7.52 (d, $J = 7.9$ Hz, 1H), 7.49 - 7.45 (m, 2H), 7.17 - 7.12 (m, 1H), 7.07 - 6.99 (m, 2H), 4.04 - 3.91 (m, 1H), 3.18 - 3.10 (m, 1H), 3.06 (q, $J = 7.5$ Hz, 2H), 2.32 (br d, $J = 10.5$ Hz, 2H), 2.21 (s, 3H), 2.13 (br d, $J = 12.3$ Hz, 2H), 1.64 - 1.42 (m, 4H), 1.32 (t, $J = 7.5$ Hz, 3H)
12		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-4-chlorobenzenesulfonamide, formate salt	Calc'd for $C_{29}H_{33}Cl$ N_5O_3S : 550.2; Found: 550.2	δ 8.98 (s, 1 H), 8.54 (br s, 1 H), 7.74 - 7.82 (m, 2 H), 7.53 (d, $J = 8.82$ Hz, 2 H), 7.44 - 7.48 (m, 2 H), 7.13 (d, $J = 7.72$ Hz, 1 H), 6.98 - 7.05 (m, 2 H), 3.92 - 4.04 (m, 1 H), 3.11 - 3.25 (m, 1 H), 3.01 - 3.09 (m, 2 H), 2.32 (br d, $J = 10.36$ Hz, 2 H), 2.20 (s, 3 H), 2.15 (br d, $J = 11.69$ Hz, 2 H), 1.43 - 1.66 (m, 4 H), 1.32 (t, $J = 7.39$ Hz, 3 H)
13		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-methoxybenzenesulfonamide, formate salt	Calc'd for $C_{30}H_{36}N_5$ O_3S : 546.2; Found: 546.2	δ 9.01 (br s, 1H), 7.84 (dd, $J = 1.5, 7.7$ Hz, 1H), 7.64 - 7.49 (m, 2H), 7.42 (d, $J = 7.0$ Hz, 2H), 7.15 (d, $J = 8.3$ Hz, 1H), 7.12 - 6.95 (m, 4H), 3.99 (m, 4H), 3.20 - 3.00 (m, 3H), 2.31 (m, 2H), 2.17 (m, 5H), 1.63 - 1.39 (m, 4H), 1.30 (t, $J = 7.5$ Hz, 3H)
15		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-methoxybenzenesulfonamide, formate salt	Calc'd for $C_{29}H_{34}N_5$ O_3S : 516.2;	δ 8.95 - 8.75 (m, 1H), 8.35 (br s, 1H), 7.76 - 7.70 (m, 2H), 7.51 - 7.44 (m, 1H), 7.43 -

		yl)-3-methylphenyl)benzenesulfonamide, formate salt	Found: 516.2	7.37 (m, 2H), 7.32 (dd, $J = 1.8, 14.6$ Hz, 2H), 7.02 - 6.97 (m, 1H), 6.95 - 6.90 (m, 2H), 3.89 (tdd, $J = 3.8, 7.5, 11.1$ Hz, 1H), 3.09 (br t, $J = 11.5$ Hz, 1H), 2.95 (q, $J = 7.5$ Hz, 2H), 2.22 (br d, $J = 11.1$ Hz, 2H), 2.14 - 2.01 (m, 5H), 1.63 - 1.30 (m, 4H), 1.21 (t, $J = 7.5$ Hz, 3H)
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[00198] Exemplary compounds were synthesized according to procedures described herein. For compounds that do not have a specific synthetic scheme described herein, such compounds can be routinely synthesized by a skilled artisan armed with the guidance presented herein and skill in the art.

Comp ID	Structure	Chemical Name	Mass ($M+H^+$)	1H NMR (MeOD, 400 MHz)
23		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-methylpyrimidin-2-yl)-2-chlorobenzenesulfonamide	Calc'd for $C_{27}H_{31}ClN_7O_2S$: 552.1; Found: 552.1	δ 9.01 (s, 1H), 8.58 (br s, 1H), 8.34 (br d, $J = 7.0$ Hz, 1H), 8.23 (br s, 1H), 7.61 - 7.46 (m, 5H), 4.05 - 3.89 (m, 1H), 3.26 - 3.13 (m, 1H), 3.07 (q, $J = 7.5$ Hz, 2H), 2.31 (m, 5H), 2.16 (br d, $J = 10.6$ Hz, 2H), 1.71 - 1.43 (m, 4H), 1.33 (t, $J = 7.5$ Hz, 3H)
24		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	Calc'd for $C_{28}H_{30}ClF$ N_5O_2S : 554.2; Found: 554.1	δ 9.03 (s, 1H), 8.56 (br s, 1H), 8.03 (dd, $J = 1.3, 7.9$ Hz, 1H), 7.80 (s, 2H), 7.68 - 7.54 (m, 2H), 7.54 - 7.34 (m, 4H), 4.05 - 3.91 (m, 1H), 3.25 - 3.15 (m, 1H), 3.09 (q, $J = 7.4$ Hz, 2H), 2.33 (br d, $J = 11.5$ Hz, 2H), 2.16 (br d, $J = 11.7$ Hz, 2H), 1.71 - 1.43 (m, 4H), 1.41 - 1.27 (m, 3H)
25		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)pyrazin-2-yl)-2-chlorobenzenesulfonamide	Calc'd for $C_{26}H_{29}ClN_7O_2S$: 538.2; Found: 538.1	δ 9.03 (s, 1H), 8.58 (br s, 2H), 8.33 - 8.23 (m, 2H), 8.13 (d, $J = 1.7$ Hz, 1H), 8.08 (d, $J = 1.8$ Hz, 1H), 7.57 - 7.44 (m, 3H), 4.06 - 3.91 (m, 3H)

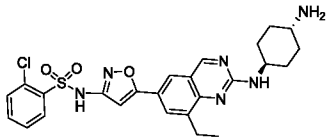
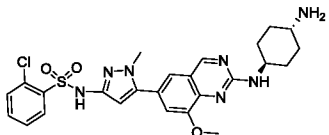
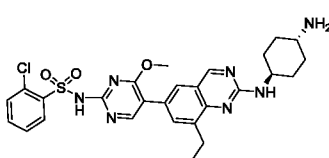
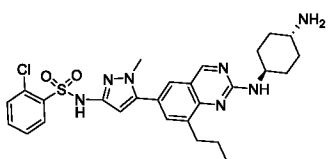
Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
		yl)-2-chlorobenzenesulfonamide		1H), 3.26 - 3.14 (m, 1H), 3.08 (q, <i>J</i> = 7.4 Hz, 2H), 2.32 (br d, <i>J</i> = 10.5 Hz, 2H), 2.16 (br d, <i>J</i> = 13.0 Hz, 2H), 1.73 - 1.44 (m, 4H), 1.38 - 1.27 (m, 3H)
26		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)phenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 508.1 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.06 (s, 1H), 8.41 (br s, 1H), 8.14 - 8.06 (m, 1H), 7.99 - 7.88 (m, 2H), 7.62 - 7.49 (m, 5H), 7.43 (m, 1H), 7.25 (d, <i>J</i> = 8.7 Hz, 2H), 4.02 - 3.89 (m, 1H), 3.21 - 3.10 (m, 1H), 2.23 (br d, <i>J</i> = 12.0 Hz, 2H), 2.12 (br d, <i>J</i> = 11.0 Hz, 2H), 1.67 - 1.55 (m, 2H), 1.53 - 1.41 (m, 2H)
27		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)pyridin-2-yl)-2-chlorobenzenesulfonamide	Calc'd for C ₂₇ H ₃₀ ClN ₆ O ₂ S: 537.2; Found: 537.1	δ 9.03 (s, 1 H), 8.55 (br s, 1 H), 8.40 (d, <i>J</i> = 2.45 Hz, 1 H), 8.05 - 8.15 (m, 3 H), 7.80 (d, <i>J</i> = 8.80 Hz, 1 H), 7.68 (dd, <i>J</i> = 8.56, 2.69 Hz, 1 H), 7.53 - 7.61 (m, 2 H), 7.41 - 7.50 (m, 1 H), 3.92 - 4.03 (m, 1 H), 3.12 - 3.21 (m, 1 H), 3.08 (q, <i>J</i> = 7.34 Hz, 2 H), 2.31 (br d, <i>J</i> = 11.25 Hz, 2 H), 2.14 (br d, <i>J</i> = 11.74 Hz, 2 H), 1.42 - 1.64 (m, 4 H), 1.34 (t, <i>J</i> = 7.58 Hz, 3 H)
28		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)pyridin-3-yl)-2-chlorobenzenesulfonamide	Calc'd for C ₂₇ H ₃₀ ClN ₆ O ₂ S: 537.2; Found: 537.2	δ 9.00 (s, 1H), 8.53 (br s, 1H), 8.30 (s, 1H), 8.23 (d, <i>J</i> = 7.7 Hz, 1H), 8.06 (dd, <i>J</i> = 2.0, 8.8 Hz, 1H), 7.76 (s, 2H), 7.55 - 7.44 (m, 3H), 7.29 (d, <i>J</i> = 9.0 Hz, 1H), 4.01 - 3.90 (m, 1H), 3.21 - 3.11 (m, 1H), 3.07 (q, <i>J</i> = 7.4 Hz, 2H), 2.30 (br d, <i>J</i> = 10.8 Hz, 2H), 2.13 (br d, <i>J</i> = 12.1 Hz, 2H), 1.66 - 1.40 (m, 4H), 1.33 (t, <i>J</i>

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
				= 7.5 Hz, 3H)
29		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-1H-pyrazol-3-yl)-2-chlorobenzenesulfonamide	Calc'd for C ₂₅ H ₂₉ ClN ₇ O ₂ S: 526.2; Found: 526.1	δ 8.99 (s, 1H), 8.09 (d, J = 7.3 Hz, 1H), 7.78 (br s, 2H), 7.62 - 7.52 (m, 2H), 7.43 (t, J = 7.2 Hz, 1H), 6.37 (s, 1H), 3.96 (m, 1H), 3.17 (m, 1H), 3.05 (q, J = 7.3 Hz, 2H), 2.30 (br d, J = 11.5 Hz, 2H), 2.14 (br d, J = 11.9 Hz, 2H), 1.65 - 1.54 (m, 2H), 1.53 - 1.43 (m, 2H), 1.33 (t, J = 7.5 Hz, 3H)
30		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-hydroxyquinazolin-6-yl)-3-methylphenyl)-2-chloro-N-methylbenzenesulfonamide	M+H ⁺ = 552.2	δ 8.99 (s, 1H), 8.51 (s, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.68 - 7.53 (m, 2H), 7.43 (t, J = 7.0 Hz, 1H), 7.22 - 7.06 (m, 4H), 7.01 (s, 1H), 4.09 (br s, 1H), 3.42 (s, 3H), 3.15 (br t, J = 11.6 Hz, 1H), 2.30 - 2.20 (m, 5H), 2.12 (br d, J = 12.7 Hz, 2H), 1.73 - 1.55 (m, 2H), 1.53 - 1.35 (m, 2H).
31		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-chloro-N-methylbenzenesulfonamide	M+H ⁺ = 564.2	δ 8.98 (s, 1H), 8.51 (br s, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.65 - 7.55 (m, 2H), 7.49 - 7.39 (m, 3H), 7.19 - 7.14 (m, 2H), 7.12 - 7.07 (m, 1H), 3.98 (br t, J = 11.0 Hz, 1H), 3.42 (d, J = 1.8 Hz, 3H), 3.17 (br t, J = 11.4 Hz, 1H), 3.06 (q, J = 7.3 Hz, 2H), 2.32 (br d, J = 11.8 Hz, 2H), 2.20 (s, 3H), 2.15 (br d, J = 12.3 Hz, 2H), 1.69 - 1.43 (m, 4H), 1.37 - 1.28 (m, 3H).
32		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)pyridazin-3-yl)-2-chlorobenzenesulfonamide	Calc'd for C ₂₆ H ₂₉ ClN ₇ O ₂ S: 538.2; Found: 538.2	δ 9.03 (s, 1H), 8.53 (br s, 1H), 8.24 - 8.18 (m, 2H), 8.15 (d, J = 1.8 Hz, 1H), 8.10 (d, J = 2.2 Hz, 1H), 7.95 (d, J = 10.1 Hz, 1H), 7.56 - 7.43 (m, 3H), 4.03 - 3.91 (m,

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
		chlorobenzenesulfonamide		1H), 3.23 - 3.11 (m, 1H), 3.06 (q, <i>J</i> = 7.5 Hz, 2H), 2.30 (br d, <i>J</i> = 10.1 Hz, 2H), 2.14 (br d, <i>J</i> = 11.8 Hz, 2H), 1.67 - 1.43 (m, 4H), 1.33 (t, <i>J</i> = 7.5 Hz, 3H)
33		N-(2-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)pyrimidin-5-yl)-2-chlorobenzenesulfonamide	Calc'd for C ₂₆ H ₂₉ ClN ₇ O ₂ S: 538.2; Found: 538.1	δ 9.06 (s, 1H), 8.61 (s, 2H), 8.55 - 8.43 (m, 3H), 8.20 - 8.12 (m, 1H), 7.66 - 7.54 (m, 2H), 7.54 - 7.45 (m, 1H), 4.06 - 3.95 (m, 1H), 3.24 - 3.14 (m, 1H), 3.09 (q, <i>J</i> = 7.5 Hz, 2H), 2.33 (br d, <i>J</i> = 12.5 Hz, 2H), 2.16 (br d, <i>J</i> = 10.8 Hz, 2H), 1.72 - 1.42 (m, 4H), 1.36 (t, <i>J</i> = 7.5 Hz, 3H)
34		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-ethylphenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 564.2	δ 8.95 (s, 1H), 8.56 (br s, 1H), 8.14 - 8.06 (m, 1H), 7.60 - 7.52 (m, 2H), 7.45 (m, 1H), 7.40 (d, <i>J</i> = 2.9 Hz, 2H), 7.11 (d, <i>J</i> = 1.8 Hz, 1H), 7.08 - 6.99 (m, 2H), 4.03 - 3.85 (m, 1H), 3.16 - 2.97 (m, 3H), 2.51 (q, <i>J</i> = 7.5 Hz, 2H), 2.30 (br d, <i>J</i> = 10.6 Hz, 2H), 2.12 (br d, <i>J</i> = 12.1 Hz, 2H), 1.62 - 1.42 (m, 4H), 1.30 (t, <i>J</i> = 7.5 Hz, 3H), 0.98 (t, <i>J</i> = 7.5 Hz, 3H)
35		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-fluorophenyl)-2-chlorobenzenesulfonamide	Calc'd for C ₂₈ H ₃₀ ClF N ₅ O ₂ S: 554.2; Found: 554.1	δ 8.97 (br d, <i>J</i> = 3.1 Hz, 1H), 8.55 (br s, 1H), 8.15 (br dd, <i>J</i> = 2.6, 7.5 Hz, 1H), 7.64 (br s, 2H), 7.57 (br d, <i>J</i> = 3.1 Hz, 2H), 7.51 - 7.43 (m, 1H), 7.37 (dt, <i>J</i> = 3.5, 8.6 Hz, 1H), 7.07 - 6.97 (m, 2H), 4.02 - 3.90 (m, 1H), 3.20 - 3.11 (m, 1H), 3.04 (br dd, <i>J</i> = 3.1, 7.3 Hz, 2H), 2.30 (br d, <i>J</i> = 11.2 Hz, 2H), 2.13 (br d, <i>J</i> = 11.2 Hz,

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
				2H), 1.66 - 1.40 (m, 4H), 1.31 (dt, <i>J</i> = 3.6, 7.3 Hz, 3H)
36		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-methoxyquinazolin-6-yl)-3-methylphenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 552.1	δ 8.98 (s, 1H), 8.47 (s, 1H), 8.15 - 8.04 (m, 1H), 7.58 - 7.52 (m, 2H), 7.44 (ddd, <i>J</i> = 2.6, 5.9, 8.1 Hz, 1H), 7.16 (d, <i>J</i> = 1.8 Hz, 1H), 7.12 - 7.03 (m, 4H), 4.05 (br t, <i>J</i> = 11.2 Hz, 1H), 3.95 (s, 3H), 3.14 (ddd, <i>J</i> = 3.9, 7.7, 11.6 Hz, 1H), 2.27 - 2.17 (m, 5H), 2.11 (br d, <i>J</i> = 11.4 Hz, 2H), 1.67 - 1.53 (m, 2H), 1.52 - 1.38 (m, 2H)
37		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 567.2	δ 8.95 (s, 1 H), 8.54 (br s, 1 H), 8.31 (d, <i>J</i> = 7.72 Hz, 1 H), 7.65 (t, <i>J</i> = 7.50 Hz, 3 H), 7.56 - 7.60 (m, 2 H), 7.48 - 7.54 (m, 1 H), 6.63 (d, <i>J</i> = 7.94 Hz, 1 H), 3.91 - 4.01 (m, 1 H), 3.65 (s, 3 H), 3.10 - 3.21 (m, 1 H), 3.03 (q, <i>J</i> = 7.35 Hz, 2 H), 2.30 (br d, <i>J</i> = 12.13 Hz, 2 H), 2.13 (br d, <i>J</i> = 12.13 Hz, 2 H), 1.44 - 1.65 (m, 4 H), 1.30 (t, <i>J</i> = 7.50 Hz, 3 H)
38		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-methylthiazol-2-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 557.2	δ 9.02 (s, 1 H) 8.52 (br s, 1 H) 8.15 (d, <i>J</i> = 7.06 Hz, 1 H) 7.64 (s, 1 H) 7.51 - 7.59 (m, 3 H) 7.43 - 7.49 (m, 1 H) 3.92 - 4.04 (m, 1 H) 3.02 - 3.21 (m, 3 H) 2.30 (s, 5 H) 2.14 (br d, <i>J</i> = 12.13 Hz, 2 H) 1.44 - 1.64 (m, 4 H) 1.33 (t, <i>J</i> = 7.50 Hz, 3 H)
39		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)pyrimidin-2-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 538.1	δ 9.02 (br s, 1H), 8.51 (br s, 2H), 8.19 (s, 1H), 8.04 (br s, 1H), 7.78 (br d, <i>J</i> = 6.8 Hz, 2H), 7.36 (br s, 4H), 3.78 (br s, 1H), 3.03 (br s, 1H), 2.94 (q, <i>J</i> = 7.4 Hz, 2H),

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
		chlorobenzenesulfonamide		2.09 (br s, 2H), 1.99 (br d, <i>J</i> = 10.8 Hz, 2H), 1.52 (br s, 2H), 1.42 - 1.30 (m, 2H), 1.23 (t, <i>J</i> = 7.4 Hz, 3H)
40		N-(5-(2-(((1R,4R)-4-aminocyclohexyl)amino)-8-isopropylquinazolin-6-yl)-1-methyl-1H-pyrazol-3-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 554.2	δ 9.01 (s, 1H), 8.53 (br s, 1H), 8.12 - 8.07 (m, 1H), 7.60 (dd, <i>J</i> = 1.8, 10.5 Hz, 2H), 7.57 - 7.54 (m, 1H), 7.52 (d, <i>J</i> = 1.8 Hz, 1H), 7.47 - 7.41 (m, 1H), 6.09 (s, 1H), 4.03 - 3.87 (m, 2H), 3.71 (s, 3H), 3.17 (br t, <i>J</i> = 11.4 Hz, 1H), 2.30 (br d, <i>J</i> = 11.8 Hz, 2H), 2.14 (br d, <i>J</i> = 11.0 Hz, 2H), 1.68 - 1.41 (m, 5H), 1.34 (d, <i>J</i> = 7.0 Hz, 6H)
41		N-(5-(2-(((1R,4R)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)thiazol-2-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 543.1	δ 8.98 (s, 1H), 8.51 (br s, 1H), 8.17 (d, <i>J</i> = 7.0 Hz, 1H), 7.73 (s, 1H), 7.65 (s, 1H), 7.58 - 7.40 (m, 4H), 4.01 - 3.89 (m, 1H), 3.19 - 2.98 (m, 3H), 2.30 (br d, <i>J</i> = 12.3 Hz, 2H), 2.13 (br d, <i>J</i> = 13.2 Hz, 2H), 1.66 - 1.41 (m, 4H), 1.33 (t, <i>J</i> = 7.5 Hz, 3H)
42		N-(4-(2-(((1R,4R)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluoro-5-methoxyphenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 584.2	δ 8.95 (s, 1 H), 8.55 (br s, 1 H), 8.09 (d, <i>J</i> = 7.28 Hz, 1 H), 7.54 - 7.67 (m, 4 H), 7.41 - 7.47 (m, 1 H), 7.05 - 7.11 (m, 2 H), 3.96 (br t, <i>J</i> = 11.36 Hz, 1 H), 3.70 (s, 3 H), 3.10 - 3.19 (m, 1 H), 3.03 (q, <i>J</i> = 7.72 Hz, 2 H), 2.30 (br d, <i>J</i> = 12.57 Hz, 2 H), 2.13 (br d, <i>J</i> = 11.47 Hz, 2 H), 1.42 - 1.65 (m, 4 H), 1.31 (t, <i>J</i> = 7.39 Hz, 3 H)
43		N-(1-(2-(((1R,4R)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-1H-imidazol-5-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 526.0	δ 9.09 (br s, 1H), 8.40 (br s, 1H), 8.05 (s, 1H), 8.01 - 7.95 (m, 2H), 7.88 (d, <i>J</i> = 2.3 Hz, 1H), 7.65 - 7.47 (m, 2H),

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
		6-yl)-1H-pyrazol-4-yl)-2-chlorobenzenesulfonamide		7.44 - 7.34 (m, 2H), 3.77 (br s, 1H), 3.05 - 2.90 (m, 3H), 2.12 - 1.96 (m, 4H), 1.49 - 1.24 (m, 7H)
44		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)isoxazol-3-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 527.1	δ 9.13 (br s, 1H), 8.39 (br s, 1H), 8.06 - 7.90 (m, 2H), 7.79 (d, <i>J</i> = 1.6 Hz, 1H), 7.55 (br s, 1H), 7.46 - 7.40 (m, 1H), 7.39 - 7.29 (m, 2H), 6.53 (s, 1H), 3.80 (br s, 1H), 2.98 (q, <i>J</i> = 7.4 Hz, 3H), 2.17 - 1.94 (m, 4H), 1.53 - 1.32 (m, 4H), 1.31 - 1.22 (m, 3H).
45		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-methoxyquinazolin-6-yl)-1-methyl-1H-pyrazol-3-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 542.2	δ 9.05 (br s, 1H), 8.33 (br s, 2H), 8.02 (d, <i>J</i> = 7.7 Hz, 1H), 7.60 - 7.34 (m, 5H), 7.10 (br s, 1H), 6.02 (s, 1H), 3.89 (br s, 4H), 3.68 (s, 3H), 2.96 (br s, 1H), 1.97 (br s, 4H), 1.49 - 1.26 (m, 4H).
46		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-methoxypyrimidin-2-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 568.2	δ 8.98 (s, 1 H), 8.50 (br s, 1 H), 8.33 (d, <i>J</i> = 7.94 Hz, 1 H), 8.14 (s, 1 H), 7.61 - 7.68 (m, 2 H), 7.48 - 7.58 (m, 3 H), 3.91 - 4.02 (m, 1 H), 3.71 (s, 3 H), 3.11 - 3.23 (m, 1 H), 3.04 (q, <i>J</i> = 7.72 Hz, 2 H), 2.31 (br d, <i>J</i> = 11.69 Hz, 2 H), 2.14 (br d, <i>J</i> = 11.47 Hz, 2 H), 1.43 - 1.66 (m, 4 H), 1.31 (t, <i>J</i> = 7.50 Hz, 3 H)
47		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-propylquinazolin-6-yl)-1-methyl-1H-pyrazol-3-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 554.2	δ 9.02 (s, 1H), 8.48 (br s, 1H), 8.09 (dd, <i>J</i> = 1.3, 7.9 Hz, 1H), 7.62 (d, <i>J</i> = 2.0 Hz, 1H), 7.61 - 7.54 (m, 2H), 7.52 (d, <i>J</i> = 2.0 Hz, 1H), 7.44 (ddd, <i>J</i> = 1.9, 6.7, 8.1 Hz, 1H), 6.10 (s, 1H), 4.00 - 3.90 (m, 1H), 3.72 (s, 3H),

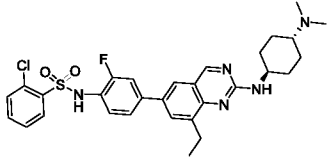
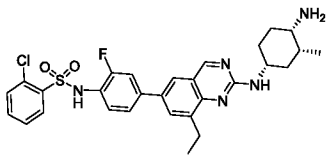
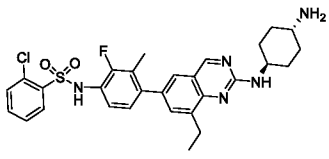
Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
		onamide		3.23 - 3.12 (m, 1H), 3.05 - 2.96 (m, 2H), 2.32 (br d, <i>J</i> = 11.7 Hz, 2H), 2.15 (br d, <i>J</i> = 11.2 Hz, 2H), 1.76 (qd, <i>J</i> = 7.4, 15.0 Hz, 2H), 1.67 - 1.41 (m, 4H), 1.01 (t, <i>J</i> = 7.3 Hz, 3H)
48		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-3-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 526.1	δ 9.06 (s, 1H), 8.50 (br s, 1H), 8.18 (d, <i>J</i> = 7.6 Hz, 1H), 7.91 - 7.80 (m, 2H), 7.62 - 7.56 (m, 3H), 7.53 - 7.48 (m, 1H), 7.46 - 7.40 (m, 1H), 7.11 - 7.02 (m, 2H), 4.04 - 3.93 (m, 1H), 3.22 - 3.11 (m, 1H), 2.25 (br d, <i>J</i> = 13.0 Hz, 2H), 2.14 (br d, <i>J</i> = 11.9 Hz, 2H), 1.71 - 1.40 (m, 4H)
49		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)pyridazin-3-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 510.1	δ 9.13 (s, 1H), 8.42 (br s, 1H), 8.37 - 8.27 (m, 3H), 8.23 (d, <i>J</i> = 6.7 Hz, 1H), 8.07 (d, <i>J</i> = 10.0 Hz, 1H), 7.68 - 7.44 (m, 4H), 4.01 (br t, <i>J</i> = 11.2 Hz, 1H), 3.24 - 3.11 (m, 1H), 2.33 - 2.10 (m, 4H), 1.72 - 1.44 (m, 4H)
50		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 526.1	δ 9.08 (br s, 1H), 8.25 (s, 1H), 8.00 - 7.91 (m, 3H), 7.50 - 7.29 (m, 5H), 7.24 - 7.12 (m, 2H), 3.81 (br d, <i>J</i> = 8.1 Hz, 1H), 3.03 (br d, <i>J</i> = 10.9 Hz, 1H), 2.11 - 1.92 (m, 4H), 1.53 - 1.29 (m, 4H)
51		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-5-fluoropyridin-3-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 527.1	δ 9.08 (s, 1H), 8.45 (br s, 1H), 8.29 (s, 1H), 8.24 - 8.15 (m, 3H), 7.64 - 7.55 (m, 3H), 7.54 - 7.45 (m, 2H), 3.98 (br t, <i>J</i> = 11.4 Hz, 1H), 3.21 - 3.09 (m, 1H), 2.24 (br d, <i>J</i> = 11.7 Hz, 2H), 2.13 (br d, <i>J</i> = 11.7 Hz, 2H), 1.71 - 1.41 (m, 4H)

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
52		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-fluoropyridin-3-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 555.2	δ 9.02 (s, 1H), 8.51 (br s, 1H), 8.28 (s, 1H), 8.19 (d, J = 7.9 Hz, 1H), 8.05 (br d, J = 7.5 Hz, 2H), 7.64 - 7.56 (m, 2H), 7.54 - 7.42 (m, 2H), 3.99 (br t, J = 11.0 Hz, 1H), 3.18 (br t, J = 11.5 Hz, 1H), 3.08 (q, J = 7.5 Hz, 2H), 2.32 (br d, J = 11.2 Hz, 2H), 2.15 (br d, J = 11.2 Hz, 2H), 1.70 - 1.43 (m, 4H), 1.34 (t, J = 7.4 Hz, 3H).
53		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-2,5-difluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 544.1	δ 9.10 (br s, 1 H), 8.17 (br s, 1 H), 7.97 (dd, J = 7.28, 1.98 Hz, 1 H), 7.85 - 7.89 (m, 1 H), 7.80 (br d, J = 8.82 Hz, 1 H), 7.36 - 7.47 (m, 4 H), 7.13 - 7.23 (m, 1 H), 6.98 (br dd, J = 14.33, 7.50 Hz, 1 H), 3.80 (br s, 1 H), 3.03 (br s, 1 H), 1.88 - 2.12 (m, 4 H), 1.22 - 1.57 (m, 4 H)
54		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-3-fluoropyridin-2-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 527.1	δ 9.10 (s, 1H), 8.29 (br dd, J = 2.1, 5.6 Hz, 3H), 8.23 (d, J = 1.8 Hz, 1H), 8.02 - 7.91 (m, 2H), 7.63 - 7.57 (m, 2H), 7.57 - 7.51 (m, 1H), 3.99 (br t, J = 11.2 Hz, 1H), 3.21 - 3.09 (m, 1H), 2.25 (br d, J = 12.3 Hz, 2H), 2.14 (br d, J = 12.0 Hz, 2H), 1.71 - 1.41 (m, 4H)
55		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-fluoropyridin-2-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 555.2	δ 9.00 (s, 1H), 8.49 (br s, 1H), 8.25 (d, J = 8.1 Hz, 1H), 8.16 (s, 1H), 7.85 (br d, J = 11.6 Hz, 1H), 7.76 (br s, 2H), 7.57 - 7.51 (m, 2H), 7.51 - 7.44 (m, 1H), 4.01 - 3.87 (m, 1H), 3.22 - 3.12 (m, 1H), 3.06 (q, J = 7.5 Hz, 2H), 2.30 (br d, J = 11.5 Hz, 2H), 2.14 (br d, J = 12.2

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
				Hz, 2H), 1.72 - 1.41 (m, 4H), 1.32 (t, <i>J</i> = 7.5 Hz, 3H)
56		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-2,3-difluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 544.1	δ 9.06 (s, 1H), 8.42 (br s, 1H), 8.08 - 8.02 (m, 1H), 7.89 (s, 1H), 7.83 (br d, <i>J</i> = 9.0 Hz, 1H), 7.65 - 7.55 (m, 3H), 7.48 - 7.41 (m, 1H), 7.32 - 7.20 (m, 2H), 4.04 - 3.91 (m, 1H), 3.21 - 3.08 (m, 1H), 2.23 (br d, <i>J</i> = 11.2 Hz, 2H), 2.12 (br d, <i>J</i> = 12.3 Hz, 2H), 1.68 - 1.38 (m, 4H)
57		N-(4-(3-(((1r,4r)-4-aminocyclohexyl)amino)isoquinolin-7-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 525.1	δ 8.83 (s, 1H), 8.46 (br s, 1H), 8.05 - 7.93 (m, 2H), 7.71 (dd, <i>J</i> = 1.9, 8.7 Hz, 1H), 7.62 - 7.53 (m, 3H), 7.50 - 7.44 (m, 1H), 7.44 - 7.37 (m, 3H), 6.68 (s, 1H), 3.68 (tt, <i>J</i> = 3.8, 11.2 Hz, 1H), 3.16 (tt, <i>J</i> = 3.9, 11.7 Hz, 1H), 2.29 - 2.18 (m, 2H), 2.12 (br d, <i>J</i> = 12.1 Hz, 2H), 1.61 (dq, <i>J</i> = 3.1, 12.6 Hz, 2H), 1.48 - 1.33 (m, 2H)
58		(S)-2-amino-N-(((1r,4S)-4-((6-(4-(2-chlorophenyl)sulfonamido)-3-fluorophenyl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)-3-methylbutanamide	M+H ⁺ = 653.2	δ 8.98 (s, 1H), 8.54 (br s, 1H), 8.02 (dd, <i>J</i> = 1.2, 7.9 Hz, 1H), 7.73 (br d, <i>J</i> = 4.3 Hz, 2H), 7.64 - 7.52 (m, 2H), 7.50 - 7.44 (m, 1H), 7.44 - 7.34 (m, 3H), 3.96 (br s, 1H), 3.80 (br s, 1H), 3.52 (br d, <i>J</i> = 6.0 Hz, 1H), 3.06 (q, <i>J</i> = 7.3 Hz, 2H), 2.24 (br s, 2H), 2.15 (br dd, <i>J</i> = 6.6, 13.2 Hz, 1H), 2.05 (br s, 2H), 1.50 (br d, <i>J</i> = 8.6 Hz, 4H), 1.33 (br t, <i>J</i> = 7.4 Hz, 3H), 1.07 (br dd, <i>J</i> = 4.0, 6.7 Hz, 6H).

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
59		N-(((1r,4r)-4-((6-(4-((2-chlorophenyl)sulfonamido)-3-fluorophenyl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)acetamide	M+H ⁺ = 596.1	δ 8.98 (s, 1H), 8.00 (dd, J = 1.5, 7.9 Hz, 1H), 7.75 (s, 2H), 7.63 - 7.52 (m, 2H), 7.50 - 7.44 (m, 1H), 7.43 - 7.36 (m, 3H), 3.98 - 3.88 (m, 1H), 3.68 (br d, J = 15.7 Hz, 1H), 3.06 (q, J = 7.4 Hz, 2H), 2.20 (br d, J = 11.7 Hz, 2H), 1.99 (br d, J = 9.3 Hz, 2H), 1.93 (s, 3H), 1.50 - 1.37 (m, 4H), 1.33 (t, J = 7.5 Hz, 3H).
60		2-chloro-N-(4-(8-ethyl-2-(((1r,4r)-4-(methylamino)cyclohexyl)amino)quinazolin-6-yl)-2-fluorophenyl)benzenesulfonamide	M+H ⁺ = 568.2	δ 9.05 (br s, 1H), 8.25 (br s, 1H), 7.95 (dd, J = 2.0, 7.5 Hz, 1H), 7.80 (d, J = 1.3 Hz, 2H), 7.47 - 7.43 (m, 1H), 7.41 - 7.30 (m, 4H), 7.20 - 7.13 (m, 2H), 3.79 (br s, 1H), 2.98 (q, J = 7.6 Hz, 2H), 2.91 (br s, 1H), 2.55 (s, 3H), 2.09 (br d, J = 9.3 Hz, 4H), 1.46 - 1.33 (m, 4H), 1.28 (t, J = 7.4 Hz, 3H)
62		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-3,5-difluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 544.1	δ 8.93 (s, 1H), 8.42 (br s, 1H), 8.18 - 8.04 (m, 1H), 7.67 (s, 1H), 7.61 - 7.55 (m, 1H), 7.53 - 7.50 (m, 2H), 7.48 - 7.39 (m, 2H), 6.82 - 6.75 (m, 2H), 3.96 - 3.83 (m, 1H), 3.06 (tt, J = 3.9, 11.6 Hz, 1H), 2.15 (br d, J = 11.0 Hz, 2H), 2.03 (br d, J = 12.2 Hz, 2H), 1.59 - 1.46 (m, 2H), 1.44 - 1.31 (m, 2H).
63		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-2,6-difluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 572.2	δ 9.04 (br s, 1H), 8.43 (br s, 2H), 7.95 (br d, J = 7.8 Hz, 1H), 7.82 (br d, J = 15.6 Hz, 2H), 7.70 - 7.57 (m, 2H), 7.43 (br t, J = 7.4 Hz, 1H), 7.33 (br d, J = 8.9 Hz, 2H), 3.99 (br s, 1H), 3.25 - 3.03 (m, 3H),

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
		onamide		2.33 (br d, <i>J</i> = 10.3 Hz, 2H), 2.17 (br d, <i>J</i> = 9.8 Hz, 2H), 1.70 - 1.46 (m, 4H), 1.36 (br t, <i>J</i> = 7.2 Hz, 3H).
65		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-methoxypyridazin-3-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 568.2 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.04 (s, 1H), 8.52 (br s, 1H), 8.24 (dd, <i>J</i> = 1.5, 7.7 Hz, 1H), 8.06 (d, <i>J</i> = 2.0 Hz, 1H), 7.98 - 7.91 (m, 1H), 7.61 - 7.45 (m, 3H), 7.34 (s, 1H), 4.05 - 3.95 (m, 4H), 3.19 (br t, <i>J</i> = 11.4 Hz, 1H), 3.07 (q, <i>J</i> = 7.5 Hz, 2H), 2.32 (br d, <i>J</i> = 11.1 Hz, 2H), 2.17 (br d, <i>J</i> = 11.4 Hz, 2H), 1.70 - 1.43 (m, 4H), 1.39 - 1.27 (m, 3H)
66		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-methoxypyridazin-3-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 568.2 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 8.96 (s, 1H), 8.35 (br s, 1H), 8.19 - 8.05 (m, 3H), 7.52 - 7.32 (m, 4H), 4.03 - 3.79 (m, 4H), 3.14 - 2.93 (m, 3H), 2.21 (br d, <i>J</i> = 11.0 Hz, 2H), 2.05 (br d, <i>J</i> = 10.6 Hz, 2H), 1.61 - 1.33 (m, 4H), 1.25 (t, <i>J</i> = 7.5 Hz, 3H)
67		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-methylpyridazin-3-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 552.1 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.04 (s, 1H), 8.56 (br s, 1H), 8.22 (br d, <i>J</i> = 7.3 Hz, 1H), 7.75 (s, 1H), 7.68 (br s, 2H), 7.57 - 7.41 (m, 3H), 3.98 (br t, <i>J</i> = 11.0 Hz, 1H), 3.22 - 3.01 (m, 3H), 2.41 - 2.25 (m, 5H), 2.14 (br d, <i>J</i> = 11.5 Hz, 2H), 1.70 - 1.42 (m, 4H), 1.33 (br t, <i>J</i> = 7.5 Hz, 3H)
68		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-4-aminopyridazin-3-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 524	δ = 9.04 (s, 1H), 8.50 (br s, 1H), 8.31 (dd, <i>J</i> = 1.3, 7.7 Hz, 1H), 8.22 (s, 1H), 7.71 - 7.61 (m, 2H), 7.60 - 7.47 (m,

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
		methylpyrimidin-2-yl)-2-chlorobenzenesulfonamide		4H), 4.03 - 3.90 (m, 1H), 3.15 (tt, <i>J</i> = 3.9, 11.6 Hz, 1H), 2.29 (s, 3H), 2.23 (br d, <i>J</i> = 11.5 Hz, 2H), 2.12 (br d, <i>J</i> = 12.6 Hz, 2H), 1.66 - 1.40 (m, 4H).
69		2-chloro-N-(4-((1R,4R)-4-(dimethylamino)cyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)benzenesulfonamide	M+H ⁺ = 582.2 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.01 (s, 1H), 8.56 (br s, 1H), 8.03 (d, <i>J</i> = 7.7 Hz, 1H), 7.77 (br s, 2H), 7.66 - 7.54 (m, 2H), 7.51 - 7.34 (m, 4H), 3.98 (br t, <i>J</i> = 11.6 Hz, 1H), 3.22 - 3.02 (m, 3H), 2.82 (s, 6H), 2.39 (br d, <i>J</i> = 12.0 Hz, 2H), 2.18 (br d, <i>J</i> = 12.1 Hz, 2H), 1.78 - 1.63 (m, 2H), 1.57 - 1.41 (m, 2H), 1.34 (t, <i>J</i> = 7.5 Hz, 2H)
70		N-(4-(2-(((1R,3R,4S)-4-amino-3-methylcyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 568.2 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.04 (s, 1H), 8.55 (br s, 1H), 8.03 (dd, <i>J</i> = 1.3, 7.9 Hz, 1H), 7.79 (s, 2H), 7.65 - 7.55 (m, 2H), 7.52 - 7.32 (m, 4H), 4.07 (ddd, <i>J</i> = 3.9, 7.6, 11.4 Hz, 1H), 3.46 (br s, 1H), 3.16 - 3.02 (m, 2H), 2.27 - 2.04 (m, 4H), 2.03 - 1.88 (m, 1H), 1.52 - 1.26 (m, 5H), 1.11 (d, <i>J</i> = 6.8 Hz, 3H)
71		N-(4-(2-(((1R,4R)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluoro-3-methylphenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 568.0 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 8.98 (s, 1H), 8.53 (br s, 1H), 8.03 (dd, <i>J</i> = 1.2, 8.0 Hz, 1H), 7.66 - 7.53 (m, 2H), 7.49 - 7.39 (m, 3H), 7.28 (t, <i>J</i> = 8.2 Hz, 1H), 6.97 (d, <i>J</i> = 8.4 Hz, 1H), 4.04 - 3.91 (m, 1H), 3.23 - 3.12 (m, 1H), 3.06 (q, <i>J</i> = 7.5 Hz,

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
				2H), 2.32 (br d, <i>J</i> = 11.9 Hz, 2H), 2.20 - 2.05 (m, 5H), 1.67 - 1.42 (m, 4H), 1.31 (t, <i>J</i> = 7.4 Hz, 3H).
72		N-(4-(2-(((1R,3S)-3-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 554.3 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.00 (s, 1H), 8.55 (br s, 1H), 8.02 (dd, <i>J</i> = 1.4, 8.0 Hz, 1H), 7.79 - 7.71 (m, 2H), 7.64 - 7.50 (m, 2H), 7.49 - 7.27 (m, 4H), 4.08 (ddd, <i>J</i> = 4.0, 7.7, 11.5 Hz, 1H), 3.23 (ddd, <i>J</i> = 3.9, 8.2, 11.8 Hz, 1H), 3.17 - 2.97 (m, 2H), 2.52 (br d, <i>J</i> = 11.2 Hz, 1H), 2.27 - 1.88 (m, 3H), 1.66 - 1.46 (m, 1H), 1.43 - 1.26 (m, 6H)
73		(S)-2-chloro-N-(4-(8-ethyl-2-(piperidin-3-ylamino)quinazolin-6-yl)-2-fluorophenyl)benzenesulfonamide	M+H ⁺ = 540.2 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.08 (s, 1H), 8.51 (br s, 1H), 8.01 (dd, <i>J</i> = 1.3, 7.9 Hz, 1H), 7.81 (s, 2H), 7.66 - 7.34 (m, 6H), 4.45 - 4.24 (m, 1H), 3.66 (br dd, <i>J</i> = 3.3, 12.1 Hz, 1H), 3.20 - 2.97 (m, 4H), 2.24 - 2.06 (m, 2H), 1.97 - 1.76 (m, 2H), 1.34 (t, <i>J</i> = 7.5 Hz, 3H)
74		N-(4-(2-(((1R,3R,4R)-4-amino-3-methylcyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 568.2 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.04 (s, 1H), 8.56 (br s, 1H), 8.09 - 7.99 (m, 1H), 7.80 (s, 2H), 7.66 - 7.54 (m, 2H), 7.54 - 7.38 (m, 4H), 4.05 (br t, <i>J</i> = 11.6 Hz, 1H), 3.17 - 3.04 (m, 2H), 2.83 (dt, <i>J</i> = 3.9, 10.9 Hz, 1H), 2.37 - 2.25 (m, 2H), 2.16 (br dd, <i>J</i> = 3.5, 12.3 Hz, 1H), 1.76 (br s, 1H),

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
				1.67 - 1.41 (m, 2H), 1.38 - 1.19 (m, 4H), 1.14 (d, <i>J</i> = 6.5 Hz, 3H).
75		N-(4-(2-(((1R,3S)-3-aminocyclohexyl)amino)quinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 526.1 (LCMS)	¹ H NMR (400MHz, DMSO- <i>d</i> ₆) δ 9.08 (s, 1H), 8.22 (br s, 1H), 7.98 - 7.88 (m, 3H), 7.46 - 7.28 (m, 5H), 7.18 - 7.11 (m, 2H), 3.93 (brs, 1H), 2.27 (br s, 1H), 1.91 (br s, 2H), 1.79 (br d, <i>J</i> = 12.8 Hz, 1H), 1.49 - 1.11 (m, 4H)
76		(S)-2-chloro-N-(2-fluoro-4-(2-(piperidin-3-ylamino)quinazolin-6-yl)phenyl)benzenesulfonamide	M+H ⁺ = 512.1 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.11 (s, 1H), 8.56 (br s, 1H), 8.06 - 7.91 (m, 3H), 7.62 - 7.52 (m, 3H), 7.50 - 7.44 (m, 1H), 7.44 - 7.38 (m, 3H), 4.42 - 4.24 (m, 1H), 3.60 (br dd, <i>J</i> = 3.1, 12.1 Hz, 1H), 3.30 (br s, 1H), 3.04 - 2.94 (m, 2H), 2.24 - 2.01 (m, 2H), 1.95 - 1.67 (m, 2H).
77		N-(4-(2-(((1R,3R)-3-aminocyclopentyl)amino)quinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 512.1 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.05 (s, 1H), 8.52 (br s, 1H), 8.00 (dd, <i>J</i> = 1.3, 7.9 Hz, 1H), 7.95 - 7.88 (m, 2H), 7.61 - 7.51 (m, 3H), 7.50 - 7.43 (m, 1H), 7.43 - 7.34 (m, 3H), 4.66 - 4.56 (m, 1H), 3.81 (quin, <i>J</i> = 6.9 Hz, 1H), 2.40 - 2.25 (m, 2H), 2.15 (t, <i>J</i> = 6.9 Hz, 2H), 1.84 - 1.66 (m, 2H).
78		N-(4-(2-(((1R,3R)-3-aminocyclopentyl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 540.1 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.00 (s, 1H), 8.48 (br s, 1H), 8.00 (dd, <i>J</i> = 1.3, 7.9 Hz, 1H), 7.75 (s, 2H), 7.61 - 7.51 (m, 2H),

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
		fluorophenyl)-2-chlorobenzenesulfonamide		7.49 - 7.34 (m, 4H), 4.60 (quin, <i>J</i> = 6.6 Hz, 1H), 3.80 (quin, <i>J</i> = 7.1 Hz, 1H), 3.08 (q, <i>J</i> = 7.4 Hz, 2H), 2.41 - 2.28 (m, 2H), 2.27 - 2.12 (m, 2H), 1.88 - 1.67 (m, 2H), 1.32 (t, <i>J</i> = 7.5 Hz, 3H)
79		N-(4-(2-(((1R,3S)-3-aminocyclopentyl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 540.1 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.05 (s, 1H), 8.56 (br s, 1H), 8.03 (d, <i>J</i> = 7.9 Hz, 1H), 7.83 - 7.78 (m, 2H), 7.66 - 7.53 (m, 2H), 7.52 - 7.37 (m, 4H), 4.48 (quin, <i>J</i> = 7.0 Hz, 1H), 3.72 (quin, <i>J</i> = 7.2 Hz, 1H), 3.11 (q, <i>J</i> = 7.4 Hz, 2H), 2.85 - 2.71 (m, 1H), 2.33 - 2.14 (m, 2H), 2.01 - 1.81 (m, 2H), 1.76 - 1.64 (m, 1H), 1.39 - 1.31 (m, 3H)
80		N-(4-(2-(((1R,3S)-3-aminocyclopentyl)amino)quinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 512.1 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.11 (s, 1H), 8.54 (br s, 1H), 8.08 - 7.95 (m, 3H), 7.67 - 7.37 (m, 7H), 4.55 - 4.39 (m, 1H), 3.80 - 3.66 (m, 1H), 2.77 - 2.61 (m, 1H), 2.29 - 2.11 (m, 2H), 2.05 - 1.83 (m, 2H), 1.77 - 1.63 (m, 1H)
81		N-(4-(2-((4-aminobicyclo[2.2.2]octan-1-yl)amino)quinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 552.1 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.02 (s, 1H), 8.44 (br s, 1H), 8.00 (d, <i>J</i> = 7.9 Hz, 1H), 7.93 (br s, 2H), 7.62 - 7.52 (m, 3H), 7.51 - 7.44 (m, 1H), 7.41 (br d, <i>J</i> = 8.2 Hz, 3H), 2.35 - 2.27 (m, 6H), 1.99 - 1.92 (m, 6H)

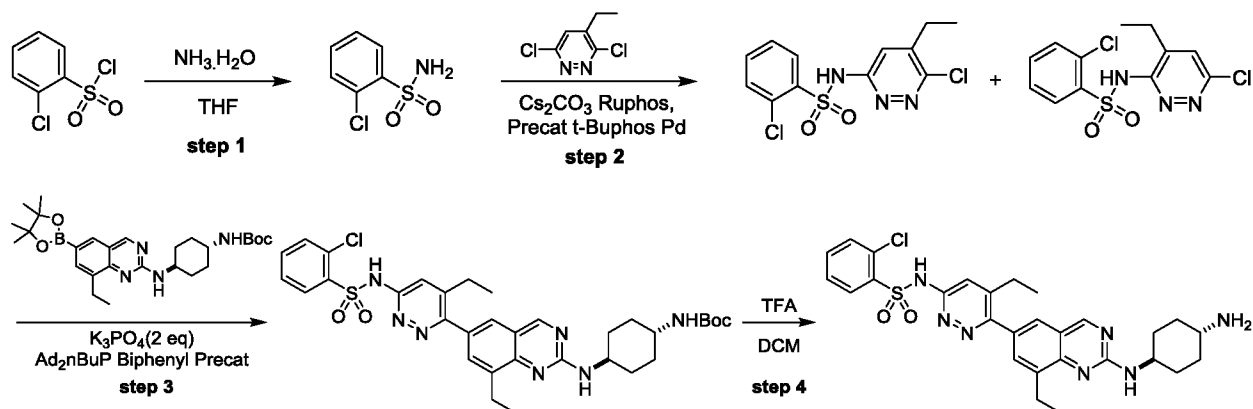
Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
82		N-(4-(2-(((2r,5r)-5-amino-octahydro-2H-pentalen-2-yl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 580.1 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 8.91 (s, 1H), 8.40 (br s, 1H), 7.91 (dd, <i>J</i> = 1.3, 7.9 Hz, 1H), 7.68 (s, 2H), 7.54 - 7.44 (m, 2H), 7.41 - 7.25 (m, 4H), 4.50 - 4.41 (m, 2H), 3.00 (q, <i>J</i> = 7.4 Hz, 2H), 2.68 - 2.55 (m, 2H), 2.36 - 2.22 (m, 2H), 1.97 (br dd, <i>J</i> = 5.9, 12.5 Hz, 2H), 1.66 (td, <i>J</i> = 9.0, 12.5 Hz, 2H), 1.38 - 1.21 (m, 5H)
83		N-(4-(2-(((2r,5r)-5-amino-octahydro-2H-pentalen-2-yl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 580.2 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 8.99 (s, 1H), 8.54 (br s, 1H), 8.00 (d, <i>J</i> = 7.9 Hz, 1H), 7.76 (s, 2H), 7.62 - 7.52 (m, 2H), 7.49 - 7.36 (m, 4H), 4.38 - 4.17 (m, 1H), 3.83 - 3.66 (m, 1H), 3.13 - 3.00 (m, 2H), 2.73 (br s, 2H), 2.55 - 2.46 (m, 2H), 1.94 (br dd, <i>J</i> = 6.4, 12.5 Hz, 2H), 1.85 - 1.74 (m, 2H), 1.32 (t, <i>J</i> = 7.5 Hz, 3H), 1.28 - 1.21 (m, 2H)
84		N-(4-(2-(((2s,5s)-5-amino-octahydro-2H-pentalen-2-yl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 580.1 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 8.99 (s, 1H), 8.48 (br s, 1H), 8.00 (dd, <i>J</i> = 1.3, 7.9 Hz, 1H), 7.75 (s, 2H), 7.62 - 7.52 (m, 2H), 7.50 - 7.36 (m, 4H), 4.50 - 4.38 (m, 1H), 3.57 - 3.45 (m, 1H), 3.06 (q, <i>J</i> = 7.6 Hz, 2H), 2.67 - 2.57 (m, 2H), 2.52 (br dd, <i>J</i> = 6.4, 12.5 Hz, 2H), 2.44 - 2.33 (m, 2H), 1.59 - 1.39 (m, 4H), 1.32 (t, <i>J</i> = 7.5 Hz, 3H)

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
85		N-(4-(2-(((2S,5S)-5-amino-octahydro-pentalen-2-yl)amino)quinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 552.1 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.06 (s, 1H), 8.47 (br s, 1H), 8.06 - 7.89 (m, 3H), 7.64 - 7.53 (m, 3H), 7.52 - 7.36 (m, 4H), 4.52 - 4.38 (m, 1H), 3.60 - 3.44 (m, 1H), 2.72 - 2.53 (m, 2H), 2.53 - 2.31 (m, 4H), 1.55 - 1.37 (m, 4H).
86		N-(4-(2-((4-aminobicyclo[2.2.1]heptan-1-yl)amino)quinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 538.1 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.06 (s, 1H), 8.59 - 8.47 (m, 1H), 8.08 - 7.87 (m, 3H), 7.63 - 7.34 (m, 7H), 2.48 - 2.28 (m, 4H), 2.06 - 1.85 (m, 6H)
87		N-(4-(2-((4-aminobicyclo[2.2.2]octan-1-yl)amino)-8-ethylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 580.2 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 8.98 (s, 1H), 8.49 (br s, 1H), 8.02 (dd, <i>J</i> = 1.4, 7.9 Hz, 1H), 7.77 (dd, <i>J</i> = 1.9, 12.2 Hz, 2H), 7.63 - 7.55 (m, 2H), 7.51 - 7.38 (m, 4H), 3.10 (q, <i>J</i> = 7.5 Hz, 2H), 2.42 - 2.32 (m, 6H), 2.04 - 1.94 (m, 6H), 1.36 (t, <i>J</i> = 7.5 Hz, 3H)
88		2-chloro-N-(4-(8-ethyl-2-(((1R,4R)-4-(pyrrolidin-1-yl)cyclohexyl)amino)quinazolin-6-yl)-2-fluorophenyl)benzenesulfonamide	M+H ⁺ = 608.3 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.02 (s, 1H), 8.57 (br s, 1H), 8.03 (d, <i>J</i> = 7.9 Hz, 1H), 7.79 (s, 2H), 7.64 - 7.54 (m, 2H), 7.51 - 7.39 (m, 4H), 3.98 (br t, <i>J</i> = 11.4 Hz, 1H), 3.33 - 3.29 (m, 4H), 3.12 - 3.01 (m, 3H), 2.44 - 2.24 (m, 4H), 2.07 (br s, 4H), 1.73 - 1.59 (m, 2H), 1.54 - 1.42 (m, 2H), 1.35 (t, <i>J</i> = 7.5 Hz, 3H)

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
89		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-1,3,4-thiadiazol-2-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 516.1 (LCMS)	¹ H NMR (400MHz, DMSO-d ₆) δ 9.13 (br s, 1H), 8.19 (s, 1H), 8.10 (br d, J = 9.3 Hz, 1H), 8.02 (d, J = 2.0 Hz, 1H), 7.96 (dd, J = 1.9, 7.6 Hz, 1H), 7.50 - 7.31 (m, 5H), 3.80 (br d, J = 12.1 Hz, 1H), 2.98 (br s, 1H), 2.05 - 1.90 (m, 4H), 1.48 - 1.27 (m, 4H).
90		N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-methylquinazolin-6-yl)-2-fluorophenyl)-2-chlorobenzenesulfonamide	M+H ⁺ = 540.3 (LCMS)	¹ H NMR (400MHz, METHANOL-d ₄) δ 8.95 (s, 1H), 8.07 (dd, J = 1.6, 7.8 Hz, 1H), 7.60 - 7.47 (m, 3H), 7.43 - 7.32 (m, 3H), 7.07 - 6.94 (m, 2H), 4.00 - 3.89 (m, 1H), 3.04 - 2.93 (m, 1H), 2.34 (s, 3H), 2.23 - 2.16 (m, 2H), 2.12 - 2.03 (m, 2H), 1.59 - 1.41 (m, 4H)
92		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 567.1 (LCMS)	¹ H NMR (400MHz, METHANOL-d ₄) δ 8.99 (s, 1H), 8.40 (br s, 1H), 8.31 - 8.21 (m, 1H), 7.84 (s, 1H), 7.66 - 7.45 (m, 5H), 6.83 (s, 1H), 4.03 - 3.92 (m, 1H), 3.88 (s, 3H), 3.23 - 3.12 (m, 1H), 3.05 (q, J = 7.4 Hz, 2H), 2.31 (br d, J = 12.3 Hz, 2H), 2.14 (br d, J = 12.1 Hz, 2H), 1.68 - 1.42 (m, 4H), 1.31 (t, J = 7.5 Hz, 3H)
93		N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-methoxypyridin-3-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 567.2 (LCMS)	¹ H NMR (400MHz, METHANOL-d ₄) δ 8.98 (s, 1H), 8.48 (br s, 1H), 8.20 - 8.12 (m, 1H), 8.06 - 7.91 (m, 3H), 7.64 - 7.54 (m, 2H), 7.49 (ddd, J = 2.6, 5.8, 8.0 Hz, 1H), 7.34 (d, J = 2.2 Hz, 1H), 4.02 - 3.92

Comp ID	Structure	Chemical Name	Mass (M+H ⁺)	¹ H NMR (MeOD, 400 MHz)
		onamide		(m, 1H), 3.84 (s, 3H), 3.24 - 3.12 (m, 1H), 3.05 (q, <i>J</i> = 7.6 Hz, 2H), 2.30 (br d, <i>J</i> = 11.0 Hz, 2H), 2.14 (br d, <i>J</i> = 11.9 Hz, 2H), 1.66 - 1.41 (m, 4H), 1.32 (t, <i>J</i> = 7.4 Hz, 3H)
94		N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methylpyrazin-2-yl)-2-chlorobenzenesulfonamide	M+H ⁺ = 552.2 (LCMS)	¹ H NMR (400MHz, METHANOL- <i>d</i> ₄) δ 9.00 (s, 1H), 8.50 (br s, 1H), 8.30 (d, <i>J</i> = 7.3 Hz, 1H), 8.15 (s, 1H), 7.68 (s, 2H), 7.59 - 7.47 (m, 3H), 4.03 - 3.92 (m, 1H), 3.22 - 3.12 (m, 1H), 3.06 (q, <i>J</i> = 7.5 Hz, 2H), 2.37 (s, 3H), 2.30 (br d, <i>J</i> = 11.0 Hz, 2H), 2.14 (br d, <i>J</i> = 11.9 Hz, 2H), 1.66 - 1.42 (m, 4H), 1.31 (t, <i>J</i> = 7.5 Hz, 3H)

Example 5: Synthesis of N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-ethylpyridazin-3-yl)-2-chlorobenzenesulfonamide (96)



Step 1:

[00199] To a solution of 2-chlorobenzene-1-sulfonyl chloride (2.0 g, 9.5 mmol, 1.3 mL) in THF (20.0 mL) was added NH₃.H₂O (3.3 g, 28.4 mmol, 3.7 mL, 25% solution) at 0°C. The mixture was stirred at 0°C for 10 min and then warmed to 20°C for 2 h. The reaction mixture was concentrated to afford 2-chlorobenzenesulfonamide (1.8 g, 9.4 mmol, 99.1% yield). ¹H

NMR (400MHz, DMSO- d_6) δ 7.96 (dd, J = 1.4, 7.8 Hz, 1H), 7.65 - 7.55 (m, 2H), 7.54 - 7.34 (m, 7H).

Step 2:

[00200] A mixture of 3,6-dichloro-4-ethylpyridazine (500 mg, 2.8 mmol), 2-chlorobenzenesulfonamide (595 mg, 3.1 mmol), Cs_2CO_3 (2.7g, 8.5 mmol), dicyclohexyl-[2-(2,6-diisopropoxyphenyl)phenyl]phosphane (132 mg, 282.4 μmol) and [2-(2-aminoethyl)phenyl]-chloro-palladium;diter-butyl-[2-(2,4,6-triisopropylphenyl)phenyl]phosphane (194 mg, 282.4 μmol) in THF (30.0 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 12 h under N_2 atmosphere. The reaction was concentrated to give a residue. The residue was purified by column chromatography (SiO_2) to give a crude product (280 mg). The crude product was purified by prep-HPLC (TFA condition) to afford 2-chloro-N-(6-chloro-5-ethylpyridazin-3-yl)benzenesulfonamide (20 mg, 54.2 μmol , 1.9% yield). ^1H NMR (400MHz, METHANOL- d_4) δ 8.20 (d, J = 7.7 Hz, 1H), 7.64 (br s, 1H), 7.57 - 7.53 (m, 2H), 7.52 - 7.46 (m, 1H), 2.71 (q, J = 7.5 Hz, 2H), 1.23 (t, J = 7.4 Hz, 3H); and 2-chloro-N-(6-chloro-4-ethylpyridazin-3-yl)benzenesulfonamide (100 mg, 270.9 μmol , 10.7% yield). ^1H NMR (400MHz, METHANOL- d_4) δ 8.21 (d, J = 7.6 Hz, 1H), 7.60 - 7.56 (m, 2H), 7.56 - 7.48 (m, 2H), 2.61 (br d, J = 6.7 Hz, 2H), 1.18 (br t, J = 7.2 Hz, 3H).

Step 3:

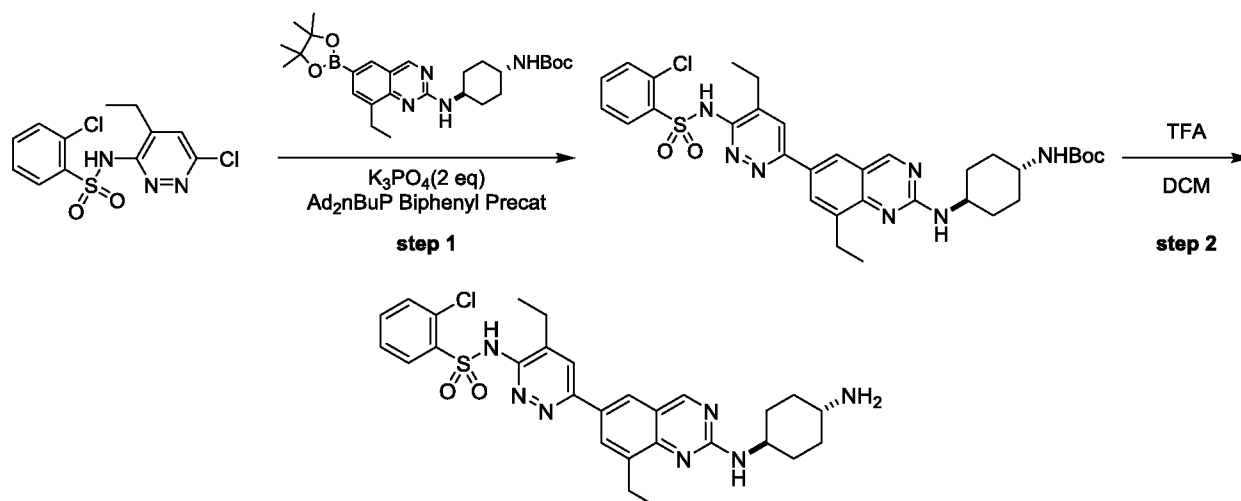
[00201] A mixture of 2-chloro-N-(6-chloro-4-ethylpyridazin-3-yl)benzenesulfonamide (54 mg, 161.1 μmol), tert-butyl ((1r,4r)-4-((8-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (80 mg, 161.1 μmol), K_3PO_4 (0.5 M, 644.6 μL) and [2-(2-aminophenyl)phenyl]-chloro-palladium;bis(1-adamantyl)-butyl-phosphane (11 mg, 16.1 μmol) were degassed and purged with N_2 for 3 times and taken up into a microwave tube in 2-methyltetrahydrofuran (2.5 mL). The sealed tube was heated at 120°C for 180 min under microwave. The reaction was concentrated to give a residue. The residue was purified by prep-TLC (SiO_2) to give tert-butyl ((1r,4r)-4-((6-(6-((2-chlorophenyl)sulfonamido)-4-ethylpyridazin-3-yl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (60 mg, crude). $\text{M}+\text{H}^+ = 666.3$ (LCMS).

Step 4:

[00202] To a solution of tert-butyl ((1r,4r)-4-((6-(6-(2-chlorophenyl)sulfonamido)-4-ethylpyridazin-3-yl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (60 mg, 90.1 μmol) in DCM (2.0 mL) was added TFA (1.0 mL). The mixture was stirred at 20°C for 0.5 h. The reaction was concentrated to give a residue. The residue was dissolved in MeOH (1.0 mL) and basified pH to 7 with $\text{NH}_3\cdot\text{H}_2\text{O}$ (25% solution). The residue was purified by prep-HPLC (FA condition) to afford N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-

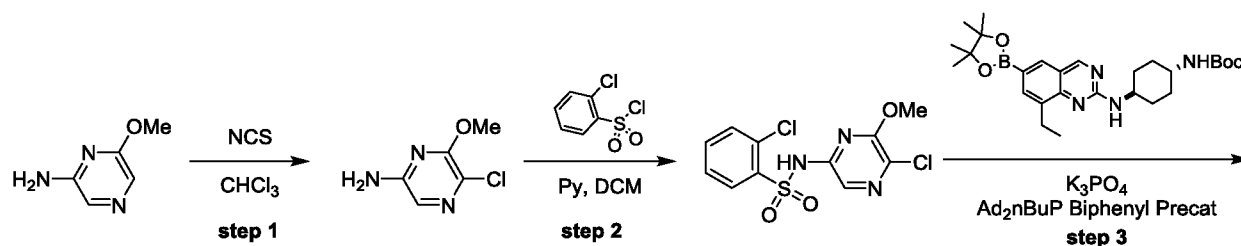
ethylpyridazin-3-yl)-2-chlorobenzenesulfonamide (5.1 mg, 7.9 μmol , 8.8% yield, FA). $M+H^+ = 566.2$ (LCMS); ^1H NMR (400MHz, $\text{METHANOL-}d_4$) δ 9.08 (br s, 1H), 8.23 (br s, 1H), 8.03 - 7.38 (m, 7H), 3.99 (br s, 1H), 3.23 - 3.01 (m, 3H), 2.67 (br s, 2H), 2.31 (br d, $J = 10.1$ Hz, 2H), 2.14 (br d, $J = 11.0$ Hz, 2H), 1.66 - 1.44 (m, 4H), 1.33 (br t, $J = 7.4$ Hz, 3H), 1.10 (br t, $J = 7.1$ Hz, 3H).

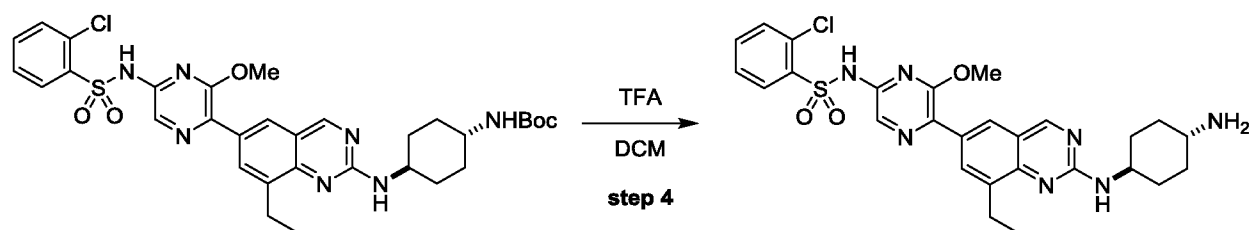
Example 6: Synthesis of N-(6-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-ethylpyridazin-3-yl)-2-chlorobenzenesulfonamide (100)



[00203] The title compound was synthesized according to the synthetic procedure reported for the preparation of compound N-(6-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-ethylpyridazin-3-yl)-2-chlorobenzenesulfonamide. (13.7 mg, 22.4 μmol , 21.3% yield, FA). $M+H^+ = 566.2$ (LCMS); ^1H NMR (400MHz, $\text{METHANOL-}d_4$) δ 9.06 (s, 1H), 8.57 (br s, 1H), 8.29 - 8.19 (m, 2H), 8.16 (d, $J = 2.0$ Hz, 1H), 8.05 (s, 1H), 7.59 - 7.46 (m, 3H), 4.05 - 3.94 (m, 1H), 3.24 - 3.14 (m, 1H), 3.09 (q, $J = 7.5$ Hz, 2H), 2.71 (q, $J = 7.4$ Hz, 2H), 2.32 (br d, $J = 11.4$ Hz, 2H), 2.16 (br d, $J = 11.1$ Hz, 2H), 1.69 - 1.44 (m, 4H), 1.36 (t, $J = 7.5$ Hz, 3H), 1.26 (t, $J = 7.5$ Hz, 3H).

Example 7: Synthesis of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyrazin-2-yl)-2-chlorobenzenesulfonamide (98)



**Step 1:**

[00204] To a solution of 6-methoxypyrazin-2-amine (100 mg, 799.2 μmol) in CHCl_3 (5.0 mL) was added NCS (107 mg, 799.2 μmol). The mixture was stirred at 40°C for 12 h. The reaction was concentrated to give a residue. The residue was purified by prep-TLC (SiO_2) to give 5-chloro-6-methoxypyrazin-2-amine (25 mg, 141.0 μmol , 17.6% yield). ^1H NMR (400MHz, $\text{CHLOROFORM-}d$) δ 7.33 (s, 1H), 4.42 (br s, 2H), 3.96 (s, 3H).

Step 2:

[00205] To a solution of 5-chloro-6-methoxypyrazin-2-amine (25 mg, 156.7 μmol) in DCM (2.0 mL) was added pyridine (37 mg, 470.0 μmol , 37.9 μL) and 2-chlorobenzenesulfonyl chloride (50 mg, 235.0 μmol , 32.0 μL). The mixture was stirred at 45°C for 12 h. The reaction was concentrated to give a residue. The residue was purified by column chromatography (SiO_2) to afford 2-chloro-N-(5-chloro-6-methoxypyrazin-2-yl)benzenesulfonamide (110 mg). $\text{M}+\text{H}^+ = 333.8$ (LCMS).

Step 3:

[00206] A mixture of tert-butyl ((1r,4r)-4-((8-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (80 mg, 161.1 μmol), 2-chloro-N-(5-chloro-6-methoxypyrazin-2-yl)benzenesulfonamide (54 mg, 161.1 μmol), K_3PO_4 (0.5 M, 644.6 μL), [2-(2-aminophenyl)phenyl]-chloro-palladium;bis(1-adamantyl)-butyl-phosphane (11 mg, 16.1 μmol) in THF (2.0 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 80°C for 12 h under N_2 atmosphere. The reaction was concentrated to give a residue. The residue was purified by prep-TLC (SiO_2) to give tert-butyl ((1r,4r)-4-((6-(5-(2-chlorophenyl)sulfonamido)-3-methoxypyrazin-2-yl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (50 mg, 17.6 μmol , 10.9% yield). $\text{M}+\text{H}^+ = 668.1$ (LCMS).

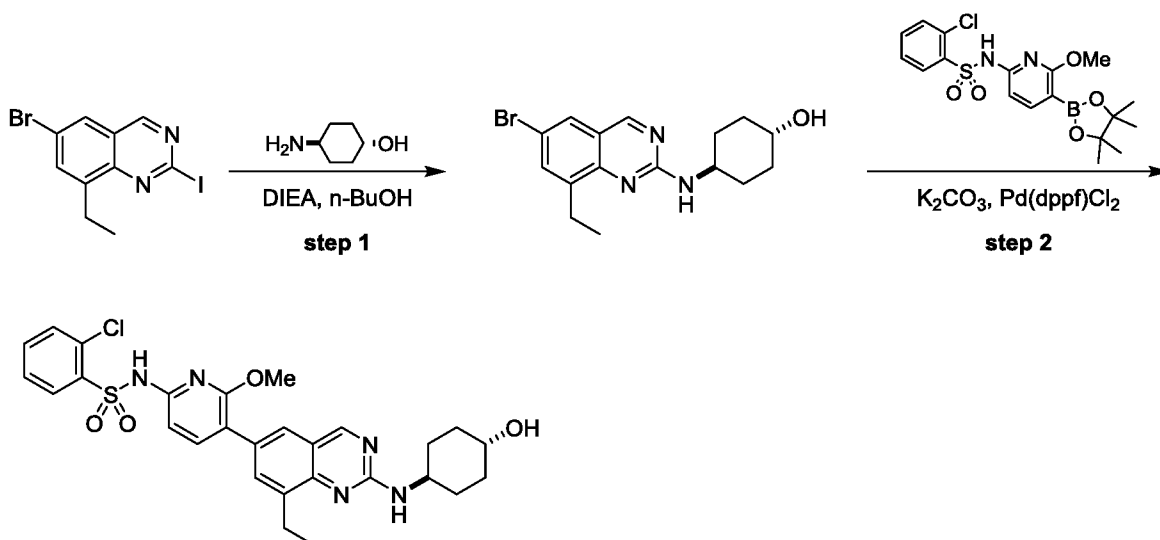
Step 4:

[00207] To a solution of tert-butyl ((1r,4r)-4-((6-(5-(2-chlorophenyl)sulfonamido)-3-methoxypyrazin-2-yl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (50 mg, 74.8 μmol) in DCM (2.0 mL) was added TFA (1.0 mL). The mixture was stirred at 20°C for 10 min. The reaction was concentrated to give a residue. The residue was dissolved in MeOH (1.0 mL) and basified pH to 7 with $\text{NH}_3\cdot\text{H}_2\text{O}$ (25% solution). The residue was purified by prep-HPLC (FA condition) to afford N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-

methoxypyrazin-2-yl)-2-chlorobenzenesulfonamide (6.4 mg, 10.1 μmol , 13.6% yield, FA).

$M+H^+ = 568.2$ (LCMS); ^1H NMR (400MHz, $\text{METHANOL-}d_4$) δ 8.97 (s, 1H), 8.48 (br s, 1H), 8.33 (d, $J = 7.3$ Hz, 1H), 8.13 (br d, $J = 3.7$ Hz, 2H), 7.87 (s, 1H), 7.64 - 7.44 (m, 3H), 3.96 (br t, $J = 11.4$ Hz, 1H), 3.74 (s, 3H), 3.23 - 3.10 (m, 1H), 3.04 (q, $J = 7.4$ Hz, 2H), 2.30 (br d, $J = 12.3$ Hz, 2H), 2.13 (br d, $J = 11.2$ Hz, 2H), 1.65 - 1.41 (m, 4H), 1.31 (t, $J = 7.5$ Hz, 3H).

Example 8: Synthesis of 2-chloro-N-(5-(8-ethyl-2-(((1*r*,4*r*)-4-hydroxycyclohexyl)amino)quinazolin-6-yl)-6-methoxypyridin-2-yl)benzenesulfonamide (101)



Step 1:

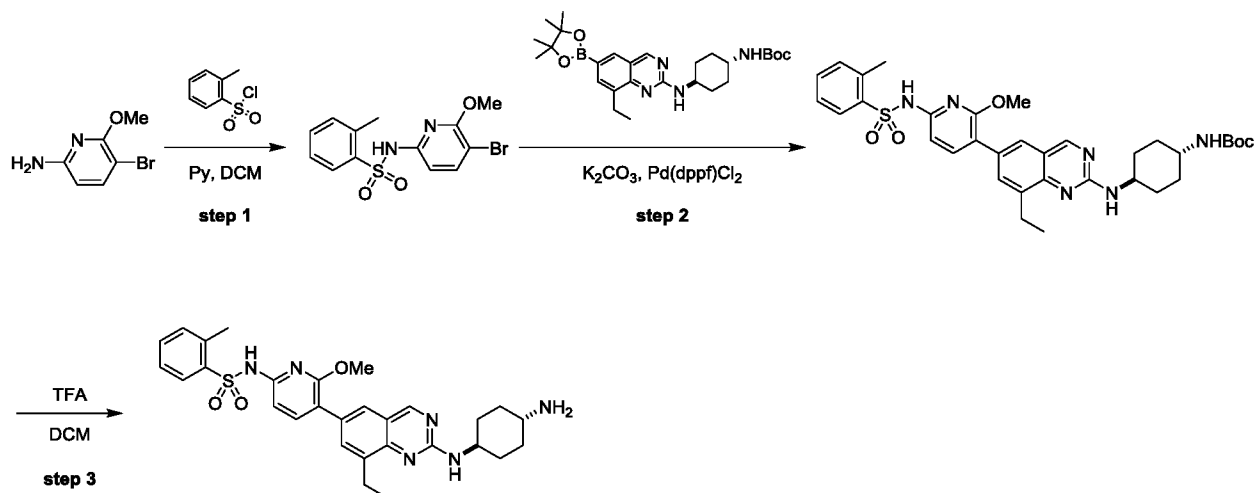
[00208] To a solution of 6-bromo-8-ethyl-2-iodoquinazoline (0.18 g, 495.8 μmol) in *n*-BuOH (10.0 mL) was added 4-aminocyclohexanol (114 mg, 991.7 μmol) and DIEA (192 mg, 1.4 mmol, 259.1 μL). The mixture was stirred at 100°C for 12 h. The mixture was concentrated to get crude residue. The residue was purified by column chromatography (SiO_2) to afford (1*r*,4*r*)-4-((6-bromo-8-ethylquinazolin-2-yl)amino)cyclohexanol (160 mg, 381.8 μmol , 77.0% yield). $M+H^+ = 352.1$ (LCMS).

Step 2:

[00209] To a solution of 2-chloro-N-(6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)benzenesulfonamide (145 mg, 342.6 μmol) and K_2CO_3 (71 mg, 513.9 μmol) in dioxane (2.0 mL) and H_2O (0.2 mL) were added (1*r*,4*r*)-4-((6-bromo-8-ethylquinazolin-2-yl)amino)cyclohexanol (60 mg, 171.3 μmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (12 mg, 17.1 μmol). The mixture was stirred at 90°C for 12 h under N_2 . The mixture was concentrated to get crude residue. The residue was purified by prep-TLC (SiO_2). The residue was purified by prep-HPLC (FA condition) to afford 2-chloro-N-(5-(8-ethyl-2-(((1*r*,4*r*)-4-

hydroxycyclohexyl)amino)quinazolin-6-yl)-6-methoxypyridin-2-yl)benzenesulfonamide (24.0 mg, 38.7 μmol , 22.6% yield, FA) as. $\text{M}+\text{H}^+ = 568.1$ (LCMS); ^1H NMR (METHANOL- d_4 , 400MHz) δ 8.92 (s, 1H), 8.34 - 8.26 (m, 1H), 7.67 - 7.61 (m, 3H), 7.61 - 7.55 (m, 2H), 7.54 - 7.48 (m, 1H), 6.64 (d, $J = 7.9$ Hz, 1H), 3.99 - 3.85 (m, 1H), 3.71 - 3.56 (m, 4H), 3.03 (q, $J = 7.5$ Hz, 2H), 2.18 (br d, $J = 9.3$ Hz, 2H), 2.02 (br d, $J = 9.8$ Hz, 2H), 1.51 - 1.34 (m, 4H), 1.30 (t, $J = 7.5$ Hz, 3H).

Example 9: Synthesis of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-methylbenzenesulfonamide (103)



Step 1:

[00210] To a solution of 5-bromo-6-methoxypyridin-2-amine (50 mg, 246.2 μmol) and 2-methylbenzene-1-sulfonyl chloride (70.4 mg, 369.3 μmol , 53.3 μL) in DCM (3.0 mL) was added pyridine (58.4 mg, 738.7 μmol , 59.6 μL), the mixture was stirred at 45°C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2) to give N-(5-bromo-6-methoxypyridin-2-yl)-2-methylbenzenesulfonamide (80 mg, 208.2 μmol , 84.5% yield). $\text{M}+\text{H}^+ = 359.1$ (LCMS).

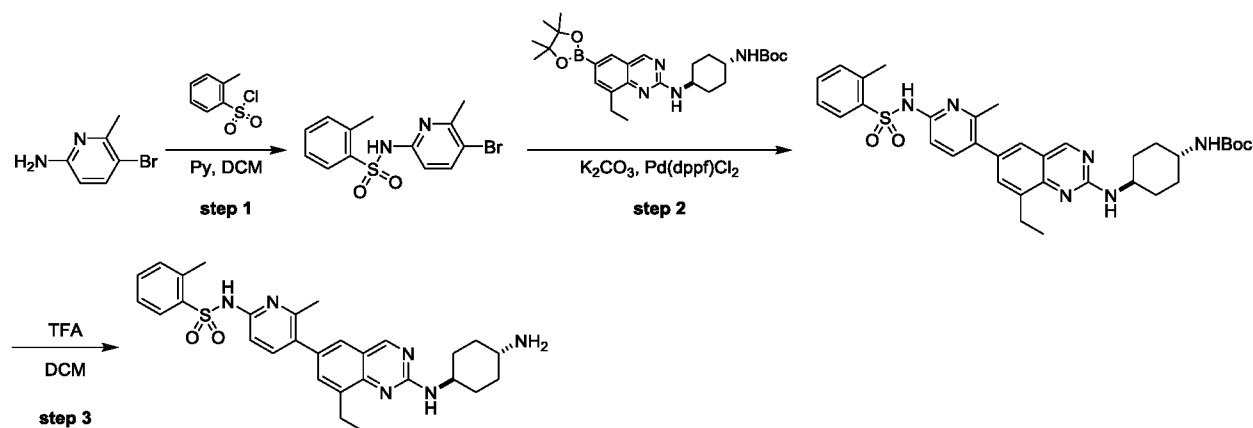
Step 2:

[00211] A mixture of N-(5-bromo-6-methoxypyridin-2-yl)-2-methylbenzenesulfonamide (29 mg, 83.9 μmol), tert-butyl ((1*r*,4*r*)-4-((8-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (50 mg, 100.7 μmol), K_2CO_3 (34 mg, 251.7 μmol), and $\text{Pd}(\text{dppf})\text{Cl}_2$ (6 mg, 8.3 μmol) in dioxane (2.0 mL) and H_2O (0.2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90°C for 12 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO_2) to give tert-butyl ((1*r*,4*r*)-4-((8-ethyl-6-(2-methoxy-6-(2-methylphenylsulfonamido)pyridin-3-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (30 mg, 36.5 μmol , 43.4% yield). $\text{M}+\text{H}^+ = 647.4$ (LCMS).

Step 3:

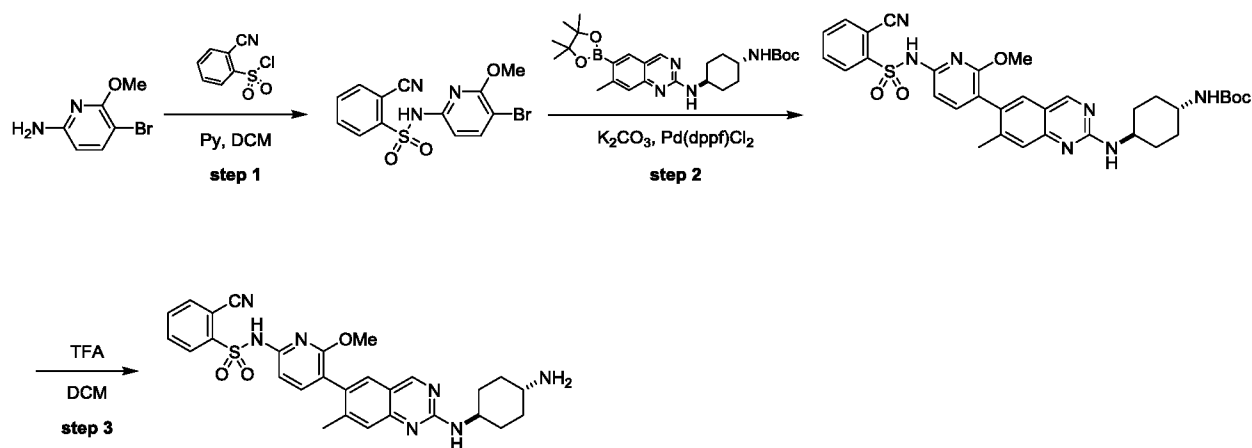
[00212] To a solution of tert-butyl (((1*r*,4*r*)-4-((8-ethyl-6-(2-methoxy-6-(2-methylphenyl)sulfonamido)pyridin-3-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (30 mg, 46.3 μ mol) in TFA (1.0 mL) and DCM (2.0 mL) was stirred at 20°C for 0.5 h. The mixture was concentrated under reduced pressure to give a residue. The residue was dissolved in MeOH (2.0 mL) and basified pH to 8 with $\text{NH}_3 \cdot \text{H}_2\text{O}$ (25% solution), concentrated to give a residue. The residue was purified by pre-HPLC (FA condition) to afford N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-methylbenzenesulfonamide (21.3 mg, 35.5 μ mol, 76.7% yield, FA). $M+H^+ = 547.3$ (LCMS); ^1H NMR (400MHz, $\text{METHANOL-}d_4$) δ 8.94 (s, 1H), 8.54 (br s, 1H), 8.16 (d, $J = 7.5$ Hz, 1H), 7.69 - 7.59 (m, 3H), 7.53 - 7.46 (m, 1H), 7.41 - 7.32 (m, 2H), 6.64 (d, $J = 7.9$ Hz, 1H), 4.02 - 3.90 (m, 1H), 3.71 (s, 3H), 3.22 - 3.11 (m, 1H), 3.03 (q, $J = 7.5$ Hz, 2H), 2.70 (s, 3H), 2.30 (br d, $J = 11.0$ Hz, 2H), 2.14 (br d, $J = 11.7$ Hz, 2H), 1.67 - 1.40 (m, 4H), 1.30 (t, $J = 7.5$ Hz, 3H).

Example 10: Synthesis of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methylpyridin-2-yl)-2-methylbenzenesulfonamide (112)



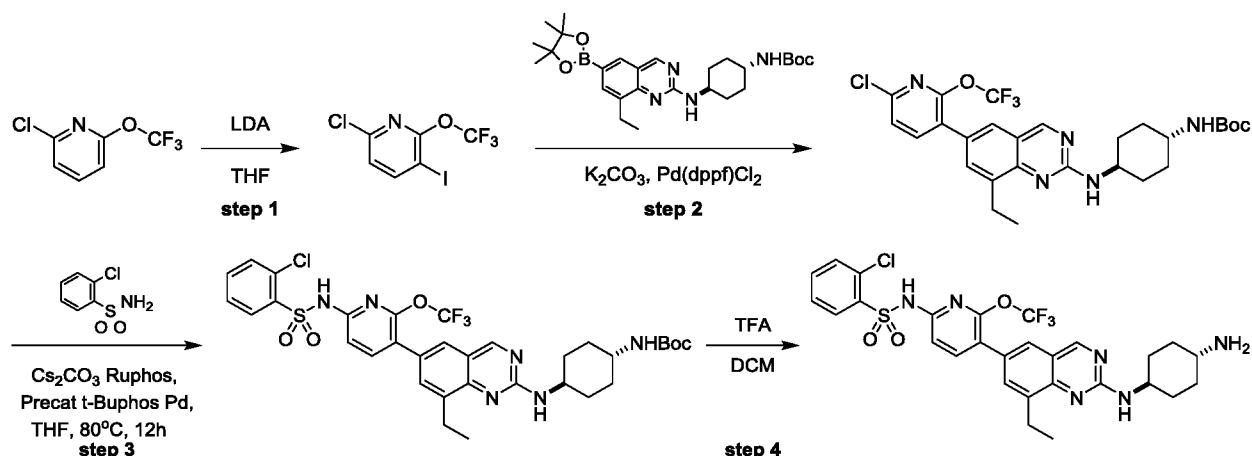
[00213] The title compound was synthesized according to the synthetic procedure reported for the preparation of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-methylbenzenesulfonamide (18.1 mg, 22.0% yield, FA). $M+H^+ = 531.2$ (LCMS); ^1H NMR (400MHz, $\text{METHANOL-}d_4$) δ 8.99 (s, 1H), 8.55 (br s, 1H), 8.09 (d, $J = 7.5$ Hz, 1H), 7.62 (d, $J = 8.8$ Hz, 1H), 7.52 - 7.39 (m, 3H), 7.37 - 7.30 (m, 2H), 7.15 (d, $J = 8.8$ Hz, 1H), 4.04 - 3.92 (m, 1H), 3.22 - 3.12 (m, 1H), 3.06 (q, $J = 7.4$ Hz, 2H), 2.72 (s, 3H), 2.43 - 2.26 (m, 5H), 2.14 (br d, $J = 11.9$ Hz, 2H), 1.68 - 1.42 (m, 4H), 1.32 (t, $J = 7.5$ Hz, 3H).

Example 11: Synthesis of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-7-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-cyanobenzenesulfonamide (102)



[00214] The title compound was synthesized according to the synthetic procedure reported for the preparation of N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-methylbenzenesulfonamide (5.6 mg, 9.4 μ mol, 15.1% yield, FA). $M+H^+$ = 544.3 (LCMS); 1H NMR (400MHz, METHANOL- d_4) δ 8.92 (s, 1H), 8.51 (br s, 1H), 8.34 (d, J = 7.7 Hz, 1H), 7.97 (d, J = 7.7 Hz, 1H), 7.91 - 7.73 (m, 2H), 7.49 - 7.33 (m, 3H), 6.67 (d, J = 7.9 Hz, 1H), 4.00 - 3.89 (m, 1H), 3.50 (s, 3H), 3.21 - 3.09 (m, 1H), 2.28 - 2.07 (m, 7H), 1.68 - 1.39 (m, 4H).

Example 12: Synthesis of N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-(trifluoromethoxy)pyridin-2-yl)-2-chlorobenzenesulfonamide (107)



Step 1:

[00215] To a solution of LDA (2 M, 2.5 mL) in THF (27.0 mL) was added dropwise a solution of 2-chloro-6-(trifluoromethoxy)pyridine (900 mg, 4.6 mmol) in THF (9.0 mL) at $-78^\circ C$ under N_2 . The mixture was stirred at $-78^\circ C$ for 2 h. A solution of I_2 (1.3 g, 5.0 mmol, 1.0 mL) in THF (9.0 mL) was added at $-78^\circ C$. Then the mixture was slowly warmed to $25^\circ C$ and stirred for 12 h. The reaction was quenched with saturated NH_4Cl (15.0 mL) and extracted with ethyl acetate ($15.0\text{ mL} \times 3$). The combined organic phase was washed with brine ($15\text{ mL} \times 3$), dried over anhydrous Na_2SO_4 , filtered and concentrated to give a residue. The residue was purified by

prep-TLC (SiO₂) to give 6-chloro-3-iodo-2-(trifluoromethoxy)pyridine (1.2 g, 3.0 mmol, 65.2% yield). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 8.10 (d, *J* = 8.1 Hz, 1H), 7.03 (d, *J* = 8.1 Hz, 1H).

Step 2:

[00216] A mixture of 6-chloro-3-iodo-2-(trifluoromethoxy)pyridine (63 mg, 193.4 μ mol), tert-butyl ((1*r*,4*r*)-4-((8-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (80 mg, 161.1 μ mol), K₂CO₃ (34 mg, 241.7 μ mol) and Pd(dppf)Cl₂ (12 mg, 16.1 μ mol) in dioxane (2.0 mL) and H₂O (0.2 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80°C for 12 h under N₂ atmosphere. The reaction was concentrated to give a residue. The residue was purified by prep-TLC (SiO₂) to afford tert-butyl ((1*r*,4*r*)-4-((6-(6-chloro-2-(trifluoromethoxy)pyridin-3-yl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (90 mg, 96.8 μ mol, 60.1% yield). *M*+*H*⁺ = 566.1(LCMS).

Step 3:

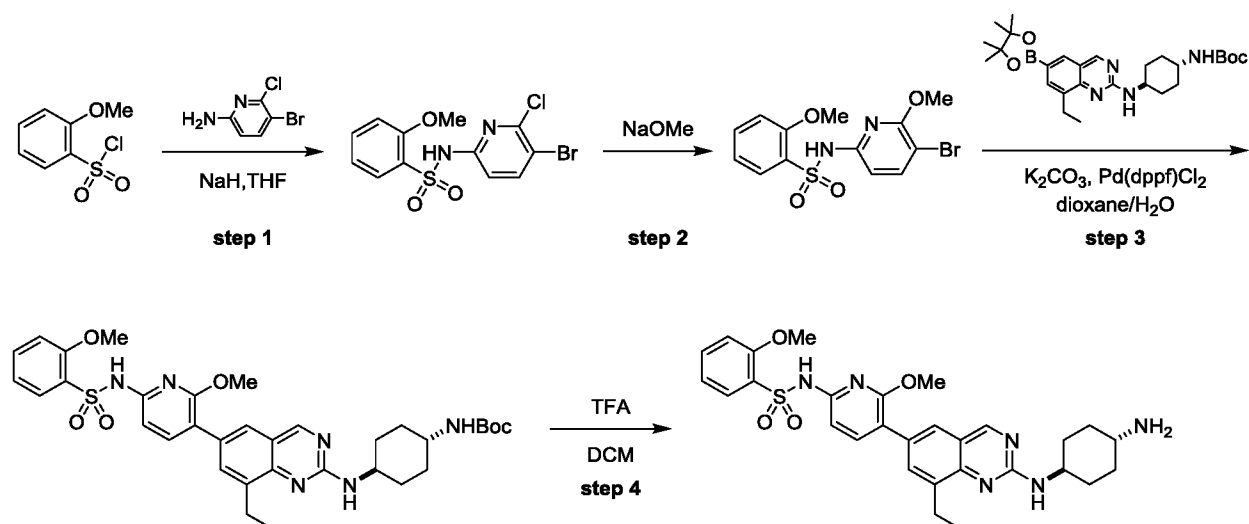
[00217] A mixture of tert-butyl ((1*r*,4*r*)-4-((6-(6-chloro-2-(trifluoromethoxy)pyridin-3-yl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (90 mg, 159.0 μ mol), 2-chlorobenzenesulfonamide (34 mg, 174.9 μ mol), Cs₂CO₃ (155 mg, 477.0 μ mol), dicyclohexyl-[2-(2,6-diisopropoxyphenyl)phenyl]phosphane (8 mg, 15.9 μ mol) and [2-(2-aminoethyl)phenyl]-chloro-palladium;dtert-butyl-[2-(2,4,6-triisopropylphenyl) phenyl]phosphane (11 mg, 15.9 μ mol) in THF (5.0 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 80°C for 12 h under N₂ atmosphere. The reaction was concentrated to give a residue. The residue was purified by prep-TLC (SiO₂) to give tert-butyl ((1*r*,4*r*)-4-((6-(2-chlorophenylsulfonamido)-2-(trifluoromethoxy)pyridin-3-yl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (80 mg, 33.3 μ mol, 20.9% yield). *M*+*H*⁺ = 721.3(LCMS).

Step 4:

[00218] To a solution of tert-butyl ((1*r*,4*r*)-4-((6-(2-chlorophenylsulfonamido)-2-(trifluoromethoxy)pyridin-3-yl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (80 mg, 110.9 μ mol) in DCM (2.0 mL) was added TFA (1.0 mL). The mixture was stirred at 20°C for 15 min. The reaction was concentrated to give a residue. The residue was dissolved in MeOH (2.0 mL) and basified pH to 7 with NH₃.H₂O (25% solution). The residue was purified by prep-HPLC (FA condition) to afford N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-(trifluoromethoxy)pyridin-2-yl)-2-chlorobenzenesulfonamide (14 mg, 20.6 μ mol, 18.6% yield, FA). *M*+*H*⁺ = 621.2 (LCMS); ¹H NMR (400MHz, METHANOL-*d*₄) δ 8.99 (s, 1H), 8.50 (br s, 1H), 8.33 - 8.24 (m, 1H), 7.88 (d, *J* = 8.2 Hz, 1H), 7.64 - 7.47 (m, 5H), 7.04 (d, *J* = 8.2 Hz, 1H), 3.99 (tt, *J* = 3.9, 11.2 Hz, 1H), 3.19 (tt, *J* = 3.9, 11.5 Hz, 1H), 3.06 (q, *J* = 7.5 Hz, 2H), 2.32

(br d, $J = 11.6$ Hz, 2H), 2.16 (br d, $J = 11.9$ Hz, 2H), 1.68 - 1.42 (m, 4H), 1.32 (t, $J = 7.5$ Hz, 3H).

Example 13: Synthesis of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-methoxybenzenesulfonamide (109)



Step 1:

[00219] To a solution of 5-bromo-6-chloropyridin-2-amine (500 mg, 2.41 mmol) in THF (8.0 mL) was added NaH (144 mg, 3.6 mmol, 60%) stirred for 30 min, then 2-methoxybenzenesulfonyl chloride (498 mg, 2.4 mmol) in THF (2.0 mL) was added. The mixture was stirred at 25°C for 2 h. The reaction mixture was quenched by addition saturated ammonium chloride solution (10.0 mL), and then added H₂O (10.0 mL) and extracted with ethyl acetate (30.0 mL × 3). The combined organic layers were washed with brine (30.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂) to afford N-(5-bromo-6-chloropyridin-2-yl)-2-methoxybenzenesulfonamide (200 mg, 490.4 μmol, 20.3% yield). $M+H^+ = 379.0$ (LCMS).

Step 2:

[00220] A solution of N-(5-bromo-6-chloropyridin-2-yl)-2-methoxybenzenesulfonamide (200 mg, 529.6 μmol) in NaOMe (5 mL, 30% solution) was stirred at 70°C for 3 h. The reaction mixture was added H₂O (30.0 mL) and extracted with ethyl acetate (20.0 mL × 3). The combined organic phase was washed with brine (10.0 mL × 3), dried with anhydrous Na₂SO₄, filtered and concentrated in vacuum to give a residue. The residue was purified by prep-TLC (SiO₂) to afford N-(5-bromo-6-methoxypyridin-2-yl)-2-methoxybenzenesulfonamide (100 mg, 219.7 μmol, 41.4% yield). $M+H^+ = 372.9$ (LCMS).

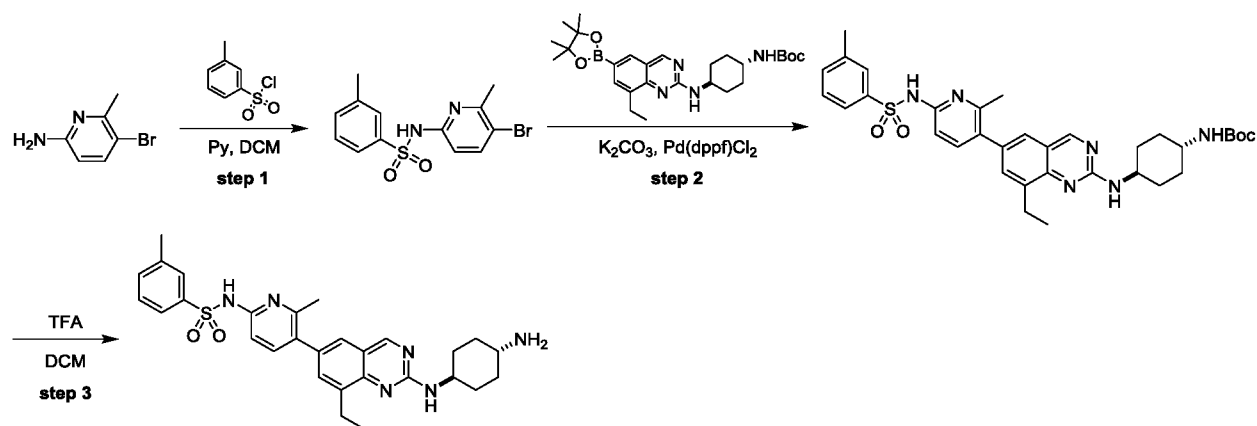
Step 3:

[00221] A mixture of N-(5-bromo-6-methoxypyridin-2-yl)-2-methoxybenzenesulfonamide (100 mg, 267.9 μmol), tert-butyl (((1r,4r)-4-((8-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (159 mg, 321.5 μmol), K_2CO_3 (111 mg, 803.8 μmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (19 mg, 26.79 μmol) in dioxane (2.0 mL) and H_2O (0.2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90°C for 12 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (SiO_2) to afford tert-butyl (((1r,4r)-4-((8-ethyl-6-(2-methoxy-6-(2-methoxyphenyl)sulfonamido)pyridin-3-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (160 mg, 91.4 μmol , 34.1% yield). $\text{M}+\text{H}^+ = 663.4$ (LCMS).

Step 4:

[00222] To a solution of tert-butyl (((1r,4r)-4-((8-ethyl-6-(2-methoxy-6-(2-methoxyphenyl)sulfonamido)pyridin-3-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (160 mg, 241.4 μmol) in DCM (2.0 mL) was added TFA (1.5 g, 13.5 mmol, 1 mL). The mixture was stirred at 25°C for 0.5 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with MeOH (2.0 mL), then used the ammonium hydroxide (25% solution) to adjust the pH to 7~8, then filtered. The mixture was purified by prep-HPLC (FA condition) to afford N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-methoxybenzenesulfonamide (14.7 mg, 23.9 μmol , 9.9% yield, FA). $\text{M}+\text{H}^+ = 563.2$ (LCMS); ^1H NMR (METHANOL- d_4 , 400MHz) δ 8.96 (s, 1H), 8.57 (br s, 1H), 8.04 (dd, $J = 1.5, 7.8$ Hz, 1H), 7.76 - 7.54 (m, 4H), 7.28 - 7.01 (m, 2H), 6.72 (d, $J = 7.9$ Hz, 1H), 3.96 (s, 4H), 3.76 (s, 3H), 3.18 (br t, $J = 11.3$ Hz, 1H), 3.04 (q, $J = 7.5$ Hz, 2H), 2.32 (br d, $J = 11.5$ Hz, 2H), 2.16 (br d, $J = 10.9$ Hz, 2H), 1.69 - 1.41 (m, 4H), 1.32 (t, $J = 7.5$ Hz, 3H).

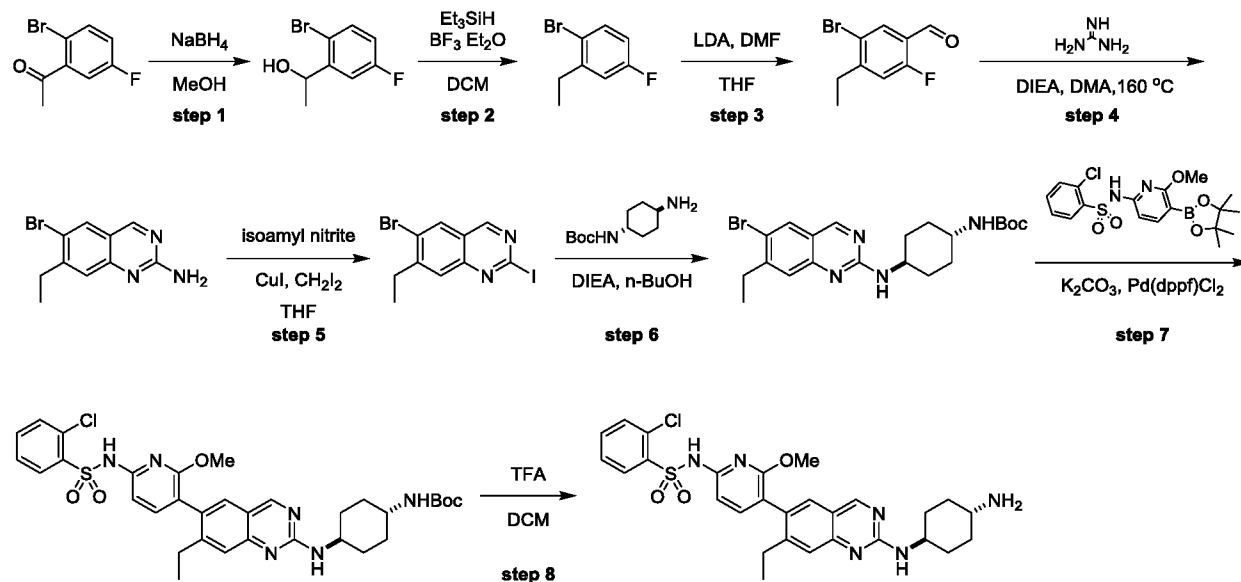
Example 14: Synthesis of N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methylpyridin-2-yl)-3-methylbenzenesulfonamide (113)



[00223] The title compound was synthesized according to the synthetic procedure reported for the preparation of N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-

methoxypyridin-2-yl)-2-methoxybenzenesulfonamide. 16.4 mg, 22.3% yield. $M+H^+ = 531.3$ (LCMS); $^1\text{H NMR}$ ($\text{DMSO}-d_6$, 400MHz) δ 9.02 (br s, 1H), 7.70 - 7.60 (m, 2H), 7.47 (br d, $J = 8.6$ Hz, 2H), 7.39 - 7.27 (m, 4H), 6.80 (br d, $J = 8.6$ Hz, 1H), 6.62 (br d, $J = 6.6$ Hz, 1H), 6.06 (br s, 1H), 3.77 (s, 1H), 3.23 (s, 1H), 2.95 (q, $J = 7.4$ Hz, 2H), 2.34 (s, 3H), 2.29 - 2.21 (m, 3H), 2.03 (brs, 2H), 1.85 (br s, 2H), 1.41 - 1.28 (m, 4H), 1.24 (br t, $J = 7.4$ Hz, 3H).

Example 15: Synthesis of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-7-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (110)



Step 1:

[00224] To a solution of 1-(2-bromo-5-fluorophenyl)ethanone (9.2 g, 42.3 mmol) in MeOH (92.0 mL) was cooled to 0°C and added NaBH_4 (2.2 g, 59.3 mmol). The mixture was stirred at 25°C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was diluted with saturated NaHCO_3 solution (100.0 mL) and the mixture was extracted with ethyl acetate ($100.0 \text{ mL} \times 3$). The combined organic layers were washed with brine ($50.0 \text{ mL} \times 3$), dried over Na_2SO_4 , filtered and concentrated to afford 1-(2-bromo-5-fluorophenyl)ethanol (9 g, crude).

Step 2:

[00225] To a solution of 1-(2-bromo-5-fluorophenyl)ethanol (9 g, 41.0 mmol) and Et_3SiH (9.5 g, 82.1 mmol, 13.1 mL) in DCM (100.0 mL) was added $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (11.6 g, 82.1 mmol, 10.1 mL) at 0°C . The mixture was stirred at 35°C for 36 h. The mixture was quenched by addition Sat. NaHCO_3 (100.0 mL) at 0°C , extracted with DCM ($100.0 \text{ mL} \times 3$). The combined organic layers were washed with brine ($50.0 \text{ mL} \times 3$), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2) to afford 1-bromo-2-ethyl-4-fluorobenzene (6.3 g, 24.8 mmol, crude). $^1\text{H NMR}$

(CHLOROFORM-*d*, 400 MHz): δ 7.53 - 7.43 (m, 1H), 6.97 (dd, J = 2.9, 9.5 Hz, 1H), 6.79 (dt, J = 3.0, 8.3 Hz, 1H), 2.74 (q, J = 7.5 Hz, 2H), 1.34 - 1.16 (m, 6H).

Step 3:

[00226] To a solution of 1-bromo-2-ethyl-4-fluorobenzene (2.0 g, 9.8 mmol) in THF (35.0 mL) was added LDA (2 M, 5.9 mL) at -78°C. The mixture was stirred at -78°C for 1 h. And then DMF (935 mg, 12.8 mmol, 985.1 μ L) was added at -78°C for 1 h. The reaction mixture was diluted with NH₄Cl (30.0 mL) and extracted with ethyl acetate (10.0 mL \times 3). The combined organic layers were washed with brine (10.0 mL \times 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂) to afford 5-bromo-4-ethyl-2-fluorobenzaldehyde (1.0 g, 3.4 mmol, 35.1% yield). ¹H NMR (CHLOROFORM-*d*, 400 MHz): δ 10.25 (s, 1H), 8.02 (d, J = 7.0 Hz, 1H), 7.08 (d, J = 11.0 Hz, 1H), 2.80 (q, J = 7.5 Hz, 2H), 1.27 (t, J = 7.5 Hz, 3H).

Step 4:

[00227] To a solution of guanidine (262 mg, 2.1 mmol, H₂CO₃) and DIEA (839 mg, 6.4 mmol, 1.1 mL) in DMA (10.0 mL) was added a solution of 5-bromo-4-ethyl-2-fluorobenzaldehyde (0.5 g, 2.1 mmol) in DMA (1.5 mL). Then the mixture was stirred at 160°C for 2 h. The mixture was concentrated to get crude residue and then H₂O (30.0 mL) was added. It was extracted with ethyl acetate (30.0 mL \times 3). The combined organic layers were washed with brine (20.0 mL \times 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂) to afford 6-bromo-7-ethylquinazolin-2-amine (130 mg, 217.2 μ mol, 10.0% yield). $M+H^+$ = 251.9 (LCMS).

Step 5:

[00228] To a solution of 6-bromo-7-ethylquinazolin-2-amine (130 mg, 515.6 μ mol) and diiodomethane (690 mg, 2.5 mmol, 207.9 μ L) in THF (2.0 mL) was added CuI (98 mg, 515.6 μ mol) isopentyl nitrite (181 mg, 1.5 mmol, 208.3 μ L). The mixture was stirred at 65°C for 12 h. The mixture was poured into NH₃.H₂O (2.0 mL, 25 %) and filtered. The filtrate was extracted with ethyl acetate (5.0 mL \times 3). The combined organic layers were washed with brine (5.0 mL \times 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂) to afford 6-bromo-7-ethyl-2-iodoquinazoline (50 mg, 110.0 μ mol, 21.3% yield). $M+H^+$ = 362.8 (LCMS);

Step 6:

[00229] To a solution of 6-bromo-7-ethyl-2-iodoquinazoline (50 mg, 137.7 μ mol) and DIEA (53 mg, 413.2 μ mol, 71.9 μ L) in n-BuOH (2.0 mL) was added tert-butyl ((1*r*,4*r*)-4-aminocyclohexyl)carbamate (59 mg, 275.4 μ mol). The mixture was stirred at 120°C for 12 h. The mixture was concentrated to get crude residue. The residue was purified by prep-TLC

(SiO₂) to afford tert-butyl ((1r,4r)-4-((6-bromo-7-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (50 mg, crude).

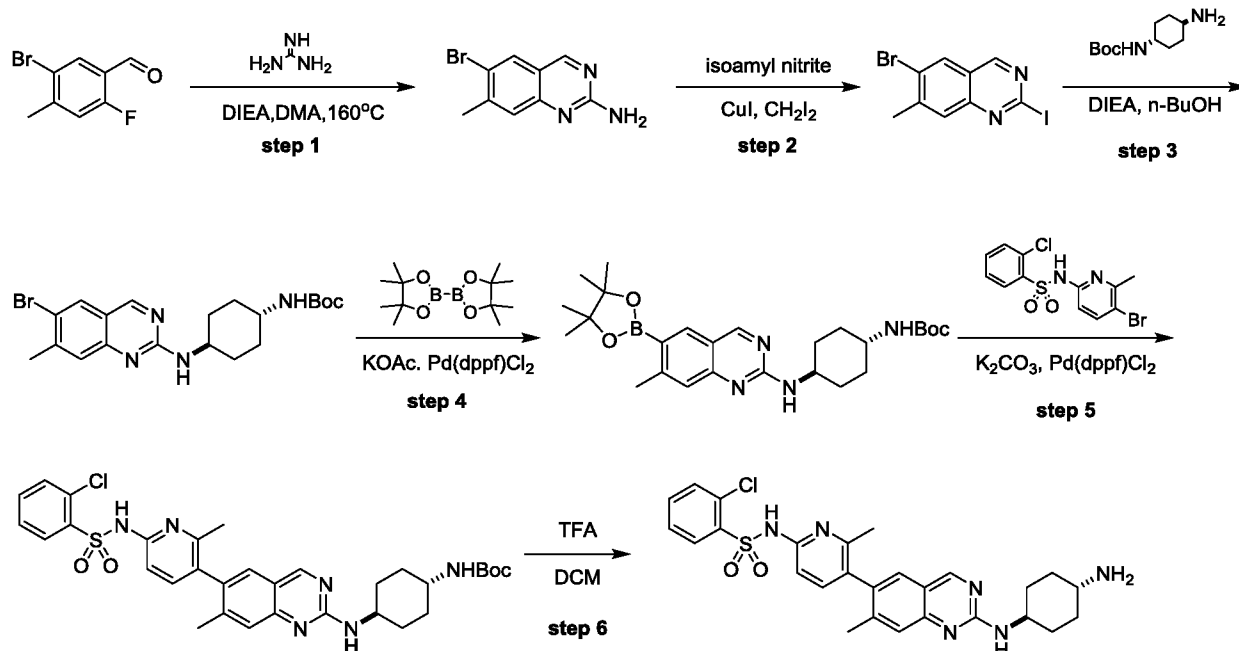
Step 7:

[00230] To a solution of tert-butyl ((1r,4r)-4-((6-bromo-7-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (50 mg, 111.2 μ mol) and K₂CO₃ (15 mg, 111.2 μ mol) in dioxane (2.0 mL) and H₂O (0.2 mL) were added 2-chloro-N-(6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)benzenesulfonamide (56 mg, 133.5 μ mol) and Pd(dppf)Cl₂ (81 mg, 111.2 μ mol). The mixture was stirred at 90°C for 12 h under N₂. The mixture was concentrated to get crude residue. The residue was purified by prep-TLC (SiO₂) to afford tert-butyl ((1r,4r)-4-((6-(6-(2-chlorophenylsulfonamido)-2-methoxypyridin-3-yl)-7-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (40 mg, crude).

Step 8:

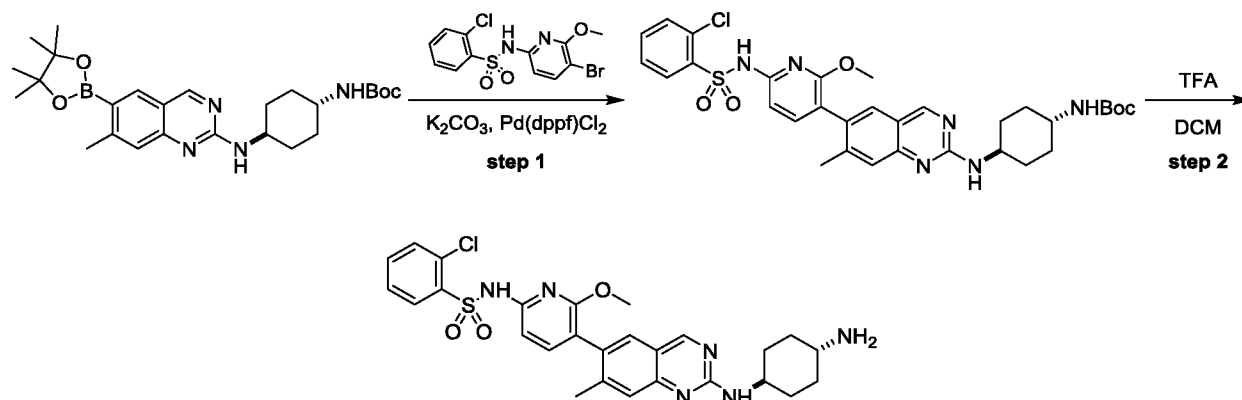
[00231] A solution of tert-butyl ((1r,4r)-4-((6-(6-(2-chlorophenylsulfonamido)-2-methoxypyridin-3-yl)-7-ethylquinazolin-2-yl)amino)cyclohexyl)carbamate (40 mg, 59.9 μ mol) in TFA (1.0 mL) and DCM (2.0 mL) was stirred at 25°C for 10 min. The mixture was concentrated to get crude residue. The residue was dissolved in MeOH (2.0 mL) and basified pH to 8 with NH₃.H₂O (25% solution), concentrated to give a residue. The residue was purified by prep-HPLC (FA condition) to afford N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (14.0 mg, 22.1 μ mol, 36.9% yield, FA). M+H⁺ = 567.2 (LCMS); ¹H NMR (METHANOL-*d*₄, 400MHz) δ 8.91 (s, 1H), 8.52 (br s, 1H), 8.33 - 8.27 (m, 1H), 7.61 - 7.56 (m, 2H), 7.53 - 7.46 (m, 1H), 7.44 - 7.37 (m, 3H), 6.62 (d, *J* = 7.7 Hz, 1H), 4.02 - 3.87 (m, 1H), 3.55 (s, 3H), 3.22 - 3.11 (m, 1H), 2.46 (br d, *J* = 7.1 Hz, 2H), 2.23 (br d, *J* = 11.5 Hz, 2H), 2.17 - 2.05 (m, 2H), 1.67 - 1.55 (m, 2H), 1.52 - 1.41 (m, 2H), 1.06 (t, *J* = 7.6 Hz, 3H).

Example 16: Synthesis of N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-methylquinazolin-6-yl)-6-methylpyridin-2-yl)-2-chlorobenzenesulfonamide (106)



[00232] The title compound was synthesized according to the synthetic procedure reported for the preparation of N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (5.5 mg, 9.1 μmol , 14.6% yield, FA). $\text{M}+\text{H}^+$ = 537.3 (LCMS); ^1H NMR (400MHz, $\text{METHANOL-}d_4$) δ 8.95 (s, 1H), 8.47 (br s, 1H), 8.26 - 8.19 (m, 1H), 7.58 - 7.42 (m, 6H), 7.18 (d, J = 8.8 Hz, 1H), 4.02 - 3.88 (m, 1H), 3.14 (dt, J = 4.0, 7.7 Hz, 1H), 2.28 - 2.05 (m, 10H), 1.72 - 1.53 (m, 2H), 1.52 - 1.39 (m, 2H).

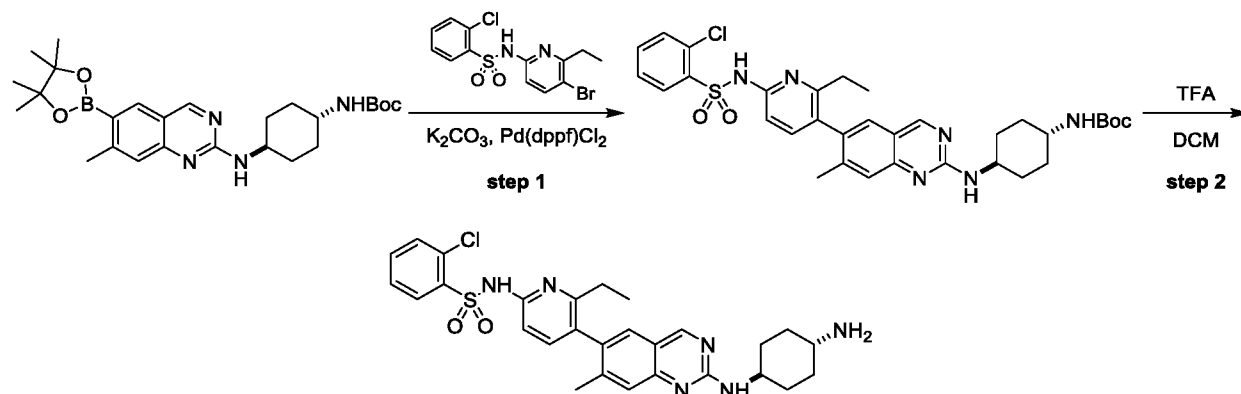
Example 17: N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (104)



[00233] The title compound was synthesized according to the synthetic procedure reported for the preparation of N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-7-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (11.6 mg, 19.1 μmol , 24.9% yield, FA). $\text{M}+\text{H}^+$ = 553.1 (LCMS); ^1H NMR (400MHz, $\text{METHANOL-}d_4$) δ 8.90 (s, 1H), 8.56 (br s, 1H), 8.29 (d, J = 7.7 Hz, 1H), 7.62 - 7.53 (m, 2H), 7.52 - 7.44 (m, 1H), 7.38 (dd, J = 7.3, 15.0 Hz,

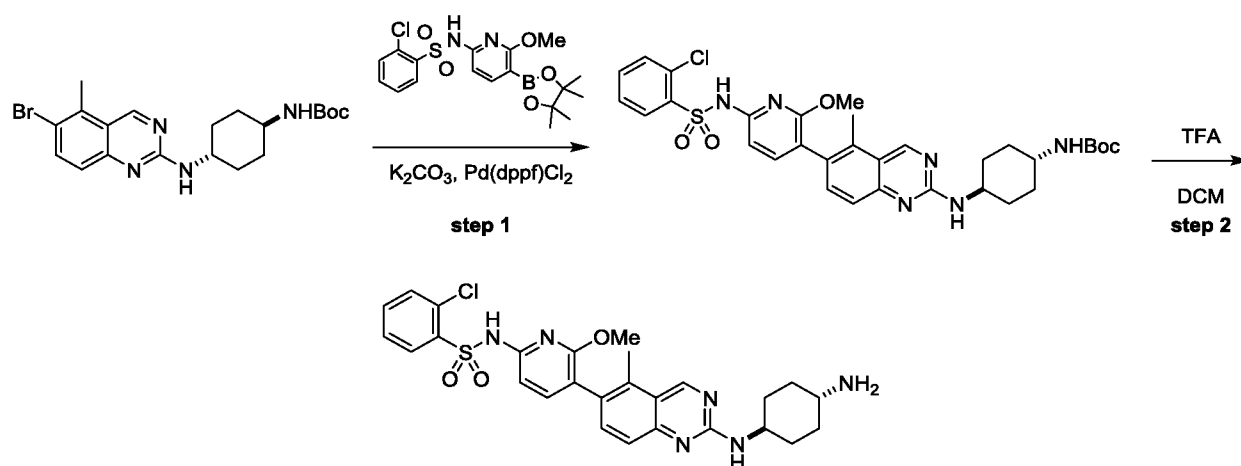
3H), 6.59 (d, $J = 7.7$ Hz, 1H), 3.93 (tt, $J = 3.8, 11.3$ Hz, 1H), 3.54 (s, 3H), 3.12 (tt, $J = 3.9, 11.7$ Hz, 1H), 2.30 - 2.00 (m, 7H), 1.66 - 1.52 (m, 2H), 1.52 - 1.39 (m, 2H).

Example 18: N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-7-methylquinazolin-6-yl)-6-ethylpyridin-2-yl)-2-chlorobenzenesulfonamide (105)



[00234] The title compound was synthesized according to the synthetic procedure reported for the preparation of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-7-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide. (16.2 mg, 26.9 μ mol, 17.6% yield, FA). $M+H^+ = 551.1$ (LCMS); 1H NMR (400MHz, METHANOL- d_4) δ 8.94 (s, 1H), 8.47 (br s, 1H), 8.24 (d, $J = 7.5$ Hz, 1H), 7.61 - 7.38 (m, 6H), 7.09 (d, $J = 8.8$ Hz, 1H), 3.95 (tdd, $J = 3.5, 7.5, 15.0$ Hz, 1H), 3.21 - 3.10 (m, 1H), 2.53 - 2.40 (m, 1H), 2.33 (qd, $J = 7.4, 14.3$ Hz, 1H), 2.26 - 2.06 (m, 7H), 1.68 - 1.54 (m, 2H), 1.53 - 1.38 (m, 2H), 0.98 (t, $J = 7.6$ Hz, 3H).

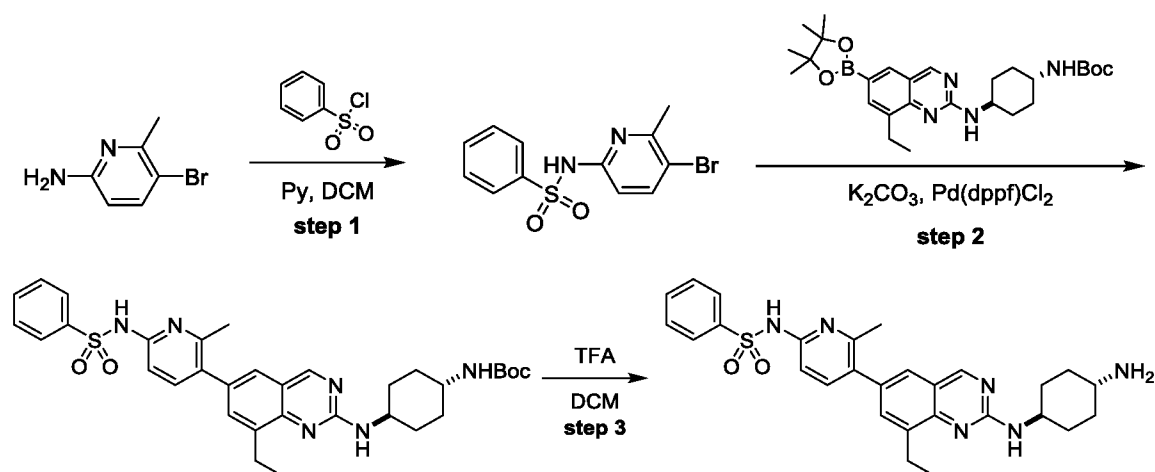
Example 19: Synthesis of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-5-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (114)



[00235] The title compound was synthesized according to the synthetic procedure reported for the preparation of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-7-ethylquinazolin-6-yl)-6-

methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (5.7 mg, 9.3 μmol , 20.3% yield, FA). $M+H^+$ = 553.3 (LCMS); ^1H NMR (400MHz, $\text{METHANOL-}d_4$) δ 9.29 (s, 1H), 8.55 (br s, 1H), 8.33 (d, J = 7.3 Hz, 1H), 7.67 - 7.57 (m, 2H), 7.57 - 7.48 (m, 1H), 7.46 - 7.34 (m, 3H), 6.65 (d, J = 7.8 Hz, 1H), 3.97 (br t, J = 11.3 Hz, 1H), 3.59 (s, 3H), 3.17 (ddd, J = 4.3, 7.6, 11.5 Hz, 1H), 2.35 (s, 3H), 2.25 (br d, J = 11.5 Hz, 2H), 2.14 (br d, J = 11.5 Hz, 2H), 1.69 - 1.56 (m, 2H), 1.55 - 1.42 (m, 2H).

Example 20: Synthesis of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methylpyridin-2-yl)benzenesulfonamide (111)



Step 1:

[00236] To a solution of 5-bromo-6-methylpyridin-2-amine (0.5 g, 2.6 mmol) in DCM (30.0 mL) was added pyridine (634 mg, 8.0 mmol, 647.3 μL) and benzenesulfonyl chloride (519 mg, 2.9 mmol, 376.4 μL). The mixture was stirred at 45°C for 12 h. The reaction was concentrated to give a residue. The residue was purified by flash silica gel chromatography (SiO_2) to afford N-(5-bromo-6-methylpyridin-2-yl)benzenesulfonamide (780 mg, 1.8 mmol, 68.3% yield). $M+H^+$ = 329.0 (LCMS).

Step 2:

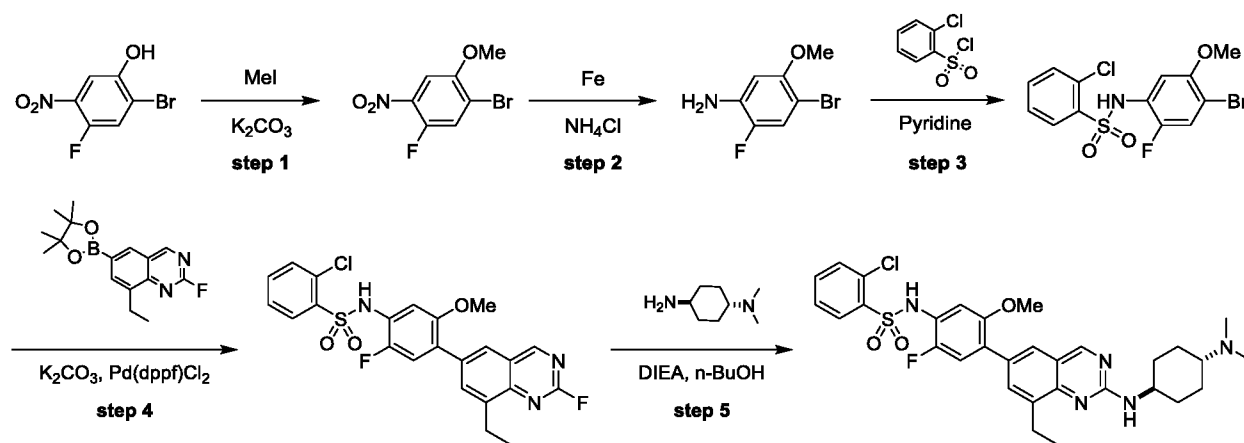
[00237] A mixture of tert-butyl ((1*r*,4*r*)-4-((8-ethyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (60 mg, 120.8 μmol), N-(5-bromo-6-methylpyridin-2-yl)benzenesulfonamide (44 mg, 132.9 μmol), K_2CO_3 (25 mg, 181.3 μmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$ (9 mg, 12.1 μmol) in dioxane (2.0 mL) and H_2O (0.2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90°C for 12 h under N_2 atmosphere. The reaction was concentrated to give a residue. The residue was purified by prep-TLC (SiO_2) to afford tert-butyl ((1*r*,4*r*)-4-((8-ethyl-6-(2-methyl-6-(phenylsulfonamido)pyridin-3-

yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (60 mg, 55.9 μmol , 46.3% yield). $M+H^+ = 617.4$ (LCMS).

Step 3:

[00238] To a solution of tert-butyl ((1*r*,4*r*)-4-((8-ethyl-6-(2-methyl-6-(phenylsulfonamido)pyridin-3-yl)quinazolin-2-yl)amino)cyclohexyl)carbamate (60 mg, 55.9 μmol) in DCM (2.0 mL) was added TFA (1.0 mL). The mixture was stirred at 20°C for 0.5 h. The reaction was concentrated to give a residue. The residue was dissolved in MeOH (2.0 mL) and basified pH to 7 with $\text{NH}_3\cdot\text{H}_2\text{O}$ (25% solution). The residue was purified by prep-HPLC (FA condition) to afford N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methylpyridin-2-yl)benzenesulfonamide (13.4 mg, 24.0 μmol , 42.8% yield, FA). $M+H^+ = 517.2$ (LCMS); ^1H NMR (400MHz, $\text{METHANOL-}d_4$) δ 9.00 (s, 1H), 8.58 (br s, 1H), 7.99 (br d, $J = 7.1$ Hz, 2H), 7.64 (d, $J = 8.8$ Hz, 1H), 7.60 - 7.45 (m, 5H), 7.22 (br d, $J = 8.7$ Hz, 1H), 4.05 - 3.93 (m, 1H), 3.22 - 3.02 (m, 3H), 2.39 (s, 3H), 2.32 (br d, $J = 11.6$ Hz, 2H), 2.15 (br d, $J = 12.0$ Hz, 2H), 1.69 - 1.43 (m, 4H), 1.39 - 1.28 (m, 3H).

Example 21: Synthesis of 2-chloro-N-(4-(2-(((1*r*,4*r*)-4-(dimethylamino)cyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluoro-5-methoxyphenyl)benzenesulfonamide (120)



Step 1:

[00239] To a solution of 2-bromo-4-fluoro-5-nitrophenol (1.0 g, 4.2 mmol) in DMF (25.0 mL) was added K_2CO_3 (1.2 g, 8.9 mmol), and then iodomethane (1.2 g, 8.4 mmol, 527.5 μL) at 0°C was added dropwise and after complete addition, the reaction mixture was warmed to 45°C and stirred for 12 h. The mixture (contain other batch 1 g) was diluted with H_2O (100 mL) and extracted with ethyl acetate (30.0 mL \times 3) and washed with brine (30.0 mL \times 3). The organic layer was dried over anhydrous Na_2SO_4 , then filtered and concentrated to afford a crude 1-bromo-5-fluoro-2-methoxy-4-nitrobenzene (2.0 g). ^1H NMR (400MHz, $\text{CHLOROFORM-}d$) δ 7.61 - 7.54 (m, 2H), 3.99 (s, 3H).

Step 2:

[00240] To a solution of 1-bromo-5-fluoro-2-methoxy-4-nitrobenzene (2.0 g, 8.0 mmol) in EtOH (45.0 mL) and H₂O (9.0 mL) was added Fe (2.2 g, 40.0 mmol) and NH₄Cl (1.2 g, 24.0 mmol, 839.0 uL). The mixture was stirred at 80°C for 12 h. The reaction mixture was filtered, the filter liquor was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂) to afford 4-bromo-2-fluoro-5-methoxyaniline (1.2 g, 4.4 mmol, 55.1% yield). $M+H^+ = 221.9$ (LCMS); ¹H NMR (400MHz, CHLOROFORM-*d*) δ 7.10 (d, $J = 10.0$ Hz, 1H), 6.29 (d, $J = 7.8$ Hz, 1H), 3.75(s, 3H).

Step 3:

[00241] To a solution of 4-bromo-2-fluoro-5-methoxyaniline (500 mg, 2.2 mmol,) in pyridine (10.0 mL) was added 2-chlorobenzenesulfonyl chloride (575 mg, 2.7 mmol, 371.3 uL). The mixture was stirred at 45°C for 12 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂) to afford N-(4-bromo-2-fluoro-5-methoxyphenyl)-2-chlorobenzenesulfonamide (890 mg, 1.5 mmol, 69.4% yield). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 7.95 (d, $J = 7.6$ Hz, 1H), 7.52 - 7.40 (m, 2H), 7.34 - 7.25 (m, 1H), 7.13 (d, $J = 9.3$ Hz, 1H), 7.06 (d, $J = 7.0$ Hz, 1H), 3.76 (s, 3H).

Step 4:

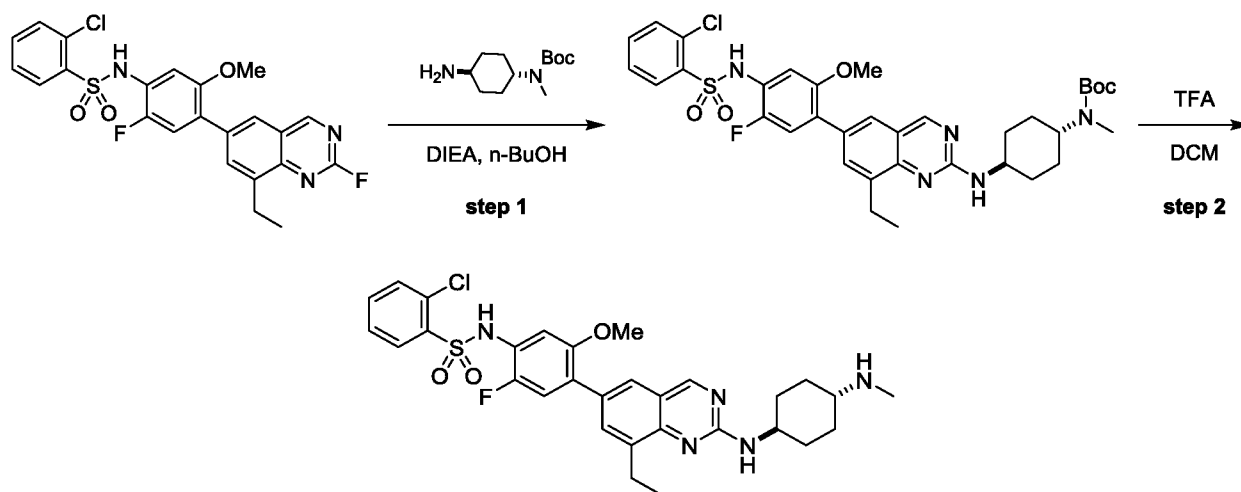
[00242] A mixture of N-(4-bromo-2-fluoro-5-methoxyphenyl)-2-chlorobenzenesulfonamide (783 mg, 1.9 mmol), 8-ethyl-2-fluoro-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazoline (500 mg, 1.6 mmol), K₂CO₃ (686 mg, 4.9 mmol), Pd(dppf)Cl₂ (121 mg, 165 umol) in dioxane (20.0 mL) and H₂O (2.0 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90°C for 12 h under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂) to afford 2-chloro-N-(4-(8-ethyl-2-fluoroquinazolin-6-yl)-2-fluoro-5-methoxyphenyl) benzenesulfonamide (760 mg, 1.0 mmol, 63.7% yield). $M+H^+ = 490.2$ (LCMS).

Step 5:

[00243] To a solution of 2-chloro-N-(4-(8-ethyl-2-fluoroquinazolin-6-yl)-2-fluoro-5-methoxyphenyl) benzenesulfonamide (200 mg, 408.2 umol) in n-BuOH (5.0 mL) was added DIEA (422 mg, 3.2 mmol, 568.8 uL) and (1*r*,4*r*)-N1,N1-dimethylcyclohexane-1,4-diamine (291 mg, 1.6 mmol, HCl). The mixture was stirred at 100°C for 12 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-HPLC (FA condition) to afford 2-chloro-N-(4-(2-(((1*r*,4*r*)-4-(dimethylamino)cyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluoro-5-methoxyphenyl)benzenesulfonamide (60.4 mg, 91.4 umol, 22.3% yield, FA). $M+H^+ = 612.2$ (LCMS); ¹H NMR (400MHz, METHANOL-*d*₄) δ 8.98 (s, 1H), 8.53 (br s, 1H), 8.09 (dd, J

= 1.3, 7.9 Hz, 1H), 7.69 - 7.58 (m, 4H), 7.47 (ddd, J = 1.8, 6.7, 8.1 Hz, 1H), 7.10 (dd, J = 2.0, 8.8 Hz, 2H), 3.99 (tt, J = 4.0, 11.6 Hz, 1H), 3.73 (s, 3H), 3.28 - 3.20 (m, 1H), 3.06 (q, J = 7.5 Hz, 2H), 2.88 (s, 6H), 2.47 - 2.35 (m, 2H), 2.26 - 2.14 (m, 2H), 1.82 - 1.67 (m, 2H), 1.57 - 1.43 (m, 2H), 1.33 (t, J = 7.5 Hz, 3H).

Example 22: Synthesis of 2-chloro-N-(4-(8-ethyl-2-(((1*r*,4*r*)-4-(methylamino)cyclohexyl)amino)quinazolin-6-yl)-2-fluoro-5-methoxyphenyl)benzenesulfonamide (121)



Step 1:

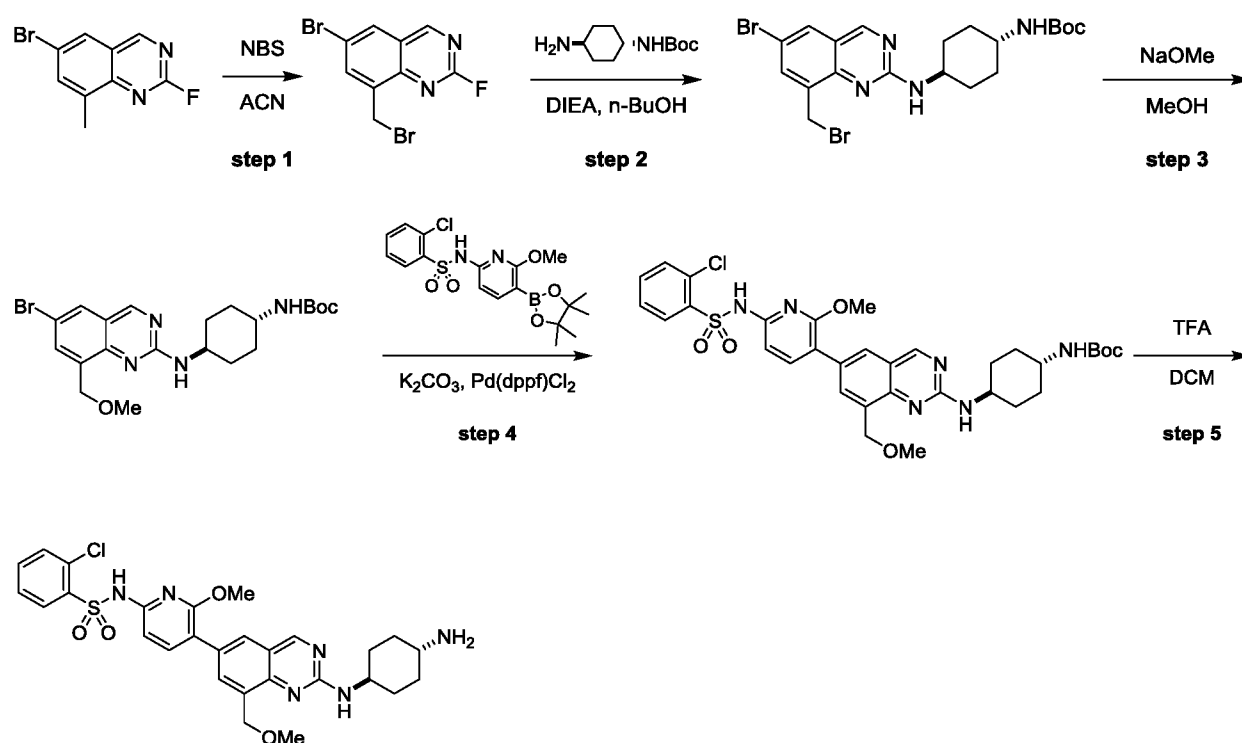
[00244] To a solution of 2-chloro-N-(4-(8-ethyl-2-fluoroquinazolin-6-yl)-2-fluoro-5-methoxyphenyl)benzenesulfonamide (200 mg, 408.2 μ mol) in n-BuOH (5.0 mL) was added DIEA (158 mg, 1.2 mmol, 213.3 μ L) and tert-butyl ((1*r*,4*r*)-4-aminocyclohexyl)(methyl)carbamate (279 mg, 1.2 mmol). The mixture was stirred at 100°C for 12 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) to afford tert-butyl ((1*r*,4*r*)-4-((6-(4-(2-chlorophenylsulfonamido)-5-fluoro-2-methoxyphenyl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)(methyl)carbamate (175 mg, 238.1 μ mol, 58.3% yield). $M+H^+$ = 698.4 (LCMS).

Step 2:

[00245] To a solution of tert-butyl ((1*r*,4*r*)-4-((6-(4-(2-chlorophenylsulfonamido)-5-fluoro-2-methoxyphenyl)-8-ethylquinazolin-2-yl)amino)cyclohexyl)(methyl)carbamate (175 mg, 250.6 μ mol) in DCM (2.0 mL) was added TFA (1.5 g, 13.5 mmol, 1.0 mL). The mixture was stirred at 25°C for 0.5 h. The reaction mixture was concentrated under reduced pressure. And then the mixture in MeOH (2.0 mL) was adjusted to pH = 7 by adding $\text{NH}_3 \cdot \text{H}_2\text{O}$ (25% solution). The residue was purified by prep-HPLC (FA condition) to give 2-chloro-N-(4-(8-ethyl-2-(((1*r*,4*r*)-4-

(methylamino)cyclohexyl)amino)quinazolin-6-yl)-2-fluoro-5-methoxyphenyl)benzenesulfonamide (101.7 mg, 157.8 μmol , 62.9% yield, FA). $M+H^+ = 598.2$ (LCMS); ^1H NMR (400MHz, METHANOL- d_4) δ 8.98 (s, 1H), 8.31 (s, 1H), 8.09 (d, $J = 8.1$ Hz, 1H), 7.71 - 7.56 (m, 4H), 7.51 - 7.42 (m, 1H), 7.16 - 7.06 (m, 2H), 4.07 - 3.93 (m, 1H), 3.73 (s, 3H), 3.16 - 2.99 (m, 3H), 2.75 (s, 3H), 2.36 (br d, $J = 11.6$ Hz, 2H), 2.26 (br d, $J = 11.7$ Hz, 2H), 1.68 - 1.41 (m, 4H), 1.32 (t, $J = 7.5$ Hz, 3H).

Example 23: Synthesis N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-(methoxymethyl)quinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (129)



Step 1:

[00246] To a solution of 6-bromo-2-fluoro-8-methylquinazoline (0.5 g, 2.2 mmol) in ACN (10.0 mL) was added AIBN (37 mg, 228.1 μmol) and NBS (487 mg, 2.7 mmol). The mixture was stirred at 90°C for 12 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) to afford 6-bromo-8-(bromomethyl)-2-fluoroquinazoline (0.7 g, 1.7 mmol, 78.6% yield). $M+H^+ = 320.9$ (LCMS).

Step 2:

[00247] To a solution of 6-bromo-8-(bromomethyl)-2-fluoroquinazoline (150 mg, 468.8 μmol) in n-BuOH (4.0 mL) was added DIEA (181 mg, 1.4 mmol, 244.9 μL), and tert-butyl N-(4-aminocyclohexyl)carbamate (100 mg, 468.8 μmol). The mixture was stirred at 25°C for 12 h.

The reaction mixture was concentrated under reduced pressure to afford tert-butyl ((1r,4r)-4-((6-bromo-8-(bromomethyl)quinazolin-2-yl)amino)cyclohexyl)carbamate (240 mg, crude).

Step 3:

[00248] To a solution of tert-butyl ((1r,4r)-4-((6-bromo-8-(bromomethyl)quinazolin-2-yl)amino)cyclohexyl)carbamate (200 mg, 388.9 μmol) in MeOH (2.0 mL) was added NaOMe (2.0 mL, 30% solution). The mixture was stirred at 25°C for 2 h. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO_2) to afford tert-butyl ((1r,4r)-4-((6-bromo-8-(methoxymethyl)quinazolin-2-yl)amino)cyclohexyl)carbamate (60 mg, 51.5 μmol , 13.2% yield). $M+H^+ = 465.3$ (LCMS).

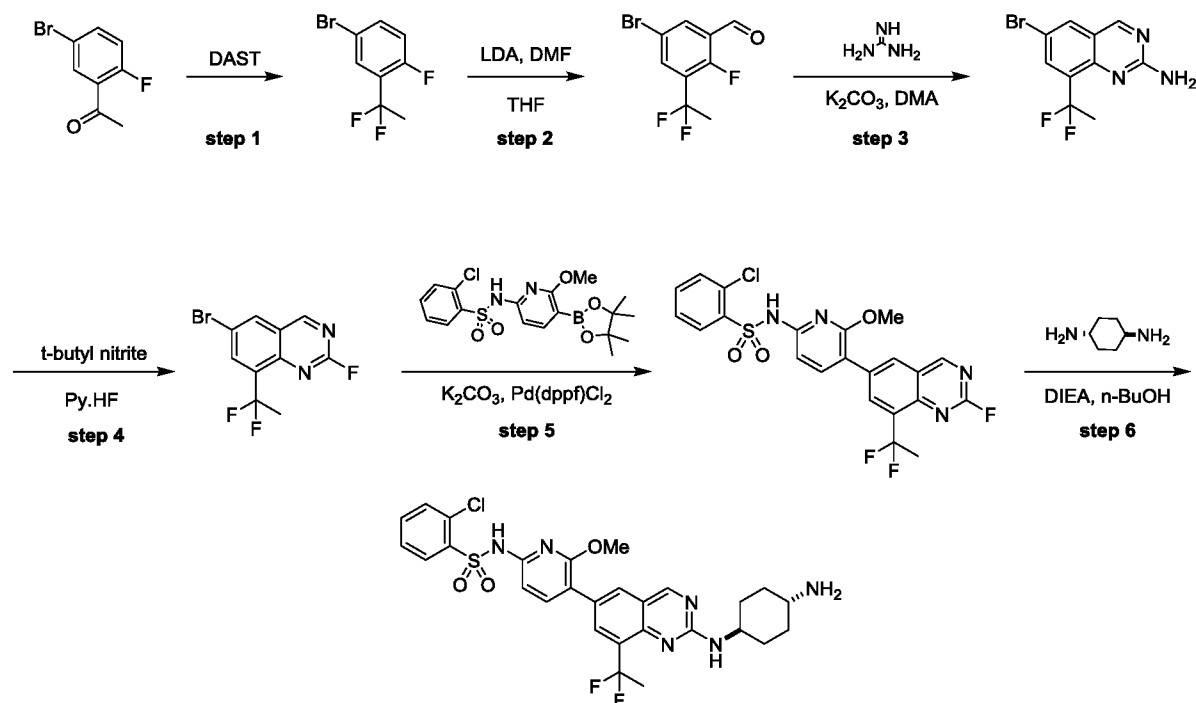
Step 4:

[00249] A mixture of tert-butyl ((1r,4r)-4-((6-bromo-8-(methoxymethyl)quinazolin-2-yl)amino)cyclohexyl)carbamate (60 mg, 128.9 μmol), 2-chloro-N-(6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)benzenesulfonamide (54 mg, 128.9 μmol), K_2CO_3 (53 mg, 386.7 μmol), $\text{Pd}(\text{dppf})\text{Cl}_2$ (9 mg, 12.8 μmol) in dioxane (2.0 mL) and H_2O (0.2 mL) was degassed and purged with N_2 for 3 times, and then the mixture was stirred at 90°C for 12 h under N_2 atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by prep-TLC (SiO_2) to afford tert-butyl ((1r,4r)-4-((6-(2-chlorophenylsulfonamido)-2-methoxypyridin-3-yl)-8-(methoxymethyl)quinazolin-2-yl)amino)cyclohexyl)carbamate (50 mg, 50.5 μmol , 39.1% yield). $M+H^+ = 683.1$ (LCMS).

Step 5:

[00250] To a solution of tert-butyl ((1r,4r)-4-((6-(2-chlorophenylsulfonamido)-2-methoxypyridin-3-yl)-8-(methoxymethyl)quinazolin-2-yl)amino)cyclohexyl)carbamate (50 mg, 73.1 μmol) in DCM (2.0 mL) was added TFA (1.0 mL). The mixture was stirred at 25°C for 0.5 h. The reaction mixture was concentrated under reduced pressure. The residue was added dichloromethane (2.0 mL) and $\text{NH}_3 \cdot \text{H}_2\text{O}$ (25% solution) to pH 7, concentrated under reduced pressure again. The residue was purified by prep-HPLC (FA condition) to afford N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-(methoxymethyl)quinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (12.4 mg, 18.5 μmol , 25.2% yield, FA). $M+H^+ = 583.2$ (LCMS); ^1H NMR (400MHz, $\text{METHANOL}-d_4$) δ 9.00 (s, 1H), 8.56 (br s, 1H), 8.33 (br d, $J = 7.7$ Hz, 1H), 7.88 (br s, 1H), 7.78 (br s, 1H), 7.67 (br d, $J = 7.5$ Hz, 1H), 7.59 (br s, 2H), 7.54 (br d, $J = 7.1$ Hz, 1H), 6.65 (br d, $J = 7.8$ Hz, 1H), 3.97 (br s, 1H), 3.67 (s, 3H), 3.49 (s, 3H), 3.17 (br s, 1H), 2.31 (br d, $J = 10.5$ Hz, 2H), 2.15 (br d, $J = 10.8$ Hz, 2H), 1.73 - 1.41 (m, 4H).

Example 24: Synthesis of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-(1,1-difluoroethyl)quinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (123)



Step 1:

[00251] The solution of 1-(5-bromo-2-fluorophenyl)ethanone (1.0 g, 4.6 mmol) in DAST (12.2 g, 75.6 mmol, 10.0 mL) was stirred at 45°C for 12 h. The mixture was poured into ice Sat. NaHCO₃ (100.0 mL) and extracted with ethyl acetate (10.0 mL × 3). The combined organic layers were washed with brine (10.0 mL × 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether / Ethyl acetate = 1/0 to 100/1) to afford 4-bromo-2-(1,1-difluoroethyl)-1-fluorobenzene (1.0 g, 4.1 mmol, 90.8% yield). ¹H NMR (CHLOROFORM-*d*, 400 MHz): δ 7.68 (dd, *J* = 2.4, 6.6 Hz, 1H), 7.57 - 7.50 (m, 1H), 7.07 - 6.98 (m, 1H), 1.99 (dt, *J* = 1.1, 18.5 Hz, 3H).

Step 2:

[00252] To a solution of 4-bromo-2-(1,1-difluoroethyl)-1-fluorobenzene (450 mg, 1.8 mmol) in THF (10.0 mL) was added LDA (2 M, 1.2 mL) at -78°C. The mixture was stirred at -78°C for 1 h. Then DMF (165 mg, 2.2 mmol, 173.8 uL) was added and stirred for 1 h at -78°C. The mixture was poured into Sat NH₄Cl (10.0 mL) and extracted with ethyl acetate (10.0 mL × 3). The combined organic layers were washed with brine (10.0 mL × 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether / Ethyl acetate = 1/0 to 10/1) to afford 5-bromo-3-(1,1-difluoroethyl)-2-fluorobenzaldehyde (0.4 g, 1.5 mmol, 79.5% yield). ¹H NMR

(CHLOROFORM-*d*, 400 MHz): δ 10.33 (s, 1H), 8.07 (dd, $J = 2.4, 5.5$ Hz, 1H), 7.92 (dd, $J = 2.4, 6.4$ Hz, 1H), 2.05 (t, $J = 18.6$ Hz, 3H)

Step 3:

[00253] To a solution of guanidine (181 mg, 1.5 mmol, H₂CO₃) and K₂CO₃ (621 mg, 4.4 mmol, 4.8 mL) in DMA (10.0 mL) was added a solution of 5-bromo-3-(1,1-difluoroethyl)-2-fluorobenzaldehyde (0.4 g, 1.5 mmol) in DMA (1.5 mL). Then the mixture was stirred at 160°C for 1 h. The mixture was concentrated to get crude residue. And then H₂O (30.0 mL) was added and extracted with Ethyl acetate (30.0 mL \times 3). The combined organic layers were washed with brine (20.0 mL \times 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether / Ethyl acetate = 1/0 to 5/1) to afford 6-bromo-8-(1,1-difluoroethyl)quinazolin-2-amine (0.4 g, 1.39 mmol, 92.69% yield).

Step 4:

[00254] To a solution of 6-bromo-8-(1,1-difluoroethyl)quinazolin-2-amine (0.4 g, 1.3 mmol) in pyridine (3.5 mL) was added pyridine hydrofluoride (7.7 g, 77.7 mmol, 7.00 mL) at -40°C. The mixture was stirred at -40°C for 15 min. Then tert-butyl nitrite (286 mg, 2.7 mmol, 330.2 μ L) was added. The mixture was stirred at 20°C for 12 h. The mixture was poured into ice water and adjusted pH = 7 with sat NaHCO₃ extracted with ethyl acetate (50.0 mL \times 3). The combined organic layers were washed with brine (20.0 mL \times 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂, Petroleum ether / Ethyl acetate = 1/0 to 10:1) to afford 6-bromo-8-(1,1-difluoroethyl)-2-fluoroquinazoline (0.3 g, 1.0 mmol, 74.2% yield). ¹H NMR (CHLOROFORM-*d*, 400 MHz): δ 9.35 (d, $J = 2.4$ Hz, 1H), 8.31 (s, 1H), 8.25 (d, $J = 2.1$ Hz, 1H), 2.30 (t, $J = 19.0$ Hz, 3H)

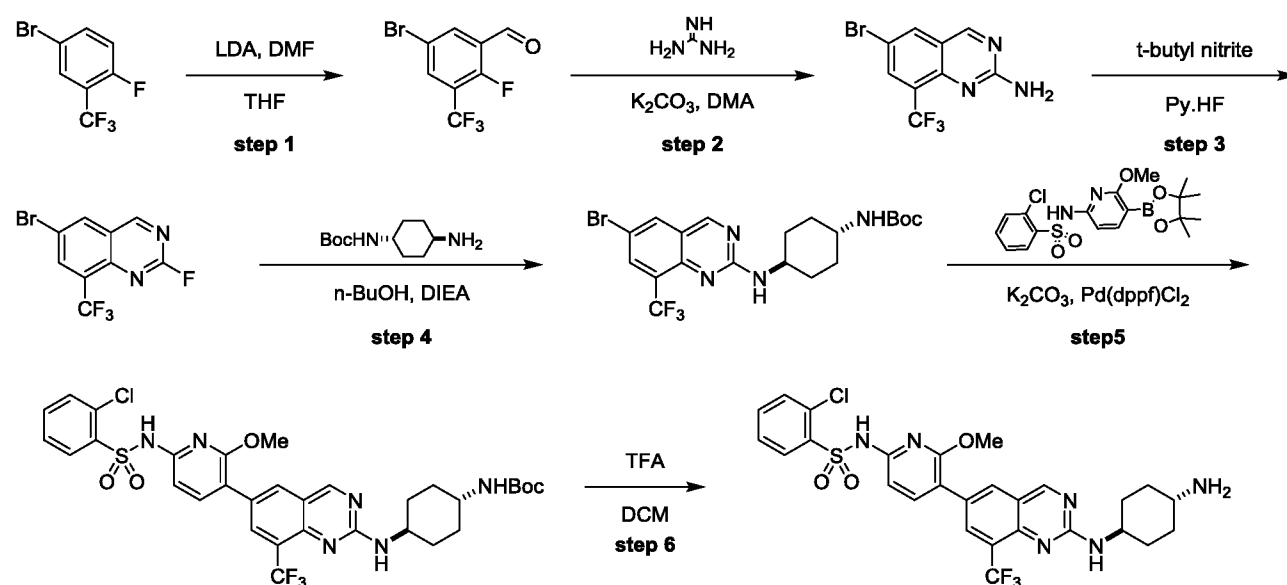
Step 5:

[00255] To a solution of 6-bromo-8-(1,1-difluoroethyl)-2-fluoroquinazoline (80 mg, 274.85 μ mol) and K₂CO₃ (114 mg, 824.5 μ mol) in dioxane (2.0 mL) and H₂O (0.2 mL) were added 2-chloro-N-(6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)benzenesulfonamide (233 mg, 549.7 μ mol) and Pd(dppf)Cl₂ (20 mg, 27.4 μ mol). The mixture was stirred at 90°C for 12 h under N₂. The mixture was concentrated to get crude residue. The residue was purified by prep-TLC to give 2-chloro-N-(5-(8-(1,1-difluoroethyl)-2-fluoroquinazolin-6-yl)-6-methoxypyridin-2-yl)benzenesulfonamide (100 mg, 196.5 μ mol, 71.4% yield).

Step 6:

[00256] To a solution of 2-chloro-N-(5-(8-(1,1-difluoroethyl)-2-fluoroquinazolin-6-yl)-6-methoxypyridin-2-yl)benzenesulfonamide (50 mg, 98.2 μmol) in n-BuOH (2.0 mL) was added cyclohexane-1,4-diamine (22. mg, 196.5 μmol) and DIEA (38 mg, 294.7 μmol , 51.3 μL). The mixture was stirred at 100°C for 12 h. The mixture was concentrated to get crude residue. The residue was purified by prep-HPLC (FA condition) to afford N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-(1,1-difluoroethyl)quinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (8.0 mg, 12.1 μmol , 12.4% yield, FA). $M+H^+ = 603.1$ (LCMS); ^1H NMR (400MHz, METHANOL- d_4) δ 9.01 (s, 1H), 8.55 (br s, 1H), 8.31 (d, $J = 7.3$ Hz, 1H), 8.04 (s, 1H), 7.88 (s, 1H), 7.65 (d, $J = 7.9$ Hz, 1H), 7.59 - 7.55 (m, 2H), 7.55 - 7.46 (m, 1H), 6.63 (d, $J = 8.1$ Hz, 1H), 3.90 (br s, 1H), 3.65 (s, 3H), 3.22 - 3.09 (m, 1H), 2.34 - 2.19 (m, 5H), 2.14 (br d, $J = 12.2$ Hz, 2H), 1.68 - 1.42 (m, 4H).

Example 25: Synthesis of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-(trifluoromethyl)quinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (134)



Step 1:

[00257] To a solution of 4-bromo-1-fluoro-2-(trifluoromethyl)benzene (5.0 g, 20.5 mmol, 2.9 mL) in THF (50.0 mL) was added LDA (2 M, 13.3 mL) at -78°C. The mixture was stirred at -78°C for 1 hr. Then DMF (1.8 g, 24.6 mmol, 1.9 mL) was added and stirred for 1 h at -78°C. The mixture was poured into Sat NH_4Cl (20.0 mL) and extracted with ethyl acetate (20.0 mL \times 3). The combined organic layers were washed with brine (20.0 mL \times 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether / Ethyl acetate = 1/0 to 10/1) to afford 5-bromo-2-fluoro-3-(trifluoromethyl)benzaldehyde (4 g, 14.7 mmol, 71.7% yield). ^1H NMR

(CHLOROFORM-*d*, 400 MHz): δ 10.35 (s, 1H), 8.19 (dd, $J = 2.5, 5.4$ Hz, 1H), 7.98 (dd, $J = 2.1, 6.1$ Hz, 1H).

Step 2:

[00258] To a solution of guanidine (1.3 g, 11.0 mmol, H_2CO_3) and K_2CO_3 (4.5 g, 33.2 mmol) in DMA (60.0 mL) was added a solution of 5-bromo-2-fluoro-3-(trifluoromethyl)benzaldehyde (3.0 g, 11.0 mmol) in DMA (9.0 mL). Then the mixture was stirred at 160°C for 1 h. The mixture was concentrated to get crude residue. And then H_2O (30.0 mL) was added and extracted with ethyl acetate (30.0 mL \times 3). The combined organic layers were washed with brine (20.0 mL \times 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether / Ethyl acetate = 1/0 to 5/1) to afford 6-bromo-8-(trifluoromethyl)quinazolin-2-amine (1.6 g, 4.6 mmol, 42.0% yield). ^1H NMR ($\text{DMSO-}d_6$, 400MHz) δ 9.19 (s, 1H), 8.34 (d, $J = 2.2$ Hz, 1H), 8.12 (d, $J = 2.0$ Hz, 1H), 7.42 (s, 2H).

Step 3:

[00259] To a solution of 6-bromo-8-(trifluoromethyl)quinazolin-2-amine (1.5 g, 5.1 mmol) in pyridine (13.0 mL) was added pyridine hydrofluoride (28.6 g, 288.5 mmol, 26.0 mL) at -40°C. The mixture was stirred at -40 °C for 15 min. Then tert-butyl nitrite (1.0 g, 10.2 mmol, 1.2 mL) was added. The mixture was stirred at 20°C for 12 h. The mixture was poured into ice water and adjusted pH = 7 with sat NaHCO_3 , extracted with ethyl acetate (50.0 mL \times 3). The combined organic layers were washed with brine (20.0 mL \times 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether / Ethyl acetate = 1/0 to 10/1) to afford 6-bromo-2-fluoro-8-(trifluoromethyl)quinazoline (1.0 g, 3.3 mmol, 64.9% yield). $\text{M}+\text{H}^+ = 294.9$ (LCMS).

Step 4:

[00260] To a solution of 6-bromo-2-fluoro-8-(trifluoromethyl)quinazoline (0.4 g, 1.3 mmol) in n-BuOH (20.0 mL) were added tert-butyl N-(4-aminocyclohexyl)carbamate (349 mg, 1.6 mmol) and DIEA (350 mg, 2.7 mmol, 472.3 μL). The mixture was stirred at 100°C for 12 h. The mixture was cooled to 25°C and filtered. The cake was washed with Petroleum ether (50.0 mL) to afford tert-butyl ((1r,4r)-4-((6-bromo-8-(trifluoromethyl)quinazolin-2-yl)amino)cyclohexyl) carbamate (0.5 g, 1.0 mmol, 74.6% yield). $\text{M}+\text{H}^+ = 491.2$ (LCMS).

Step 5:

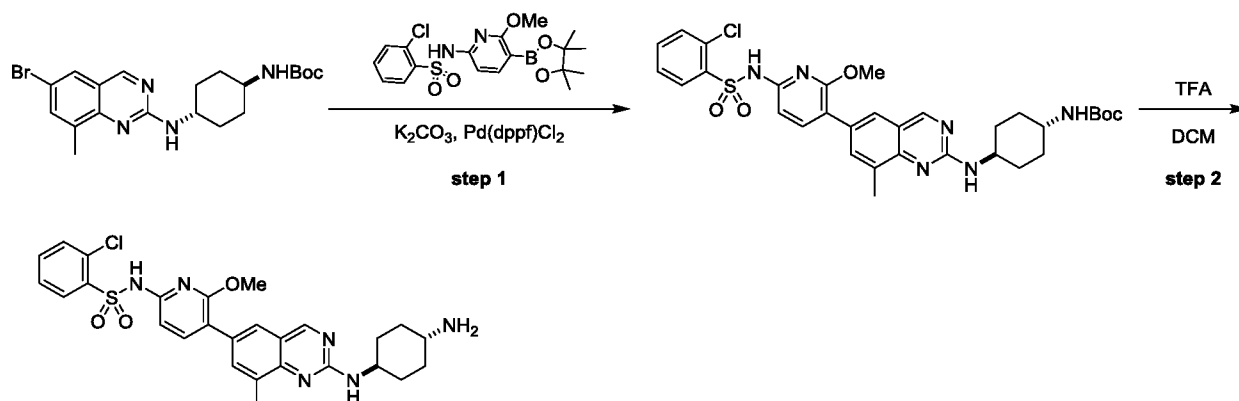
[00261] To a solution of tert-butyl ((1r,4r)-4-((6-bromo-8-(trifluoromethyl)quinazolin-2-yl)amino)cyclohexyl) carbamate (0.3 g, 613.0 μmol) and K_2CO_3 (254.2 mg, 1.8 mmol) in dioxane (6.0 mL) and H_2O (0.6 mL) were added 2-chloro-N-(6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)benzenesulfonamide (312 mg, 735.7 μmol) and $\text{Pd}(\text{dppf})\text{Cl}_2$

(45 mg, 61.3 μmol). The mixture was stirred at 90°C for 12 h under N_2 . The mixture was concentrated to get crude residue. The residue was purified by column chromatography (SiO_2 , Petroleum ether / Ethyl acetate = 1/0 to 1/1) to give tert-butyl ((1*r*,4*r*)-4-((6-(6-(2-chlorophenylsulfonamido)-2-methoxypyridin-3-yl)-8-(trifluoromethyl)quinazolin-2-yl)amino)cyclohexyl)carbamate (0.3 g, 171.1 μmol , 27.9% yield). $\text{M}+\text{H}^+ = 707.1$ (LCMS).

Step 6:

[00262] A solution of tert-butyl ((1*r*,4*r*)-4-((6-(6-(2-chlorophenylsulfonamido)-2-methoxypyridin-3-yl)-8-(trifluoromethyl)quinazolin-2-yl)amino)cyclohexyl)carbamate (0.3 g, 424.2 μmol) in DCM (2.0 mL) and TFA (1.0 mL) was stirred at 25°C for 10 min. The mixture was concentrated to get crude residue. The residue was dissolved in MeOH (2.0 mL) and basified pH to 8 with $\text{NH}_3\cdot\text{H}_2\text{O}$ (25% solution), concentrated to give a residue. The residue was purified by prep-HPLC (FA condition) to afford N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-(trifluoromethyl)quinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (141.4 mg, 215.5 μmol , 50.8% yield, FA). $\text{M}+\text{H}^+ = 607.2$ (LCMS); ^1H NMR (METHANOL- d_4 , 400MHz) δ 9.06 (s, 1H), 8.53 (s, 1H), 8.32 (dd, $J = 1.2, 7.8$ Hz, 1H), 8.15 (s, 1H), 8.02 (d, $J = 1.8$ Hz, 1H), 7.70 (d, $J = 7.9$ Hz, 1H), 7.63 - 7.55 (m, 2H), 7.55 - 7.47 (m, 1H), 6.66 (d, $J = 7.9$ Hz, 1H), 3.99 - 3.83 (m, 1H), 3.68 (s, 3H), 3.23 - 3.08 (m, 1H), 2.31 (br d, $J = 8.8$ Hz, 2H), 2.14 (br d, $J = 12.6$ Hz, 2H), 1.70 - 1.38 (m, 4H).

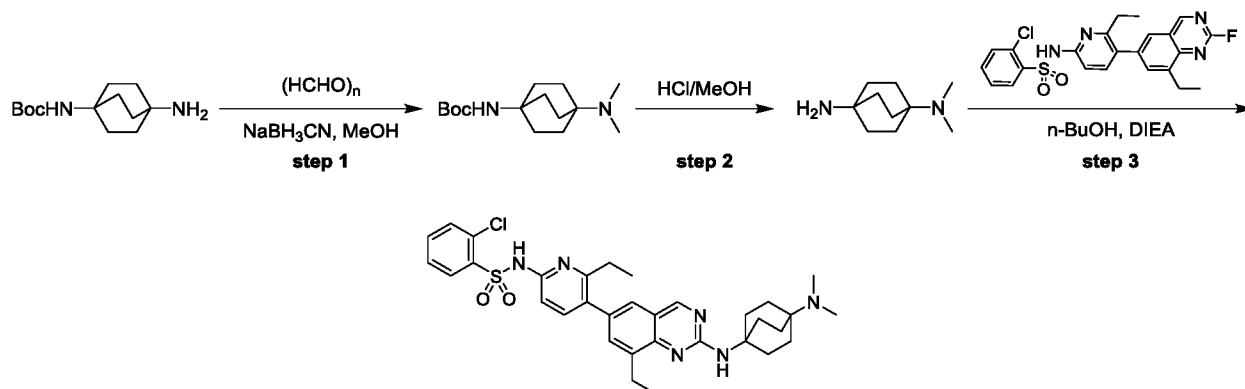
Example 26: Synthesis of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (115)



[00263] The title compound was synthesized according to the synthetic procedure reported for the preparation of N-(5-(2-(((1*r*,4*r*)-4-aminocyclohexyl)amino)-8-(trifluoromethyl)quinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (18.8 mg, 30.8 μmol , 20.1% yield, FA). $\text{M}+\text{H}^+ = 553.2$ (LCMS); ^1H NMR (METHANOL- d_4 , 400MHz) δ 8.95 (s, 1H), 8.55 (br s, 1H), 8.31 (d, $J = 7.6$ Hz, 1H), 7.70 - 7.61 (m, 3H), 7.61 - 7.55 (m, 2H), 7.54 - 7.48 (m, 1H), 6.63 (d, $J = 7.9$ Hz, 1H), 4.04 - 3.92 (m, 1H), 3.65 (s, 3H),

3.22 - 3.09 (m, 1H), 2.53 (s, 3H), 2.31 (br d, $J = 11.5$ Hz, 2H), 2.13 (br d, $J = 11.9$ Hz, 2H), 1.68 - 1.39 (m, 4H).

Example 27: Synthesis of 2-chloro-N-(5-(2-((4-(dimethylamino)bicyclo[2.2.2]octan-1-yl)amino)-8-ethylquinazolin-6-yl)-6-ethylpyridin-2-yl)benzenesulfonamide (136)



Step 1:

[00264] To a solution of tert-butyl N-(1-amino-4-bicyclo[2.2.2]octanyl)carbamate (500 mg, 2.1 mmol) and (HCHO)_n (562 mg, 6.2 mmol) in MeOH (15.0 mL) was added AcOH (125 mg, 2.1 mmol, 119 μ L) to adjust pH to 5 and then the mixture was stirred for 2 h at 30°C. Then NaBH₃CN (523 mg, 8.3 mmol) was added. The mixture was stirred at 45°C for 12 h. The reaction was concentrated to give a residue. The residue was dissolved in saturated NaHCO₃ (15.0 mL) and extracted with ethyl acetate (10 mL \times 3). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated to give tert-butyl (4-(dimethylamino)bicyclo[2.2.2]octan-1-yl)carbamate (550 mg, crude).

Step 2:

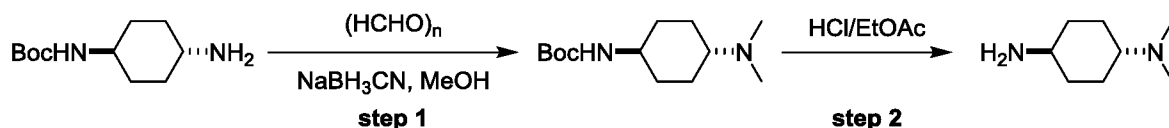
[00265] The mixture of tert-butyl (4-(dimethylamino)bicyclo[2.2.2]octan-1-yl)carbamate (500 mg, 1.8 mmol) in HCl/MeOH (4M, 10.0 mL) was stirred at 20°C for 0.5 h. The reaction was concentrated to give N1,N1-dimethylbicyclo[2.2.2]octane-1,4-diamine (380 mg, crude, HCl).

Step 3:

[00266] To a solution of 2-chloro-N-(6-ethyl-5-(8-ethyl-2-fluoroquinazolin-6-yl)pyridin-2-yl)benzenesulfonamide (50 mg, 106.2 μ mol) in n-BuOH (4.0 mL) was added DIEA (110 mg, 849.4 μ mol, 147.9 μ L) and N1,N1-dimethylbicyclo[2.2.2]octane-1,4-diamine (65 mg, 318.5 μ mol, HCl). The mixture was stirred at 120°C for 12 h. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (HCl condition) and then was purified by prep-HPLC (FA condition) to afford 2-chloro-N-(5-(2-((4-(dimethylamino)bicyclo[2.2.2]octan-1-yl)amino)-8-ethylquinazolin-6-yl)-6-ethylpyridin-2-yl)benzenesulfonamide (2.1 mg, 2.9 μ mol,

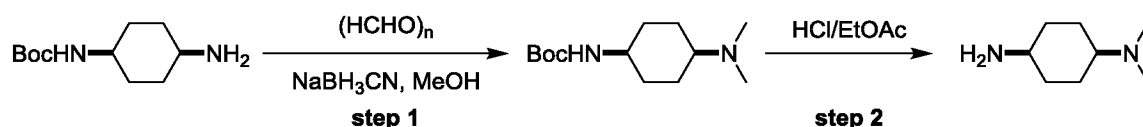
2.8% yield, FA). $M+H^+ = 619.3$ (LCMS); 1H NMR (400MHz, METHANOL- d_4) δ 8.87 (s, 1H), 8.45 (br s, 2H), 8.15 (d, $J = 7.5$ Hz, 1H), 7.51 (br d, $J = 8.8$ Hz, 1H), 7.45 (d, $J = 3.8$ Hz, 2H), 7.43 - 7.36 (m, 3H), 7.00 (br d, $J = 8.3$ Hz, 1H), 2.99 (q, $J = 7.3$ Hz, 2H), 2.71 (s, 6H), 2.53 (q, $J = 7.5$ Hz, 2H), 2.32 - 2.22 (m, 6H), 2.01 - 1.88 (m, 6H), 1.23 (t, $J = 7.5$ Hz, 3H), 0.99 (br t, $J = 7.5$ Hz, 3H).

Example 27A: Synthesis of (1r,4r)-N1,N1-dimethylcyclohexane-1,4-diamine



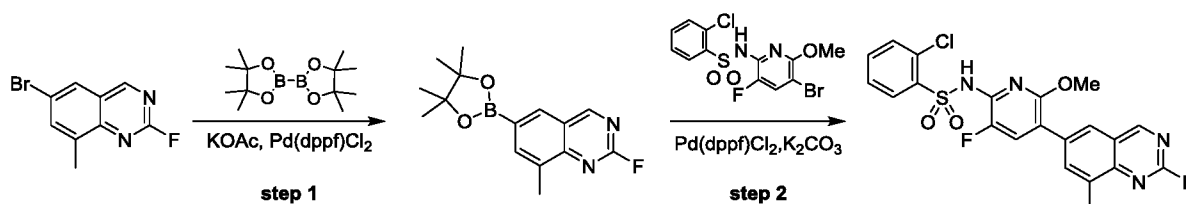
[00267] The title compound was synthesized according to the synthetic procedure reported for the preparation of N1,N1-dimethylbicyclo[2.2.2]octane-1,4-diamine (8.3 g, 46.4 mmol, 99.6% yield, HCl). 1H NMR (400MHz, DMSO- d_6) δ 11.02 (br s, 1H), 8.31 (br s, 3H), 3.62 - 3.36 (m, 1H), 3.15 - 3.03 (m, 1H), 2.96 (br d, $J = 4.0$ Hz, 1H), 2.65 (d, $J = 4.9$ Hz, 6H), 2.09 (br s, 4H), 1.65 - 1.31 (m, 4H).

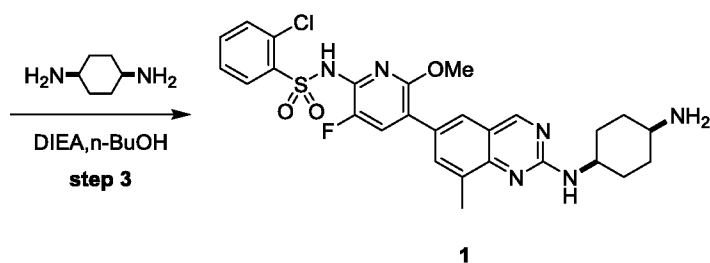
Example 27B: Synthesis of (1s,4s)-N1,N1-dimethylcyclohexane-1,4-diamine



[00268] The title compound was synthesized according to the synthetic procedure reported for the preparation of N1,N1-dimethylbicyclo[2.2.2]octane-1,4-diamine (1.7 g, crude, HCl). 1H NMR (400MHz, METHANOL- d_4) δ 3.53 (br s, 1H), 3.41 - 3.33 (m, 1H), 2.89 (s, 6H), 2.13 - 1.88 (m, 9H).

Example 28: Synthesis of N-(5-(2-(((1s,4s)-4-aminocyclohexyl)amino)-8-methylquinazolin-6-yl)-3-fluoro-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (146)



**Step 1:**

[00269] A mixture of 6-bromo-2-fluoro-8-methylquinazoline (500 mg, 2.0 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (632 mg, 2.4 mmol), KOAc (610 mg, 6.22 mmol), Pd(dppf)Cl₂ (151 mg, 207.4 μ mol) in dioxane (20.0 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90°C for 12 h under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether / Ethyl acetate = 100/1 to 10/1) to afford 2-fluoro-8-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazoline (590 mg, 1.9 mmol, crude). $M+H^+$ = 289.2 (LCMS).

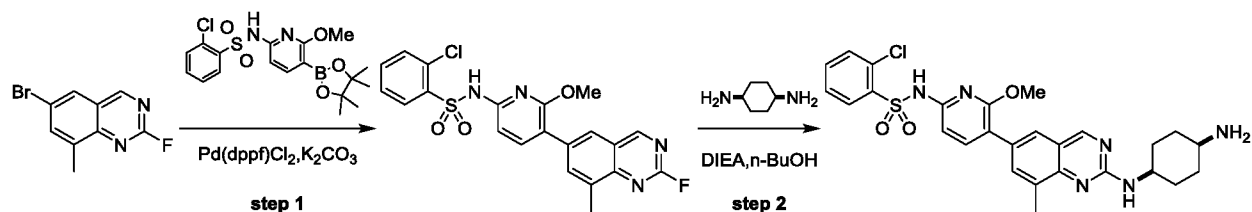
Step 2:

[00270] A mixture of 2-fluoro-8-methyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)quinazoline (349 mg, 1.2 mmol), N-(5-bromo-3-fluoro-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (400 mg, 1.0 mmol), K₂CO₃ (419 mg, 3.0 mmol), Pd(dppf)Cl₂ (73 mg, 101 μ mol) in dioxane (15.0 mL) and H₂O (1.5 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90°C for 12 h under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure. The residue was purified by column chromatography (SiO₂, Petroleum ether / Ethyl acetate = 10/1 to 1/1) to afford 2-chloro-N-(3-fluoro-5-(2-fluoro-8-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)benzenesulfonamide (450 mg, 802 μ mol, 79.3% yield). $M+H^+$ = 477.2 (LCMS).

Step 3:

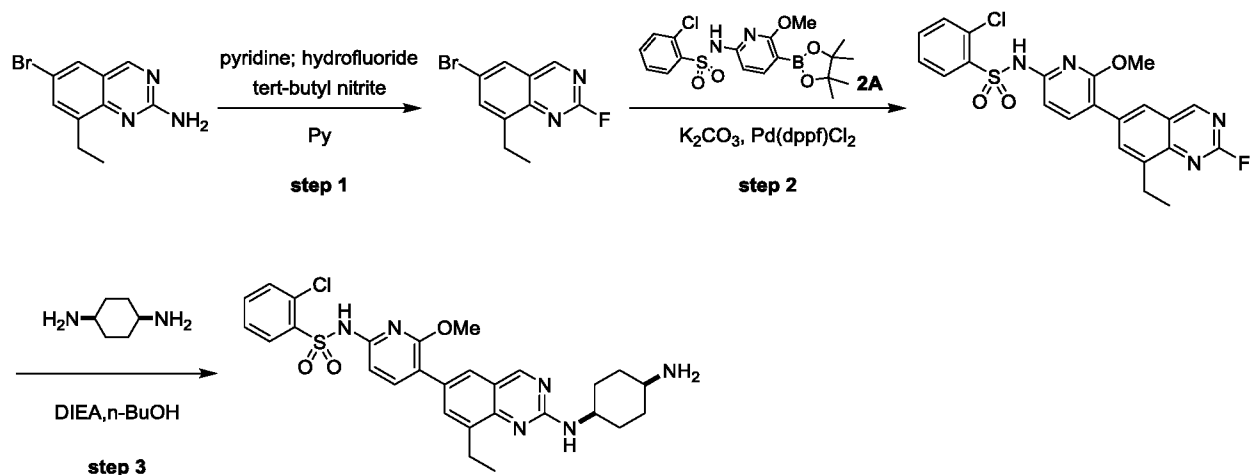
[00271] To a solution of (1s,4s)-cyclohexane-1,4-diamine (237 mg, 1.5 mmol, HCl) in n-BuOH (7.0 mL) was added DIEA (325 mg, 2.5 mmol, 438.3 μ L) and 2-chloro-N-(3-fluoro-5-(2-fluoro-8-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)benzenesulfonamide (150 mg, 314.5 μ mol). The mixture was stirred at 100°C for 24 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by prep-HPLC (FA condition) to afford N-(5-(2-(((1s,4s)-4-aminocyclohexyl)amino)-8-methylquinazolin-6-yl)-3-fluoro-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (50.0 mg, 80.2 μ mol, 25.5% yield, FA). $M+H^+$ = 571.2 (LCMS); ¹H NMR (400MHz, METHANOL-*d*₄) δ 8.97 (s, 1H), 8.56 (br s, 1H), 8.31 (d, *J* = 7.6 Hz, 1H), 7.68 (s, 2H), 7.62 - 7.54 (m, 3H), 7.54 - 7.45 (m, 1H), 4.21 (br s, 1H), 3.46 (s, 3H), 3.28 (br s, 1H), 2.53 (s, 3H), 2.13 (br d, *J* = 9.8 Hz, 2H), 2.02 - 1.69 (m, 6H).

Example 29: Synthesis of N-(5-(2-(((1s,4s)-4-aminocyclohexyl)amino)-8-methylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (138)



[00272] The title compound was synthesized according to the synthetic procedure reported for the preparation of N-(5-(2-(((1s,4s)-4-aminocyclohexyl)amino)-8-methylquinazolin-6-yl)-3-fluoro-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (40.8 mg, 67.2 μ mol, 21.4% yield, FA). $M+H^+$ = 553.1 (LCMS); ^1H NMR (400MHz, $\text{METHANOL-}d_4$) δ 8.92 (s, 1H), 8.44 (br s, 1H), 8.36 - 8.22 (m, 1H), 7.68 - 7.40 (m, 6H), 6.62 (d, J = 7.9 Hz, 1H), 4.19 (br s, 1H), 3.63 (s, 3H), 3.29 - 3.22 (m, 1H), 2.50 (s, 3H), 2.17 - 2.02 (m, 2H), 2.01 - 1.69 (m, 6H).

Example 30: Synthesis of N-(5-(2-(((1s,4s)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (140)



Step 1:

[00273] To a solution of 6-bromo-8-ethylquinazolin-2-amine (10.0 g, 39.6 mmol) in Py (100 mL) was added pyridine; hydrofluoride (220.0 g, 2.2 mol, 200.0 mL) at -40°C . The mixture was stirred at -40°C for 15 min. Then tert-butyl nitrite (8.1 g, 79.3 mmol, 9.4 mL) was added. The mixture was stirred at 20°C for 12 h. The mixture was poured into ice water and adjusted pH = 7 with sat. NaHCO_3 , extracted with EtOAc (500.0 mL \times 3). The combined organic layers were washed with brine (200.0 mL \times 3), dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO_2) to give 6-bromo-8-ethyl-2-fluoroquinazoline (11.4 g, 40.8 mmol, 55.4% yield). $M+H^+$ = 257.0

(LCMS); ^1H NMR (400MHz, CHLOROFORM-*d*) δ 9.26 (d, J = 2.6 Hz, 1H), 8.00 (d, J = 2.2 Hz, 1H), 7.87 (d, J = 1.1 Hz, 1H), 3.18 (q, J = 7.5 Hz, 2H), 1.37 (t, J = 7.5 Hz, 3H).

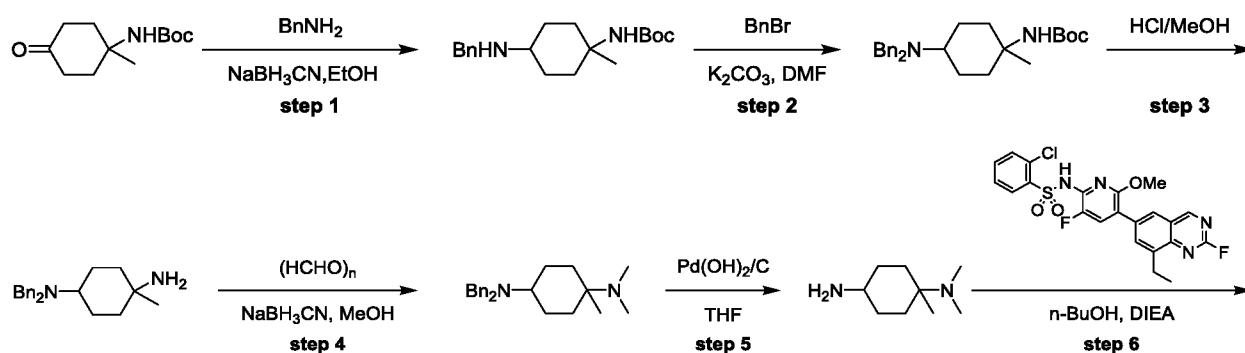
Step 2:

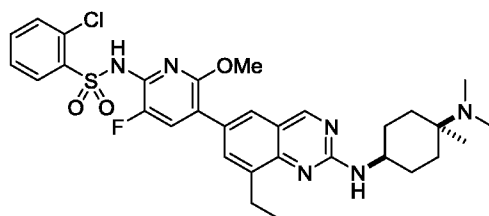
[00274] A mixture of 2-chloro-N-(6-methoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-yl)benzenesulfonamide (399 mg, 940.8 μmol), 6-bromo-8-ethyl-2-fluoroquinazoline (200 mg, 784.0 μmol), Pd(dppf)Cl₂ (57 mg, 78.4 μmol), and K₂CO₃ (325 mg, 2.3 mmol) in dioxane (6.0 mL) and H₂O (0.6 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 90°C for 12 h under N₂ atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography (SiO₂) to give 2-chloro-N-(5-(8-ethyl-2-fluoroquinazolin-6-yl)-6-methoxypyridin-2-yl)benzenesulfonamide (430 mg, crude).

Step 3:

[00275] To a solution of (1s,4s)-cyclohexane-1,4-diamine (144 mg, 1.2 mmol, HCl) in n-BuOH (6.0 mL) was basified pH to 8 by DIEA. Then the mixture was added 2-chloro-N-(5-(8-ethyl-2-fluoroquinazolin-6-yl)-6-methoxypyridin-2-yl)benzenesulfonamide (200 mg, 422.9 μmol) and DIEA (327 mg, 2.5 mmol, 441.9 μL) and stirred at 100°C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue. The residue was purified by pre-HPLC (FA condition) to afford N-(5-(2-(((1s,4s)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)-2-chlorobenzenesulfonamide (121.7 mg, 196.0 μmol , 46.3% yield, FA). $M+H^+$ = 567.2 (LCMS); ^1H NMR (400MHz, METHANOL-*d*₄) δ 8.98 (s, 1H), 8.55 (s, 1H), 8.36 - 8.26 (m, 1H), 7.71 - 7.45 (m, 6H), 6.63 (d, J = 8.2 Hz, 1H), 4.20 (br s, 1H), 3.65 (s, 3H), 3.26 (br dd, J = 3.6, 9.8 Hz, 1H), 3.03 (q, J = 7.5 Hz, 2H), 2.21 - 2.06 (m, 2H), 1.98 - 1.71 (m, 6H), 1.29 (t, J = 7.5 Hz, 3H).

Example 31: Synthesis of 2-chloro-N-(5-(2-(((1s,4s)-4-(dimethylamino)-4-methylcyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-fluoro-6-methoxypyridin-2-yl)benzenesulfonamide (144)



**Step 1:**

[00276] To a solution of tert-butyl (1-methyl-4-oxocyclohexyl)carbamate (900 mg, 4 mmol) in EtOH (20.0 mL) was added phenylmethanamine (509 mg, 4.7 mmol, 517.9 uL) and AcOH (238 mg, 4 mmol, 226.5 uL) at 0°C. The resulting mixture was stirred at 0°C for 15 min. Follow by successive addition of NaBH₃CN (498 mg, 7.9 mmol), the mixture was stirred at 20°C for 12 h. The reaction was concentrated to give a residue. The residue was dissolved in saturated aqueous NaHCO₃ (20.0 mL) and extracted with ethyl acetate (20.0 mL × 3). The combined organic phase was dried over anhydrous Na₂SO₄, filtered and concentrated to give tert-butyl (4-(benzylamino)-1-methylcyclohexyl)carbamate (1.3 g, crude).

Step 2:

[00277] To a solution of tert-butyl (4-(benzylamino)-1-methylcyclohexyl)carbamate (1.2 g, 3.7 mmol) in DMF (20.0 mL) was added K₂CO₃ (1.6 g, 11.3 mmol) and bromomethylbenzene (773 mg, 4.5 mmol, 537.1 uL). The mixture was stirred at 40°C for 12 h. The reaction was quenched with H₂O (30.0 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic was washed with brine (20 mL × 3), dried over anhydrous Na₂SO₄, filtered and concentrated to give a residue. The residue was purified by flash silica gel chromatography (SiO₂) to afford tert-butyl (4-(dibenzylamino)-1-methylcyclohexyl)carbamate (1.5 g, 3.4 mmol, 90% yield). ¹H NMR (400MHz, CHLOROFORM-*d*) δ 7.42 - 7.35 (m, 4H), 7.34 - 7.29 (m, 4H), 7.26 - 7.19 (m, 2H), 3.69 - 3.63 (m, 4H), 2.60 - 2.46 (m, 1H), 2.13 (br d, *J* = 11.9 Hz, 1H), 1.94 (br d, *J* = 9.3 Hz, 1H), 1.84 - 1.66 (m, 2H), 1.61 - 1.50 (m, 3H), 1.47 - 1.39 (m, 9H), 1.36 - 1.24 (m, 4H).

Step 3:

[00278] The mixture of tert-butyl (4-(dibenzylamino)-1-methylcyclohexyl)carbamate (500 mg, 1.2 mmol) in HCl/MeOH(4M, 10.0 mL) was stirred at 20°C for 1 h. The reaction was concentrated to give N¹,N¹-dibenzyl-4-methylcyclohexane-1,4-diamine (400 mg, crude, HCl).

Step 4:

[00279] To a solution of N¹,N¹-dibenzyl-4-methylcyclohexane-1,4-diamine (350 mg, 1 mmol, HCl) in MeOH (10.0 mL) was added TEA to basify pH to 7 and then (HCHO)_n (274 mg, 3 mmol) was added. AcOH (61 mg, 1 mmol, 58 uL) was added to adjust pH to 5 and then the mixture was stirred at 60°C for 2 h. NaBH₃CN (255 mg, 4.1 mmol) was added and the mixture was stirred at 60°C for 12 h. The reaction was concentrated to give a residue. The residue was

dissolved in saturated NaHCO_3 (10.0 mL) and extracted with ethyl acetate (10.0 mL \times 3). The combined organic phase was dried over anhydrous Na_2SO_4 , filtered and concentrated to give N^4, N^4 -dibenzyl- N^1, N^1 ,1-trimethylcyclohexane-1,4-diamine (330 mg, crude).

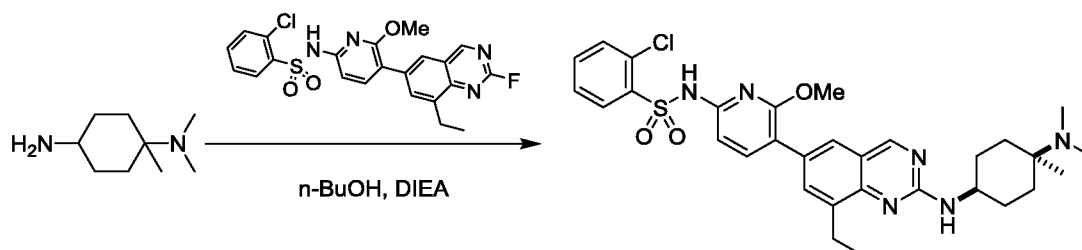
Step 5:

[00280] To a solution of N^4, N^4 -dibenzyl- N^1, N^1 ,1-trimethylcyclohexane-1,4-diamine (330 mg, 980.6 μmol) in THF (10.0 mL) and AcOH (0.1 mL) was added $\text{Pd}(\text{OH})_2/\text{C}$ (400 mg, 980.6 μmol , 10% Pd basis) under N_2 atmosphere. The suspension was degassed and purged with H_2 for 3 times. The mixture was stirred under H_2 (50 Psi) at 50°C for 12 h. The reaction was filtered and concentrated to give N^1, N^1 ,1-trimethylcyclohexane-1,4-diamine (150 mg, crude).

Step 6:

[00281] To a solution of 2-chloro-N-(5-(8-ethyl-2-fluoroquinazolin-6-yl)-3-fluoro-6-methoxypyridin-2-yl)benzenesulfonamide (30 mg, 61.1 μmol) in n-BuOH (3.0 mL) was added DIEA (63 mg, 488.9 μmol , 85.2 μL) and N^1, N^1 ,1-trimethylcyclohexane-1,4-diamine (38 mg, 244.4 μmol). The mixture was stirred at 120°C for 12 h. The reaction was concentrated to give a residue. The residue was purified by prep-HPLC (FA condition) to afford 2-chloro-N-(5-(2-(((1s,4s)-4-(dimethylamino)-4-methylcyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-fluoro-6-methoxypyridin-2-yl)benzenesulfonamide (3.7 mg, 5.4 μmol , 8.9% yield, FA). $\text{M}+\text{H}^+ = 627.3$ (LCMS); ^1H NMR (400MHz, METHANOL- d_4) δ 8.98 (br s, 1H), 8.53 (br s, 1H), 8.32 (br d, $J = 7.8$ Hz, 1H), 7.69 (s, 2H), 7.62 - 7.47 (m, 4H), 4.16 (br s, 1H), 3.46 (s, 3H), 3.03 (q, $J = 7.4$ Hz, 2H), 2.85 (s, 6H), 2.13 - 1.92 (m, 6H), 1.86 (br d, $J = 5.7$ Hz, 2H), 1.41 (s, 3H), 1.29 (br t, $J = 7.4$ Hz, 3H); ^1H NMR (400MHz, DMSO- d_6) δ 8.98 (s, 1H), 8.18 - 8.12 (m, 1H), 7.66 (s, 2H), 7.44 - 7.32 (m, 4H), 3.99 (br s, 1H), 3.31 (s, 3H), 2.96 (q, $J = 7.5$ Hz, 2H), 2.51 (br s, 6H), 2.01 - 1.75 (m, 6H), 1.58 - 1.47 (m, 2H), 1.24 (t, $J = 7.5$ Hz, 3H), 1.13 (s, 3H).

Example 32: Synthesis of 2-chloro-N-(5-(2-(((1s,4s)-4-(dimethylamino)-4-methylcyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methoxypyridin-2-yl)benzenesulfonamide (143)



[00282] The title compound was synthesized according to the synthetic procedure reported for the preparation of 2-chloro-N-(5-(2-(((1s,4s)-4-(dimethylamino)-4-methylcyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-fluoro-6-methoxypyridin-2-yl)benzenesulfonamide (6.4 mg, 9.4%

yield). $M+H^+ = 609.3$ (LCMS); 1H NMR (400MHz, METHANOL- d_4) δ 8.94 (s, 1H), 8.33 - 8.27 (m, 1H), 7.64 (dd, $J = 1.9, 13.4$ Hz, 2H), 7.60 (d, $J = 8.1$ Hz, 1H), 7.58 - 7.54 (m, 2H), 7.52 - 7.46 (m, 1H), 6.60 (d, $J = 7.9$ Hz, 1H), 4.10 (br t, $J = 5.3$ Hz, 1H), 3.62 (s, 3H), 3.02 (q, $J = 7.5$ Hz, 2H), 2.68 - 2.59 (m, 6H), 2.06 - 1.89 (m, 6H), 1.73 - 1.62 (m, 2H), 1.31 - 1.22 (m, 6H).

II. Biological Evaluation

Example 1: In Vitro FRET Assay

[00283] In vitro FRET assay was performed to evaluate the ability of select compounds to inhibit IRE1, the results of which are summarized in **Table 3**. To perform the in vitro FRET assay, 1X complete assay buffer (CAB; 1M DTT, 50 mM sodium citrate pH 7.15, 1mM magnesium acetate, 0.02% tween 20) was used to dilute SignalChem IRE1a protein to a final concentration of 2 nM. Selected compounds were serially diluted with DMSO in a non-binding black 384-well plate for a total of 15 ul in each well. 2 ul of the serially diluted compound or DMSO control were then added to new wells containing 98 ul of 1X CAB, for a total volume of 100 ul, 10 ul of which were then transferred to wells of a new plate. 5 ul of the diluted IRE1a was then added to each well. 5ul of a 400 mM XBP1 RNA probe was then added to each well. Fluorescence was then read over 30 minutes in kinetic mode (485/515 nm).

[00284] Two RNA probes were used, XBP1 wildtype (SEQ ID NO: 2) which is able to be spliced by active IRE1a or XBP1 mutant (SEQ ID NO: 3) which is unable to be spliced. Each probe contained a 5' 6-FAM modification and a 3' IOWA Black FQ modification.

[00285] A second FRET assay was performed to assess ATP-mediated inhibition. In this case, compounds and IRE1a were prepared and combined as discussed above, with the addition of ATP up to 1 mM final concentration. This mixture was incubated at room temperature for 60 minutes and then 5 ul of 400 nM XBP1 wildtype or mutant RNA probe was added. Plates were then read over 30 minutes in kinetic mode (485/515 nm).

Table 3.

Compound Ref. No.	Mean IC ₅₀
1	B
2	A
3; Formic Acid	A
4	A
5	A
6	A
7	B

Compound Ref. No.	Mean IC ₅₀
8	B
9	A
10	A
11	A
12	D
13	D
14; Formic Acid	D
15; Formic Acid	D
16; Formic Acid	A
17; Formic Acid	D
18; Formic Acid	A
19; Formic Acid	A
20; Formic Acid	A
21; Formic Acid	A
22; Formic Acid	B
23; Formic Acid	A
24; Formic Acid	A
25; Formic Acid	A
26; Formic Acid	A
27; Formic Acid	A
28; Formic Acid	A
29; Formic Acid	A
30; Formic Acid	C
31; Formic Acid	D
32; Formic Acid	A
33; Formic Acid	A
34; Formic Acid	A
35; Formic Acid	A
36; Formic Acid	A
37; HCl	A
38; Formic Acid	A
39; Formic Acid	A

Compound Ref. No.	Mean IC ₅₀
40; Formic Acid	A
41; Formic Acid	A
42; Formic Acid	A
43; Formic Acid	A
44; Formic Acid	A
45; Formic Acid	C
46; Formic Acid	A
47; Formic Acid	A
48; Formic Acid	A
49; Formic Acid	A
50; Formic Acid	A
51; Formic Acid	A
52; Formic Acid	A
53; Formic Acid	A
54; Formic Acid	A
55; Formic Acid	A
56; Formic Acid	A
57; Formic Acid	A
58; Formic Acid	B
59; Formic Acid	B
60; Formic Acid	A
62; Formic Acid	A
63; Formic Acid	A
65; Formic Acid	A
66; Formic Acid	A
67; Formic Acid	A
68; Formic Acid	A
69; Formic Acid	A
70; Formic Acid	A
71; Formic Acid	A
72; Formic Acid	A
73; Formic Acid	A

Compound Ref. No.	Mean IC ₅₀
74; Formic Acid	A
75; Formic Acid	A
76; Formic Acid	A
77; Formic Acid	A
78; Formic Acid	A
79; Formic Acid	A
80; Formic Acid	A
81; Formic Acid	A
82; Formic Acid	A
83; Formic Acid	B
84; Formic Acid	A
85; Formic Acid	A
86; Formic Acid	A
87; Formic Acid	A
88; Formic Acid	A
89; Formic Acid	A
90; Formic Acid	A
92; Formic Acid	A
93; Formic Acid	A
94; Formic Acid	A
96; Formic Acid	A
98; Formic Acid	A
100; Formic Acid	A
101; Formic Acid	B
102; Formic Acid	A
103; Formic Acid	A
104; Formic Acid	A
105; Formic Acid	A
106; Formic Acid	A
107; Formic Acid	A
109; Formic Acid	A
110; Formic Acid	A

Compound Ref. No.	Mean IC ₅₀
111; Formic Acid	A
112; Formic Acid	A
113; Formic Acid	A
114; Formic Acid	B
115; Formic Acid	A
120; Formic Acid	A
121; Formic Acid	A
123; Formic Acid	A
129; Formic Acid	A
134; Formic Acid	A
136; Formic Acid	A
138; Formic Acid	A
140; Formic Acid	A
143; Formic Acid	B
144; Formic Acid	C
146; Formic Acid	A

Note: Biochemical assay Mean IC₅₀ data are designated within the following ranges:

A: ≤ 5 nM; B: > 5 nM to ≤ 50 nM; C: > 50 nM to ≤ 100 nM; and D: > 100 nM.

Example 2: In Vitro Luciferase Assay

[00286] Compounds disclosed herein were assessed for disruption of IRE1 signaling using a IRE1a Endoribonuclease Nanoluciferase Assay. Briefly, 2.5×10^6 293T cells were seeded in a 10 cm² tissue culture plate. About 24 hours later, the cells were transfected with Effectene. In a 15 mL Tube, the following was added: 2 ug XBP1 luciferase reporter plasmid (PGK-Luc2-P2A-XBP1u-Nanoluciferase-PEST); 300 ul EC buffer; and 16 ul Enhancer, followed by incubation at room temp for 5 minutes. Next, 60 ul Effectene (Qiagen 301427) was added, followed by incubation at room temperature for 10 minutes. 2.6 mL cDMEM media was added. Old media was aspirated from the cells, followed by addition of 7 mL fresh media. Full transfection mixture was added dropwise to cells. Cells were incubated for 6 hours, followed by trypsinization, centrifugation and resuspension in 11 mL media. 100 uL of cells were plated per a well in a 96 well plate. A day later, ER stressors of choice +/- inhibitors were added. To harvest, media was aspirated from cells completely, then 50 uL 1x passive lysis buffer (Promega: E1941) was added per well and put on shaker (300rpm) for 30 minutes at room temperature. Cells were centrifuged,

and 15 uL sample per well was added to a new, opaque white 384 well plate (Corning 3570). 15 uL OneGlo (nanoluciferase kit, Promega N1630) was added. Plates were spun down, placed on shaker (300rpm) for 10 minutes. Plates were read on luminometer, 1000ms integration time per well. 15 uL Stop and Glo (nanoluciferase kit) was added. Plates were spun down, placed on shaker (300rpm) for 10 minutes. Plates were read on luminometer, 1000 ms second integration time per well. Recordings are provided below in **Table 4**.

Table 4.

Compound Ref. No.	Mean EC ₅₀
1	D
2	D
3; Formic Acid	B
4	C
5	D
6	C
11	D
16; Formic Acid	A
18; Formic Acid	A
19; Formic Acid	A
20; Formic Acid	C
21; Formic Acid	B
22; Formic Acid	D
23; Formic Acid	A
24; Formic Acid	A
25; Formic Acid	A
26; Formic Acid	A
27; Formic Acid	A
28; Formic Acid	A
29; Formic Acid	D
32; Formic Acid	A
33; Formic Acid	A
34; Formic Acid	B
35; Formic Acid	A

37; HCl	A
44; Formic Acid	A
46; Formic Acid	A
47; Formic Acid	B
48; Formic Acid	B
51; Formic Acid	C
52; Formic Acid	A
53; Formic Acid	A
54; Formic Acid	B
55; Formic Acid	A
56; Formic Acid	A
57; Formic Acid	A
58; Formic Acid	A
59; Formic Acid	C
60; Formic Acid	A
62; Formic Acid	B
65; Formic Acid	B
66; Formic Acid	C
67; Formic Acid	B
68; Formic Acid	C
69; Formic Acid	A
70; Formic Acid	A
71; Formic Acid	A
72; Formic Acid	D
73; Formic Acid	A
74; Formic Acid	A
75; Formic Acid	D
76; Formic Acid	B
77; Formic Acid	B
78; Formic Acid	A
79; Formic Acid	B
80; Formic Acid	D
81; Formic Acid	A

82; Formic Acid	B
83; Formic Acid	C
84; Formic Acid	B
85; Formic Acid	D
86; Formic Acid	C
87; Formic Acid	A
88; Formic Acid	A
89; Formic Acid	D
90; Formic Acid	B
92; Formic Acid	D
93; Formic Acid	A
94; Formic Acid	A
98; Formic Acid	A
100; Formic Acid	C
102; Formic Acid	C
103; Formic Acid	A
104; Formic Acid	C
107; Formic Acid	A
109; Formic Acid	A
110; Formic Acid	A
111; Formic Acid	C
112; Formic Acid	B
113; Formic Acid	B
115; Formic Acid	A
120; Formic Acid	A
121; Formic Acid	A
123; Formic Acid	A
129; Formic Acid	A
134; Formic Acid	A
136; Formic Acid	A
138; Formic Acid	C

Note: Biochemical assay Mean EC₅₀ data are designated within the following ranges:

A: ≤ 5 nM; B: > 5 nM to ≤ 50 nM; C: > 50 nM to ≤ 100 nM; and D: > 100 nM.

Example 3: Growth Assay

[00287] A growth assay was performed to evaluate the compounds disclosed herein for cytotoxicity. Briefly, 5,000,000 293T cells were resuspended in 18 mL of cDMEM for a final concentration of 277,777 cells/mL. 180 uL(50,000 cells) cDMEM was seeded per well in a 96 well flat bottom plate as shown in **Table 5**, with “media” wells left unfilled. In a separate 96 well dilution plate, 199 uL cDMEM and 1 uL of DMSO or any one of the compounds disclosed herein (shown as Test Compound 1, 2, 3, 4, 5, or 6 below) were added to wells A4, A8, C4, C8, E4, E8, G4, and G8. 133.3 uL cDMEM was added to wells 1, 2, 3, 5, 6, and 7 in rows A, C, E and G of the dilution plate. Compounds were serially diluted leftwards in threefold dilutions (66.7 uL into 133.3 uL cDMEM). 20 uL of each dilution was transferred in duplicate (duplicates in vertical paired wells) to the cells plated in the 96-well plate shown in **Table 5**, to the total concentrations shown below. 200 uL cDMEM was added to media wells (wells G5-H8). The plate was then placed in a humidified chamber for a 2 day incubation, and then photographed (media was more yellow in wells with potent cell growth). Absorbance was then measured at about 535 nM (lower for more acidic media) and about 450 nM (higher for more acidic media). The results of the growth assay as shown in **Table 6**.

Table 5

	1	2	3	4	5	6	7	8
A				Test Compound 1				Test Compound 5
B								
C				Test Compound 2				Test Compound 6
D								
E				Test Compound 3				DMSO
F								
G				Test Compound 4				media only
H								
Conc (uM)	0.185	0.556	1.667	5	0.185	0.5556	1.667	5

Table 6.

Compound Ref. No.	% Growth at 0.185 uM	% Growth at 0.5556 uM	% Growth at 1.667 uM	% Growth at 5 uM
3; Formic Acid	D	D	C	A
16; Formic Acid	D	D	D	B
18; Formic Acid	D	D	C	A
19; Formic Acid	D	D	C	A
20; Formic Acid	D	D	D	C
21; Formic Acid	D	D	D	B
22; Formic Acid	D	D	D	A
23; Formic Acid	D	C	C	D
24; Formic Acid	D	D	C	C
25; Formic Acid	D	D	D	D
27; Formic Acid	D	D	C	B
28; Formic Acid	D	D	C	B
29; Formic Acid	D	D	D	D
32; Formic Acid	D	D	C	B
33; Formic Acid	D	D	D	C
34; Formic Acid	D	D	D	A
35; Formic Acid	D	D	C	B
37; HCl	n/a	D	C	B
46; Formic Acid	D	D	D	D
52; Formic Acid	D	D	D	C
55; Formic Acid	D	D	D	D
65; Formic Acid	D	D	D	C
67; Formic Acid	D	D	C	C
69; Formic Acid	n/a	D	C	C
71; Formic Acid	D	D	C	B

Note: % Growth data are designated within the following ranges:

A: $\leq 25\%$; B: $> 25\%$ to $\leq 50\%$; C: $> 50\%$ to $\leq 75\%$; D: $> 75\%$ to $\leq 100\%$;

Example 4: Microsome Stability Assay

[00288] The formic acid salt of Compound 3 was tested under the microsome stability assay outlined below. Test compounds were incubated at 37°C with liver microsomes (pooled from multiple donors) at 1 µM in the presence of a NADPH regenerating system at 0.5 mg/ml microsomal protein. Positive controls included Testosterone (3A4 substrate), Propafenone (2D6) and Diclofenac (2C9), which were incubated with microsomes in the presence of an NADPH regenerating system. At time points (0, 5, 10, 20, 30 and 60 minutes), samples were removed and immediately mixed with cold acetonitrile containing internal standard (IS). Test compounds incubated with microsomes without the NADPH regenerating system for 60 min was also included. A single point for each test condition (n=1) was obtained, and samples were analyzed by LC/MS/MS. Disappearance of the test compound was assessed based on peak area ratios of analyte/IS (no standard curve).

[00289] The results of the microsome stability assay are shown below in the following table:

Table 7.

Human Liver Microsome (HLM) T _{1/2}	47.5 min
Human CI	29.2 uL/min/mg
HLM Remaining at 60 min	44%
Mouse Liver Microsome T _{1/2}	43.5 min
Mouse Liver Microsome CI	31.9 uL/min/mg
Mouse Liver Microsome Remaining at 60 min	41%

[00290] No issues with plasma stability were observed.

Example 5: ELISA Assay

[00291] Total human or mouse CD4 T cells are isolated by negative selection with Miltenyi MACS beads. Mouse CD4 T cells are isolated from mouse spleen while human CD4 T cells were isolated from human PBMCs. CD4 T cells are washed and then mixed with CD3/CD28 activator Dynabeads at 8 pm. After a 36 hour incubation, select IRE1a inhibitor compounds or IRE1a inhibitor controls are added and incubated for 2 hours.

[00292] After the two hour incubation, mouse or human cell-free malignant ascites supernatants or cRPMI control are added. After a 10 hour incubation, supernatants are isolated and used in an IFN-γ ELISA assay. Trizol is added to each ELISA well containing T Cells for

isolating RNA. ELISA assay is performed with the eBioscience Ready-Set-Go IFN-g ELISA kit according to the manufacturer's recommended protocol.

Example 6: T Cell Metabolism Assay

[00293] Total human or mouse CD4 T cells are isolated by negative selection with Miltenyi MACS beads. Mouse CD4 T cells are isolated from mouse spleen while human CD4 T cells are isolated from human PBMCs. One and a half million CD4 T cells are washed and then mixed with CD3/CD28 activator Dynabeads at a 1:1 bead:cell ratio and plated in complete RPMI in a 6 well plate. After a 24 hour incubation, select IRE1a inhibitor compounds or IRE1a inhibitor control compounds are added and incubated for 2 hours. After the two hour incubation, mouse or human cell-free malignant ascites supernatants or cRPMI control are added. After a 16 hour incubation, the dynabeads are removed by magnetic separation and mitochondrial oxygen consumption rate (OCR) and glycolytic extracellular acidification rate (ECAR) is measured with the Seahorse XFe96 Analyzer (Agilent). Samples are assayed in triplicate with 150,000 viable cells plated in each well of the assay plate. Supernatants are additionally isolated and used in downstream IFN-g ELISA assays. IRE1a activity is also measured by quantifying XBP1 splicing with quantitative PCR or by intracellular flow cytometric staining with an XBP1s-specific monoclonal antibody (clone: Q3-695; BD Pharmingen).

Example 7: DC Lipid Accumulation Assay

[00294] Approximately 3×10^6 bone marrow cells (after RBC lysis) are seeded in 10 mL cRPMI with 20 ng/mL GM-CSF in a petri dish. On culture day 3, 10 mL of cRPMI + 20 ng/mL GM-CSF is added. On culture day 6, non-adherent cells from each plate are collected and resuspended in 20 mL of fresh cRPMI + 20 ng/mL GM-CSF. On culture day 7, suspension cells are harvested, counted, and the resuspended at 500,000 cells per 180 microliters in fresh cRPMI + 20 ng/mL GM-CSF + 110% final concentration of IRE1a inhibitor compounds or DMSO as a control. 180 microliters of cell suspension are added to each well of a 96 well flat bottom TC-treated plate and incubated for 2 hours. 20 ul of 10X LPS (1 ug/mL) prepared in cRPMI + 20 ng/mL GM-CSF is added to indicated wells and incubated for another 6 hours. Cells are spun down and supernatant was stored in a new 96-well V-bottom plate. 200 microliters of trizol is added to pelleted cells for subsequent RNA analysis.

Example 8: Bioavailability Studies

[00295] **Figure 3** depicts the mean plasma concentration of compound 3 (left) after intravenous (IV, 1mg/kg), oral (PO, 25mg/kg), and intraperitoneal (IP, 25mg/kg) dosing and

compound 37 (right) after intravenous (IV, 1mg/kg), oral (PO, 30mg/kg), and intraperitoneal (IP, 30mg/kg) dosing.

Example 9: Suppression of XBP1 Splicing by Compound 3

[00296] **Figure 4** shows the results of the suppression of XBP1 splicing by Compound 3. Mice were injected with 0.25 mg/kg tunicamycin dissolved in DMSO: PBS at a ratio of 1:3. After 2 hours, the mice were injected with 10 mg/kg of Compound 3 dissolved in water or water alone as a vehicle control. After an additional 4 hours, the animals were euthanized, livers dissected out, and 2-3 mm³ liver pieces are flash frozen on dry ice. Liver pieces were then thawed in Trizol on ice, homogenized for 3 minutes with a bead mill at medium-high speed. RNA was then extracted from the Trizol solution according to the manufacturer's recommendation. Gene expression analysis was also performed via Reverse Transcription quantitative PCR (RT-qPCR) using a Stratagene Mx3005 instrument and SYBR green I (Life Technologies). Gene expression was measured of the spliced *Xbp1s* transcript, a primer set measuring all *Xbp1* transcripts, *Xbp1s* target genes including *Sec24d* and general ER stress response markers *Hspa5* (*BiP*) and *Ddit3* (*CHOP*). These data indicate that Compound 3 potently suppresses IRE1a-mediated XBP1 splicing *in vivo* after low-dose intraperitoneal injection.

Example 10: Inhibition of IRE1a Signaling in Cell Types within the Tumor

Microenvironment

[00297] A syngeneic mouse model for metastatic, orthotopic ovarian cancer was used to analyze the *in vivo* effects of compounds described herein. Assay conditions were similar to those described in Example 11, administering compound 3 for comparison against controls. As shown in the top panel of **Figure 5** shows that mice with metastatic ovarian cancer were injected with 11 mg/kg of Compound 3 or a vehicle. After 12 hours, the ascites were drained and FACS was used to purify the cells into four populations: tumor cells, dendritic cells (DC), CD4⁺ T cells, and CD8⁺ T cells. Then, PCR and qPCR was used to quantify spliced *Xbp1* transcripts and total *Xbp1* transcripts. The bottom panel of **Figure 5** shows that the splicing ratio of XBP1, calculated as the amount of spliced *Xbp1* transcripts divided by the total *Xbp1* transcripts, in the different cell types of mice treated with Compound 3 was markedly reduced compared to the vehicle-treated mice. Compound 3 can therefore inhibit IRE1a-mediated XBP1 splicing *in vivo* in tumor cells and key immune cell types found within the tumor microenvironment.

Example 11: Xbp1 Activation in ID8 Mouse Model

[00298] A syngeneic mouse model for metastatic, orthotopic ovarian cancer is used to analyze the *in vivo* effects of compounds described herein. In a first analysis, IRE1a/XBP1 activation is assessed in the ID8 mouse model for ovarian cancer.

[00299] Parental ID8 or aggressive ID8-Defb29/Vegf-A intraperitoneal ovarian tumors are generated. About $1-2 \times 10^6$ tumor cells are injected into wild type female C57BL/6 mice. After 3 weeks, a first group of 3-5 tumor bearing mice (parental ID8 and ID8-Defb29/Vegf-A mice) and tumor-free naïve mice are injected intraperitoneally with a compound from **Table 1**. Additional groups of 3-5 tumor bearing mice and naïve mice are injected with vehicle (PBS) as a control. Tumors are resected and ascites drained from the mice 12-24 hours after the injection for analyzing IRE1a pathway activation in the tumor microenvironment.

[00300] Fluorescently activated cell sorting (FACS) is then performed to purify cells from the tumors and ascites. Tumor dendritic cells (tDCs) ($CD45^+CD11c^+CD11b^+MHC-II^+CD8\alpha^{low}$), tumor cells ($CD45^-SSC^{hi}$), $CD4^+$ T cells ($CD45^+CD3^+CD4^+$) and $CD8^+$ T cells ($CD45^+CD3^+CD4^+$) are isolated from tumors and ascites of parental ID8 mice and ID8-Defb29/Vegf-A mice. Control splenic dendritic cells (sDCs) ($CD45^+CD11c^+CD11b^+MHC-II^+CD8\alpha^-$) or splenic T cells ($CD45^+CD3^+CD4^+$ or $CD45^+CD3^+CD8^+$) are isolated from spleens of naïve mice or ID8 mice and ID8-Defb29/Vegf-A mice. During sorting, viable cells are identified using the LIVE/DEAD Fixable Yellow Dead Cell Stain Kit (Life Technologies).

[00301] Total *Xbp1* mRNA expression and spliced *Xbp1* (*Xbp1s*) are quantified in sDCs and T cells from naïve mice, sDCs and T cells from parental ID8 mice and ID8-Defb29/Vegf-A mice, and tDCs, tumor cells, and tumor-infiltrating T cells from parental ID8 mice and ID8-Defb29/Vegf-A mice administered either vehicle or a compound from **Table 1**. Briefly, RNA from sorted cells are isolated using the Trizol reagent. 0.1-1 ug of RNA are used to generate cDNA using the High Capacity cDNA Reverse Transcription Kit (Life Technologies). Mouse *Xbp1* splicing assays are performed using conventional Reverse Transcription PCR (RT-PCR) and primers shown in **Table 8**. Gene expression analysis is also performed via Reverse Transcription quantitative PCR (RT-qPCR) using a Stratagene Mx3005 instrument and SYBR green I (Life Technologies). Gene expression is measured of *Xbp1* target genes including *ERdj4*, *Sec24d*, and *Sec61a1* and general ER stress response markers *Hspa5* (*BiP*) and *Ddit3* (*CHOP*). Murine *Xbp1s* transcript expression is analyzed using a primer that spans the splicing junction site.

Table 8

Species	Gene	Oligo name	Sequence 5'-3'	SEQ ID NO	Purpose
Mouse	Xbp1	Xbp1-SA-F	ACACGTTTGGGAATGGACAC		Splicing Assay
		Xbp1-SA-F	CCATGGGAAGATGTTCTGGG		
Mouse	Actb	actb1083	CTCAGGAGGAGCAATGATCTTGAT		RT-qPCR
		actb987	TACCACCATGTACCCAGGCA		
Mouse	Xbp1	Xbp1.total-F	GACAGAGAGTCAAACCTAACGTGG		RT-qPCR
		Xbp1.total-R	GTCCAGCAGGCAAGAAGGT		
Mouse	Xbp1s	XBPsA406F	AAGAACACGCTTGGGAATGG		RT-qPCR
		XBPsAa518R	CTGCACCTGCTGCGGAC		
Mouse	Xbp1 (exon 2)	XBPIWT205-F	CCTGAGCCCCGGAGGAGAA		RT-qPCR
		XBPIWT272-R	CTCGAGCAGTCTGCGCTG		
Mouse	Dnajb9/Erdj4	ERdj4-F	TAAAAGCCCTGATGCTGAAGC		RT-qPCR
		ERdj4-R	TCCGACTATTGGCATCCGA		
Mouse	Sec61a1	Sec61a1-F	CTATTTCAGGGCTTCCGAGT		RT-qPCR
		Sec61a1-R	AGGTGTTGTACTGGCCTCGGT		
Mouse	Edem1	EDEM-F	AAGCCCTCTGGAACCTTGCG		RT-qPCR
		EDEM-R	AACCCAATGGCCTGTCTGG		
Mouse	Hspa5/BiP	Grp78-F	TCATCGGACGCACTTGGA		RT-qPCR
		Grp78-R	CAACCACCTTGAATGGCAAGA		
Mouse	Ddit3/CHOP	CHOP-F	GTCCCTAGCTTGGCTGACAGA		RT-qPCR
		CHOP-R	TGGAGAGCGAGGGCTTTG		

Mouse	Agpat6	Agpat6-F	AGCTTGATTGTCAACCTCCTG		RT-qPCR
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[00302] Protein analysis of XBP1S is performed by Western blot or intracellular flow cytometric analysis of sDCs and T cells from naïve mice, sDCs and T cells from parental ID8 mice and ID8-Defb29/Vegf-A mice, and tDCs, tumor cells and tumor-infiltrating T cells from parental ID8 mice and ID8-Defb29/Vegf-A mice administered either vehicle or a compound from **Table 1**. Briefly, for Western blotting 5×10^6 sDCs, tumor cells, T cells, or tDCs are washed twice in 1X cold PBS and nuclear proteins are purified using the Nuclear Extraction Kit (Life Technologies). Proteins are quantified using the BCA method (Pierce) and 15-20 ug of nuclear proteins are separated via SDS-PAGE and are transferred onto nitrocellulose membranes. Anti-mouse XBP1s (GL Biochem) is raised in rabbit using a peptide corresponding to the XBP1s C-terminus, and is used at a 1:500 dilution for immunoblotting. Goat anti-mouse Lamin B (Santa Cruz) is used at 1:2000. HRP-conjugated secondary antibodies to rabbit and mouse (Santa Cruz) are used at a 1:2000 dilution. SuperSignal West Femto (Pierce) is used as Chemiluminescent Substrate and blots are imaged using a FluorChemE instrument (ProteinSimple). For intracellular flow cytometry of XBP1s protein, 1-2 million splenocytes or dissociated cells from solid tumors or ascites are washed in cold PBS and stained with the Ghost Dye 510 fixable viability dye diluted 1:1000 in PBS for 30 minutes on ice. The staining reaction is quenched with 2 mL of FACS buffer (PBS with 2% fetal bovine serum and 1 mM EDTA), cells pelleted by centrifugation at 300xg for 5 minutes, and then surface stained with antibodies directed at key lineage defining markers such as CD45/CD3/CD4/CD8 (for T cells) or CD45/CD11c/MHC-II (for DCs) for 30 minutes in FACS buffer on ice. Cells are washed twice with FACS buffer and then fixed and permeabilized for 30 minutes with the eBioscience FoxP3 nuclear staining kit according to the manufacturer's protocol. Cells are washed twice with 1x permeabilization buffer, then Fc receptors are blocked with TruStain FcX anti-mouse CD16/32 (Biolegend) for 15 minutes at room temperature. Finally, 5 microliters of XBP1s antibody (clone Q3-695) or an equivalent amount of isotype control antibody are added directly to cells and stained for 30 minutes at room temperature protected from light. Cells are washed twice with 1x permeabilization buffer and resuspended in FACS buffer, then analyzed on a flow cytometer such as the BD LSR II.

Example 12: Ovarian Cancer Progression

[00303] Tumor progression is measured in parental ID8 and aggressive ID8-Defb29/Vegf-A mice administered vehicle or a compound from **Table 1**. Similar to Example 1, parental ID8 or aggressive ID8-Defb29/Vegf-A intraperitoneal ovarian tumors are generated. Briefly, 1-2 x

10^6 tumor cells are injected into wild type C57BL/6 mice. After 2 weeks, a first group of 8-10 tumor bearing mice (parental ID8 and ID8-Defb29/Vegf-A mice) and a separate group of naïve mice are injected intraperitoneally once per day with a compound from **Table 1**. Additional groups of tumor bearing mice and naïve mice are injected with PBS as a control. In combination therapy studies, additional groups of mice are injected every other day with 200 ug isotype control antibody or blocking antibodies against CTLA-4 or PD-1. A final group of mice receives a combination therapy consisting of compound from **Table 1** and 200 ug checkpoint blocking antibody directed against either CTLA-4 or PD-1.

[00304] Tumor size, tumor volume, number of tumor masses as well as spleen size are then measured from vehicle or compound treated naïve mice, parental ID8 mice, and aggressive ID8-Defb29/Vegf-A mice. Naïve mice are monitored weekly for signs of morbidity or mortality from compound treatment. Malignant ascites accumulation is measured weekly as the percentage of body weight gain, and animals are euthanized once they reach 40% body weight gain. Survival of mice bearing parental ID8 tumors or aggressive ID8-Defb29/Vegf-A tumors that are treated with vehicle or a compound from **Table 1** is calculated as the number of days required to reach 40% weight gain since the tumor cells are originally injected. Compounds listed in **Table 1** are assessed for reduction in tumor-associated weight gain compared with vehicle control-treated animals.

Example 13: Lipid Analysis and Transcriptional Profiling

[00305] Lipid peroxidation byproducts are measured in mice described in Examples 1-2. Intracellular lipid content is evaluated via flow cytometry using 4,4-Difluoro1,3,5,7,8-Pentamethyl-4-Bora-3a,4a-Diaza-s-Indacene (BODIPY 493/503; Life Technologies). Briefly, 5×10^6 splenic cells or dendritic cells from naïve mice, parental ID8 mice, and aggressive ID8-Defb29/Vegf-A mice that are administered vehicle or a compound from **Table 1** are stained for surface markers using antibodies that do not overlap with BODIPY 493/503, namely CD11c-APC, CD45-APC-Cy7, and CD11b-Pacific Blue, followed by staining with 500 mL of BODIPY 493/503 at 0.5 mg/mL in PBS for 15 minutes at room temperature in the dark. BODIPY 493/503 staining is then detected in the PE or FITC channel. Lipid analysis is also performed using electron microscopy analysis and mass spectrometry. In addition to lipid content, intracellular reactive oxygen species (ROS) and 4-HNE adducts are measured with 2',7'-dichlorofluorescein diacetate (DCFDA) and a competitive ELISA assay (Cell Biolabs), respectively.

[00306] Transcriptional profiling is performed in naïve mice, parental ID8 mice, and aggressive ID8-Defb29/Vegf-A mice that are treated with vehicle or a compound from **Table 1**. Gene expression of genes that are involved in unfolded protein response (UPR)/ endoplasmic

reticulum (ER) stress and genes involved in lipid metabolism are measured in tDCs purified by FACS. These include but are not limited to *Sec24d*, *Sec61a1*, *P4hb*, *Fasn*, *Agpat4*, and *Agpat6*. XBP1 pathway activation and key effector functions are also measured by quantitative PCR in tumor-infiltrating lymphocytes purified by FACS. Compounds listed in **Table 1** are assessed for reduction in XBP1s target gene expression and BODIPY 493/503 fluorescence in tumor-associated DCs.

Example 14: T Cell Activation

[00307] T cell activation is determined in ovarian cancer bearing mice following administration of compounds described herein. *In vivo* antigen presentation experiments are performed in wild-type C57BL/6 female mice bearing parental ID8 or ID8-Defb29/Vegf-A ovarian tumors. After three weeks, naïve mice, parental ID8 mice, or ID8-Defb29/Vegf-A mice are intraperitoneally injected with 0.6 mg of full length endotoxin-free ovalbumin (OVA) (SIGMA, grade VII). Mice are then injected with vehicle or a compound from **Table 1** 3 hours later. After 18 hours, mice receive intraperitoneally 2×10^6 CFSE-labeled T cells negatively purified from OT-1 transgenic mice. Peritoneal wash samples (10 mL) are collected after 72 hours and analyzed for CFSE dilution via FACS to calculate number of T cell divisions. Data are analyzed using FlowJo version 9 or 10.

[00308] *In vitro* antigen presentation experiments are performed with isolated tDCs from wild-type C57BL/6 female mice bearing parental ID8 or ID8-Defb29/Vegf-A ovarian tumors. After 3-4 weeks of tumor burden, tDCs are purified by FACS from the peritoneal cavity of naïve mice, parental ID8 mice, or ID8-Defb29/Vegf-A, and are pulsed with full-length endotoxin-free ovalbumin protein (Sigma, grade VII) in cRPMI containing 25% cell-free ovarian cancer ascites supernatants overnight at 37°C. Antigen-loaded tDCs are then washed twice with cRPMI and co-cultured with CFSE-labeled OT-I CD8+ T cells immunopurified from OT-1 mice at a 1:10 (DC to T cell) ratio. After 3-5 days, cultures analyzed for CFSE dilution via FACS to calculate number of T cell divisions. Data are analyzed using FlowJo version 9 or 10. Isolated tDCs from animals treated with a compound from **Table 1** are assessed for enhancement of T cell proliferation relative to tDCs isolated from vehicle-treated controls.

Example 15: Anti-tumor Immunity

[00309] Effects of test compounds in inducing anti-tumor immunity are analyzed. Mice are intraperitoneally injected with ID8-Defb29/Vegf-A ovarian cancer cells and are treated with a compound from **Table 1** (n=3-5/group) or vehicle daily starting at day 14 after tumor challenge.

After 1-2 weeks of daily treatment, peritoneal lavage samples are analyzed for the number of metastatic cancer cells and tumor ascites accumulation in the peritoneal cavity.

[00310] The capacity for T cells to respond to tumor antigens is also measured. Freshly isolated ascites cells are cultured in 96-well flat bottom plates for 6 hours in the presence of PMA, Ionomycin and Brefeldin A to induce cytokine translation and retention within the secretory pathway. After this stimulation period, the cells are washed twice with FACS buffer (PBS + 2% FBS and 1 mM EDTA) and stained for 30 minutes with Ghost Dye 510 Violet (Tonbo Biosciences) in PBS on ice according to the manufacturer's protocol. Cells are then washed twice more with FACS buffer and then stained with antibodies directed against CD45, CD3, CD4, CD8, and CD44 on ice for 30 minutes. Fc receptors are also blocked at this time with the TrueStain FcX Antibody (anti-CD16/32, Biolegend). After this staining period, cells are washed twice more with FACS buffer, resuspended in 1x Fix/Perm reagent (eBioscience Foxp3/Transcription Factor Staining Buffer Set), mixed well by pipetting 2-3 times and incubated for 30 minutes at room temperature protected from light. Cells are then washed twice with 1x permeabilization buffer and stained at room temperature with antibodies directed against murine Fc receptor CD16/32 (Fc Block), IFN-gamma and Granzyme-B for 30 minutes. After this incubation period, cells are washed once with 1x permeabilization buffer, once with FACS buffer, and resuspended in FACS buffer for analysis by flow cytometry. Data are analyzed using FlowJo version 9 or 10.

[00311] Total splenic T cells or Ficoll-enriched leukocytes ($2-3 \times 10^5$) from peritoneal wash samples are obtained 4 days after the last treatment (day 27) and are cocultured in 10% FBS RPMI with $2-3 \times 10^4$ bone marrow-derived DCs that are pulsed overnight with irradiated ID8-Defb29/Vegf-A ovarian cancer cells. Supernatants are collected after 48-72 hours of stimulation. IFN- γ and Granzyme B secretion is determined by ELISA using the Ready-SET-Go Kit (eBioscience). Tumor-resident T cells from animals treated with a compound from **Table 1** are assessed for increased IFN- γ and Granzyme B production relative to T cells isolated from vehicle-treated controls.

Example 16: IC₅₀ Measurements for hERG Potassium Ion Channel

[00312] Blockade of the cardiac ion channel coded by the hERG gene can lead to cardiac arrhythmia. Many small compounds have been found to bind to the hERG gene leading to problems in the QT response. To determine the viability of the compounds disclosed herein as pharmacological agents that would not affect the hERG channel blockade, a standard automated planar clamp method was employed to determine the IC₅₀ for various test compounds on their inhibition of the channel. An electrophysiological assay was prepared to measure the electric

current passing through the hERG channel expressed in a stable CHO cell line by applying the planar clamp method. This assay was performed using the automated QPatch platform (Sophion, Denmark) which allows fast and accurate electrophysiological characterization of the hERG ion channel and the determination of IC₅₀ values for the test compounds, as shown in **Table 9**. The significant separation (100-1000x) between effects against IRE1a-mediated XBP1 splicing in 293T cells and the effect on hERG channels suggest that there is a good safety margin for targeting IRE1a.

Table 9

Compound Ref. No.	Mean IC ₅₀
3; Formic Acid	B
16; Formic Acid	B
24; Formic Acid	C
37; HCl	B
69; Formic Acid	B

Note: hERG channel blockade Mean IC₅₀ data are designated within the following ranges:

A: > 50 uM; B: > 10 uM to ≤ 50 uM, C: >1 uM to ≤ 10 uM; and D: ≤ 1 uM.

Example 17: Pharmacokinetic Studies

[00313] Compounds are tested in a pharmacokinetic (“PK”) study to determine the half-life (T_{1/2}) in mice. A compound from **Table 1** is dissolved in a vehicle to make a test antibiotic composition. The vehicle might be, for example, a water or a 25% PEG400 in saline solution. Administration to each mouse is performed via intravenous (IV) cannulation of the tail vein. Blood is collected over K2-EDTA anticoagulant from the submandibular or saphenous vein at predetermined time points. Following collection, the blood samples are stored at -70°C until analysis by LC-MS and comparison to a standard calibration curve results in the T_{1/2} for each compound.

[00314] Alternatively, on study day, the animals (fasted) usually receive a compound from **Table 1** (typically 10 or 30 mg/kg) by IP injection (typically 10 mL/kg). The IP dose is typically delivered via a bolus into the IP space for mice. All dosages are expressed as target dose in mg free base/acid equivalent/kg; actual doses are calculated for each individual animal and are recorded. The plasma samples are then collected as above and plasma levels determined.

Example 18: Protein Binding - Plasma Protein Binding Assay-HTD Method

[00315] The plasma protein binding is determined according to the following steps. Frozen plasma or freshly prepared plasma from various subjects are used as test matrix. They are purchased from commercial vendors or prepared in house from animals. Warfarin is used as a positive control. Other control compound(s) may be used according to specific requirement. One or more compounds from **Table 1** are spiked into blank matrix at the final concentration of 2 μM (or other test concentrations based on specific requirement). Final organic solvent concentration is $\leq 1\%$. If plasma samples are collected from in-life studies, they are used as test matrix without spiking compounds. An appropriate volume of spiked plasma solution is removed before incubation for recovery calculation. An aliquot (e.g., 150 μL) of matrix sample is added to one side of the chamber (donor chamber) in a 96-well equilibrium dialyzer plate (HTD dialysis device) and an equal volume of dialysis buffer is added to the other side of the chamber (receiver chamber). Triplicate incubations are performed (or other replicate number according to specific requirement). The dialyzer plate is placed into a humidified incubator with 5% CO_2 and incubated at 37°C for 4 to 6 hours. After incubation, samples are taken from the donor chamber as well as the receiver chamber. The plasma sample is matched with an appropriate volume of blank buffer; and buffer samples are matched with an appropriate volume of blank plasma. The matrix-matched samples are quenched with stop solution containing internal standard. Samples are analyzed by LC/MS/MS. Test compound concentrations in donor and receiver samples are expressed as peak area ratios of analyte/internal standard. If a quantitative analysis is needed, a set of calibration curve and quality controls could be included.

Example 19: Inhibition of Triple Negative Breast Cancer

[00316] XBP1 is known to binds directly to HIF1 α in triple negative breast cancer, and this cooperative binding enhances the upregulation of HIF1 α -dependent downstream target genes. Compounds in **Table 1** are screened for impact on XBP1 protein level, thereby removing a key binding partner for HIF1 α and reducing expression of HIF1 α -dependent target genes such as VEGFA, PDK1, GLUT1, and JMJD1A. Specifically, human triple-negative breast cancer cell lines are treated with vehicle control or a compound shown in **Table 1**, then cultured under hypoxia (0.1% O_2) for 24 hours. Cells are then lysed with RLT buffer, RNA extracted with the RNeasy 96 kit (Qiagen) and complementary DNA generated from the pure RNA. Semi-quantitative PCR and quantitative PCR are then used to quantify spliced Xbp1 transcripts, total Xbp1 transcripts, target genes regulated by XBP1s (e.g. SEC61A1, P4HB, EDEM1, AND SEC24D) and target genes regulated by HIF1 α (e.g. VEGFA, PDK1, GLUT1, and JMJD1A). The splicing ratio of XBP1 is calculated by determining the amount of spliced Xbp1 transcripts

divided by the total number of spliced and unspliced Xbp1 transcripts, an indicator for compounds that inhibit critical intracellular signaling required for TNBC tumor-initiating cell function and metastatic capacity. Compounds shown in **Table 1** are assessed for downregulation of XBP1s, XBP1 splicing ration, XBP1s-dependent target gene expression, and HIF1a target gene expression relative to DMSO control-treated samples.

Example 20: Soft agar Colony Formation Assay

[00317] One hundred thousand breast cancer cells are mixed 4:1 (v/v) with 2.0% agarose in growth medium containing vehicle control or a compound listed in **Table 1** for a final concentration of 0.4% agarose. The cell mixture is plated on top of a solidified layer of 0.8% agarose in growth medium. Cells are fed every 6–7 days with growth medium containing 0.4% agarose and vehicle control or a compound from **Table 1**, matching the initial plating conditions. The number of colonies are counted after 20 days, with the number of colonies visible at the end of the growth period to identify colonies with reduced growth.

Example 21: Inhibition of Metastatic Breast cancer

[00318] Mice with established metastatic breast cancer are separately injected with each of the compounds in **Table 1**. After 12 hours, the tumors are excised, mechanically separated, and enzymatically digested to single cell suspensions. Flow-assisted cell sorting is then used to purify four populations of cells: tumor cells, dendritic cells (DC), CD4+ T cells, and CD8+ T cells. The cells are sorted directly into RLT buffer for instant cell lysis and RNase deactivation. Then, cellular RNA is purified with the RNeasy 96 kit (Qiagen), and complementary DNA generated from the pure RNA. Semi-quantitative PCR and quantitative PCR are then used to quantify spliced Xbp1 transcripts, total Xbp1 transcripts, and target genes regulated by XBP1s such as SEC61A1, P4HB, EDEM1, AND SEC24D. The splicing ratio of XBP1 is calculated by determining the amount of spliced Xbp1 transcripts divided by the total number of spliced and unspliced Xbp1 transcripts, an indicator for compounds that inhibit metastatic breast cancer. Compounds shown in **Table 1** are assessed for reduction in XBP1s transcripts, XBP1 splicing and downstream XBP1s target genes relative to vehicle control-treated mice.

Example 22: Inhibition of Lung Cancer

[00319] Mice with established primary or metastatic lung cancer are separately injected with each of the compounds in **Table 1**. After 12 hours, the tumors are excised, mechanically separated, and enzymatically digested to single cell suspensions. Flow-assisted cell sorting is

then used to purify four populations of cells: tumor cells, dendritic cells (DC), CD4+ T cells, and CD8+ T cells. The cells are sorted directly into RLT buffer for instant cell lysis and RNase deactivation. Then, cellular RNA is purified with the RNeasy 96 kit (Qiagen), and complementary DNA generated from the pure RNA. Semi-quantitative PCR and quantitative PCR are then used to quantify spliced Xbp1 transcripts, total Xbp1 transcripts, and target genes regulated by XBP1s such as SEC61A1, P4HB, EDEM1, AND SEC24D. The splicing ratio of XBP1 is calculated by determining the amount of spliced Xbp1 transcripts divided by the total number of spliced and unspliced Xbp1 transcripts, an indicator for compounds that inhibit primary or metastatic lung cancer. Compounds shown in **Table 1** are assessed for reduction in XBP1s transcripts relative to vehicle control-treated mice.

Example 23: Inhibition of Bladder Cancer

[00320] Mice with established primary or metastatic bladder cancer are separately injected with each of the compounds in **Table 1**. After 12 hours, the tumors are excised, mechanically separated, and enzymatically digested to single cell suspensions. Flow-assisted cell sorting is then used to purify four populations of cells: tumor cells, dendritic cells (DC), CD4+ T cells, and CD8+ T cells. The cells are sorted directly into RLT buffer for instant cell lysis and RNase deactivation. Then, cellular RNA is purified with the RNeasy 96 kit (Qiagen), and complementary DNA generated from the pure RNA. Semi-quantitative PCR and quantitative PCR are then used to quantify spliced Xbp1 transcripts, total Xbp1 transcripts, and target genes regulated by XBP1s such as SEC61A1, P4HB, EDEM1, AND SEC24D. The splicing ratio of XBP1 is calculated by determining the amount of spliced Xbp1 transcripts divided by the total number of spliced and unspliced Xbp1 transcripts, an indicator for compounds from that inhibit primary or metastatic bladder cancer. Compounds shown in **Table 1** are assessed for reduction in XBP1s transcripts, XBP1 splicing and downstream XBP1s target genes relative to vehicle control-treated mice.

[00321] While preferred embodiments of the present invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions will now occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed in practicing the invention. It is intended that the following claims define the scope of the invention and that methods and structures within the scope of these claims and their equivalents be covered thereby.

SEQUENCE LISTING

SEQ ID NO: 1

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NYWLLIGHHETPLSASTKMLERFPNNLPKHRENVIPADSEKKSFEVINLVDQTSENAPT
TVSRDVEEKPAHAPARPEAPVDSMLKDMATIILSTFLLIGWVAFIITYPLSMHQQQQQLQH
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QRQANILLGACSLDCLHPEKHEDVIARELIEKMIAMDPQKRPSAKHVLKHPFFWSLEKQL
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SEQ ID NO: 2

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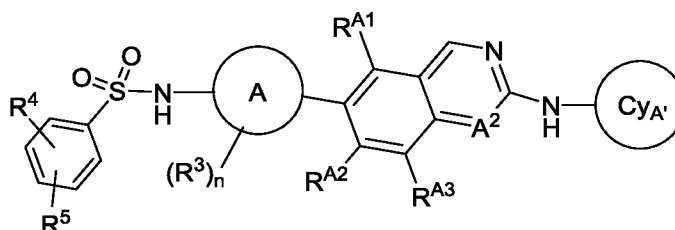
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CAUGUCCCCAGCAC AUG

CLAIMS

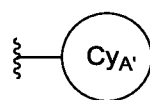
WHAT IS CLAIMED IS:

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



Formula (I)

wherein,



is a substituted C₃-C₁₀ cycloalkyl that is substituted with 1-3R¹ and 0-3R²; each R¹ is independently -OR⁶, -SR⁶, -S(=O)R⁷, -S(=O)₂R⁷, or -N(R⁶)₂;

each R² is independently H, halogen, -CN, -OR⁸, -SR⁸, -S(=O)R⁹, -S(=O)₂R⁹, -S(=O)₂N(R⁸)₂, -NR⁸S(=O)₂R⁹, -C(=O)R⁹, -OC(=O)R⁹, -CO₂R⁸, -OCO₂R⁹, -N(R⁸)₂, -OC(=O)N(R⁸)₂, -NR⁸C(=O)R⁹, -NR⁸C(=O)OR⁹, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

each R⁶ is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₁-C₄fluoroalkyl, -X-optionally substituted C₁-C₄alkyl, -X-optionally substituted C₁-C₄heteroalkyl, -X-optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl; or two R⁶ are taken together with the N atom to which they are attached to form an optionally substituted heterocycle;

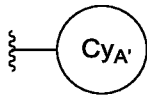
X is -(C=O)-;

each R⁷ is independently optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₁-C₄fluoroalkyl, optionally substituted C₃-C₆cycloalkyl, optionally substituted C₂-C₁₀heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;

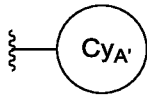
each R⁸ is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₁-C₄fluoroalkyl, , optionally substituted C₃-

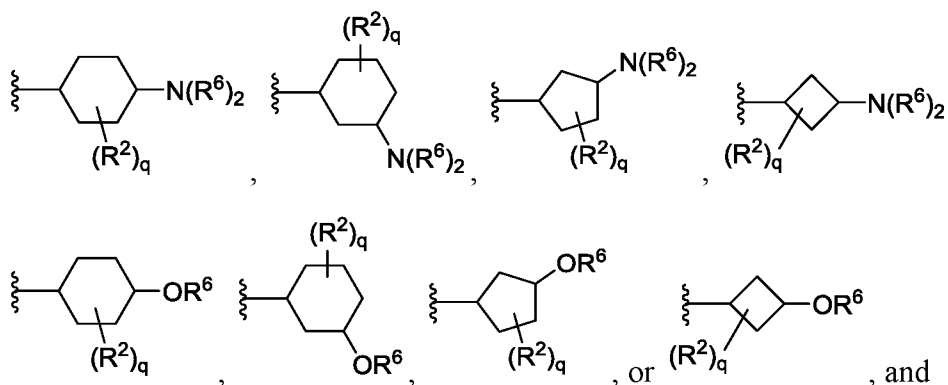
C_6 cycloalkyl, optionally substituted C_2 - C_{10} heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;
 or two R^8 are taken together with the N atom to which they are attached to form an optionally substituted heterocycle;
 each R^9 is independently optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, or optionally substituted C_1 - C_4 fluoroalkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted C_2 - C_{10} heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;
 A^2 is N or CR^A ;
 R^A , R^{A1} , R^{A2} , and R^{A3} are each independently H, halogen, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, optionally substituted aryl, or $-OR^{10}$;
 R^{10} is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted C_2 - C_{10} heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;
 ring A is a monocyclic carbocycle or a monocyclic heterocycle;
 each R^3 is independently H, halogen, $-CN$, $-OR^{11}$, $-SR^{11}$, $-N(R^{11})_2$, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted C_2 - C_{10} heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;
 each R^{11} is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted C_2 - C_{10} heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;
 n is 0, 1, 2, 3, or 4;
 R^4 and R^5 are each independently H, halogen, $-CN$, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})_2$, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted C_2 - C_{10} heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl;
 and
 R^{12} is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_3 - C_6 cycloalkyl, optionally substituted C_2 - C_{10} heterocycloalkyl, optionally substituted aryl, or optionally substituted heteroaryl.

2. The compound of claim 1, or a pharmaceutically acceptable salt, or solvate thereof,

wherein  is substituted C₄-C₇ cycloalkyl that is substituted with 1-3R¹ and 0-3R².

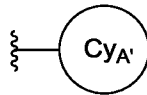
3. The compound of claim 2, or a pharmaceutically acceptable salt, or solvate thereof,

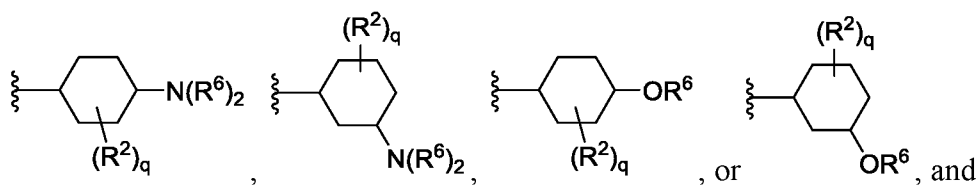
wherein  is



q is 0, 1, 2, or 3.

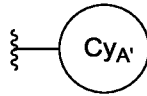
4. The compound of any one of claims 1-3, or a pharmaceutically acceptable salt, or

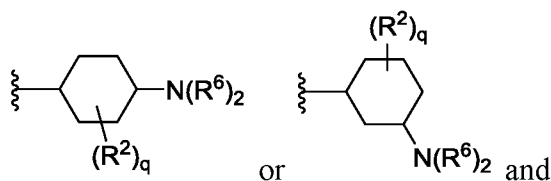
solvate thereof, wherein  is



q is 0, 1, 2, or 3.

5. The compound of any one of claims 1-4, or a pharmaceutically acceptable salt, or

solvate thereof, wherein  is



q is 0, 1, 2, or 3.

6. The compound of any one of claims 3-5, wherein q is 0 or 1.

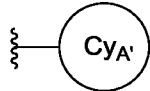
7. The compound of any one of claims 1-6, or a pharmaceutically acceptable salt, or solvate thereof, wherein each R⁶ is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₁-C₄fluoroalkyl, -X-optionally substituted

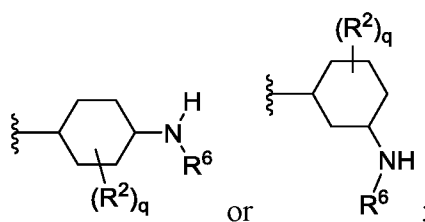
C₁-C₄alkyl, -X-optionally substituted C₁-C₄heteroalkyl, or -X-optionally substituted C₁-C₄fluoroalkyl.

8. The compound of claim 7, or a pharmaceutically acceptable salt, or solvate thereof, wherein each R⁶ is independently H.

9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt, or solvate thereof, wherein each R² is independently H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, or optionally substituted C₁-C₄fluoroalkyl.

10. The compound of any one of claims 3-5, or a pharmaceutically acceptable salt, or

solvate thereof, wherein  is



R⁶ is H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, optionally substituted C₁-C₄fluoroalkyl, -X-optionally substituted C₁-C₄alkyl, -X-optionally substituted C₁-C₄heteroalkyl, or -X-optionally substituted C₁-C₄fluoroalkyl; q is 0 or 1; and

R² is H, optionally substituted C₁-C₄alkyl, optionally substituted C₁-C₄heteroalkyl, or optionally substituted C₁-C₄fluoroalkyl.

11. The compound of claim 10, or a pharmaceutically acceptable salt, or solvate wherein R⁶ is H.

12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, or solvate thereof, wherein A² is N.

13. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt, or solvate thereof, wherein A² is CR^A.

14. The compound of claim 13, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^A is H, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl.

15. The compound of claim 14, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^A is H.

16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A1} is H, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl.

17. The compound of claim 16, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A1} is H.

18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A2} is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

19. The compound of claim 18, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A2} is H.

20. The compound of any one of claims 1-19, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A3} is H, halogen, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, optionally substituted aryl, or $-OR^{10}$.

21. The compound of claim 20, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A3} is H, halogen, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, or $-OR^{10}$.

22. The compound of claim 21, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A3} is optionally substituted C_1 - C_4 alkyl.

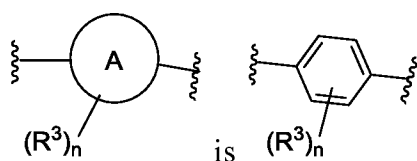
23. The compound of claim 22, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A3} is methyl, ethyl, propyl or butyl.

24. The compound of claim 21, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A3} is $-OR^{10}$ and R^{10} is methyl, ethyl, propyl or butyl.

25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is phenylene or a monocyclic C_3 - C_8 cycloalkylene that is selected from cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cycloheptylene, and cyclooctylene.

26. The compound of claim 25, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is phenylene.

27. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

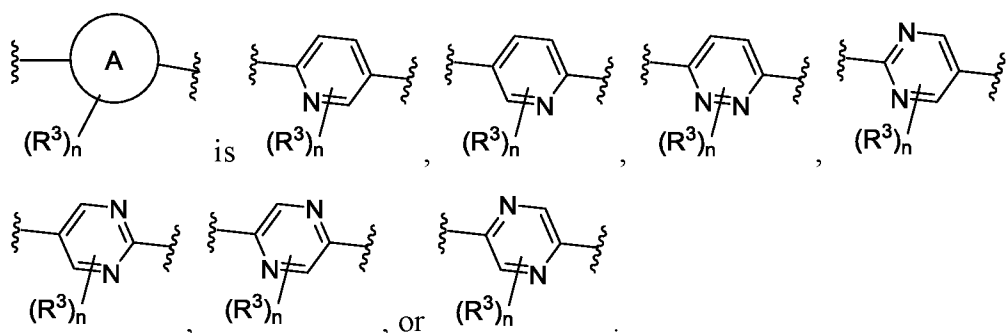


28. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is a monocyclic C_1 - C_5 heteroarylene containing 1-4 N atoms, and 0 or 1 O or S atom, or a monocyclic C_1 - C_5 heteroarylene containing 0-4 N atoms, and 1 O or S atom.

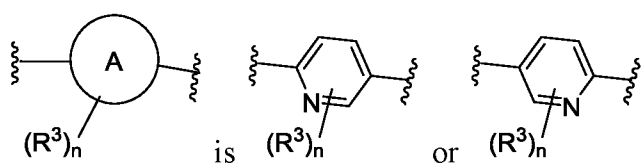
29. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is a monocyclic 6-membered heteroarylne selected from pyridinylene, pyrimidinylene, pyrazinylene, and pyridazinylene.

30. The compound of claim 29, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is pyridinylene.

31. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt, or solvate thereof, wherein:



32. The compound of claim 31, or a pharmaceutically acceptable salt, or solvate thereof, wherein:

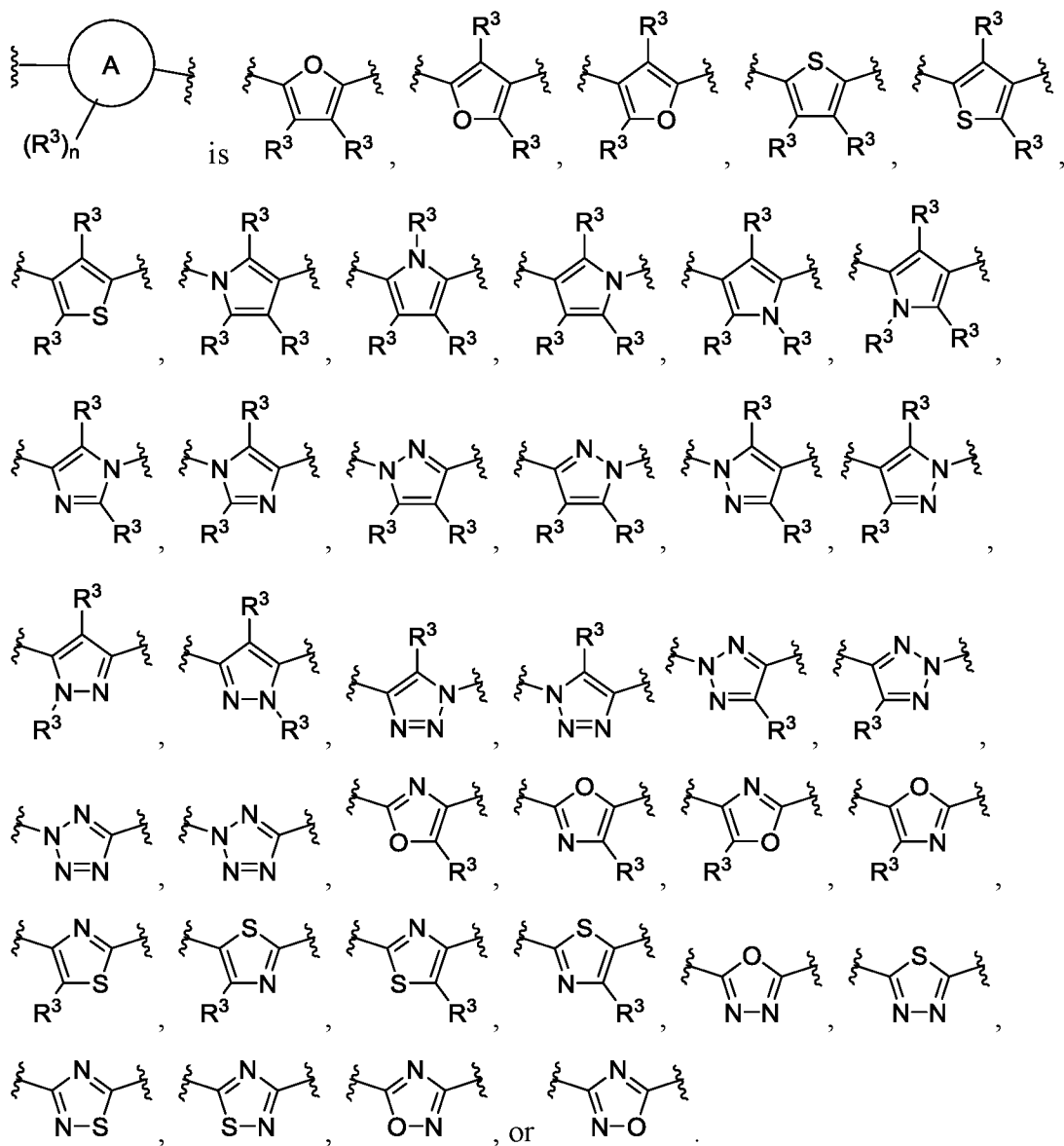


33. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is a monocyclic 5-membered heteroarylne selected from furanlylene, thienylene, pyrrolylene, oxazolyne, thiazolyne, imidazolyne, pyrazolyne, triazolyne, tetrazolyne, isoxazolyne, isothiazolyne, oxadiazolyne, and thiadiazolyne.

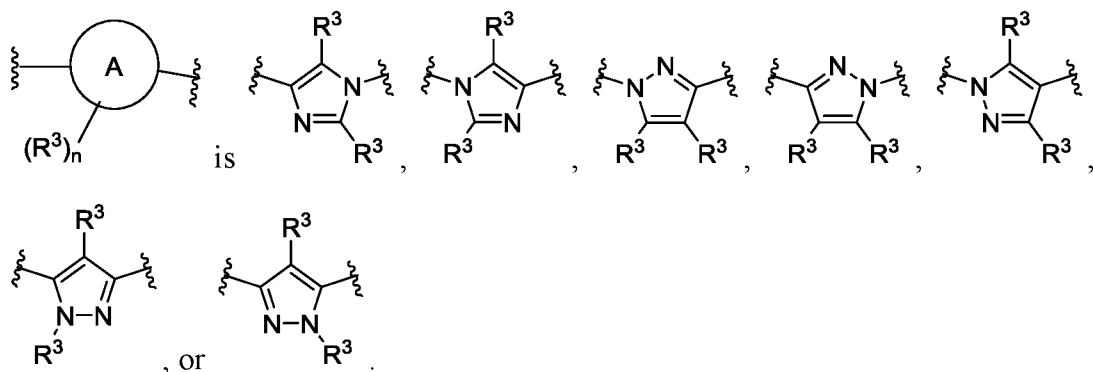
34. The compound of claim 33, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is oxazolyne, thiazolyne, imidazolyne, pyrazolyne, or oxadiazolyne.

35. The compound of claim 33, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is pyrazolyne.

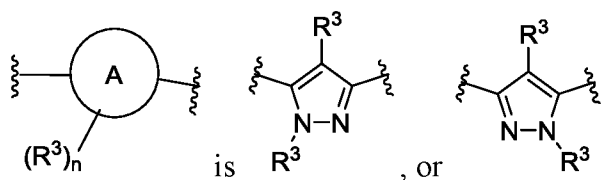
36. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt, or solvate thereof, wherein:



37. The compound of claim 36, or a pharmaceutically acceptable salt, or solvate thereof, wherein:



38. The compound of claim 36, or a pharmaceutically acceptable salt, or solvate thereof, wherein:



39. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is a ring A is a monocyclic C₂-C₈heterocycloalkylene containing at least 1 N atom in the ring that is selected from aziridinylene, azetidinylen, pyrrolidinylene, piperidinylene, piperazinylene, and azepanylene.

40. The compound of any one of claims 1-39, or a pharmaceutically acceptable salt, or solvate thereof, wherein each R³ is independently H, halogen, -CN, -OR¹¹, -SR¹¹, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl; and n is 1, 2, or 3.

41. The compound of claim 40, or a pharmaceutically acceptable salt, or solvate thereof, wherein R³ is optionally substituted C₁-C₄alkyl.

42. The compound of claim 41, or a pharmaceutically acceptable salt, or solvate thereof, wherein R³ is methyl, ethyl, propyl, or butyl.

43. The compound of claim 40, or a pharmaceutically acceptable salt, or solvate thereof, wherein R³ is -OR¹¹.

44. The compound of claim 43, or a pharmaceutically acceptable salt, or solvate thereof, wherein R¹¹ is H, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl.

45. The compound of claim 44, or a pharmaceutically acceptable salt, or solvate thereof, wherein R¹¹ is methyl, ethyl, propyl, or butyl.

46. The compound of claim 44, or a pharmaceutically acceptable salt, or solvate thereof, wherein R¹¹ is -CF₃ or -CH₂CF₃.

47. The compound of any one of claims 1-46, or a pharmaceutically acceptable salt, or solvate thereof, wherein R⁴ is H, halogen, -CN, -OR¹², -SR¹², -N(R¹²)₂, optionally substituted C₁-C₄alkyl, or optionally substituted C₁-C₄fluoroalkyl.

48. The compound of claim 47, or a pharmaceutically acceptable salt, or solvate thereof, wherein R⁴ is H.

49. The compound of claim 47, or a pharmaceutically acceptable salt, or solvate thereof, wherein R⁴ is halogen.

50. The compound of claim 49, or a pharmaceutically acceptable salt, or solvate thereof, wherein R⁴ is -Cl, -Br, -F, or -I.

51. The compound of claim 47, or a pharmaceutically acceptable salt, or solvate thereof, wherein R⁴ is -OR¹².

52. The compound of claim 51, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{12} is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

53. The compound of claim 47, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^4 is optionally substituted C_1 - C_4 alkyl.

54. The compound of claim 53, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^4 is methyl, ethyl, propyl, or butyl.

55. The compound of claim 47, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^4 is optionally substituted C_1 - C_4 fluoroalkyl.

56. The compound of claim 55, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^4 is $-CF_3$ or $-CH_2CF_3$.

57. The compound of any one of claims 1-56, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^5 is H, halogen, $-CN$, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})_2$, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

58. The compound of claim 57, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^5 is H.

59. The compound of claim 57, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^5 is halogen.

60. The compound of claim 59, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^5 is $-Cl$, $-Br$, $-F$, or $-I$.

61. The compound of claim 57, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^5 is $-OR^{12}$.

62. The compound of claim 61, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{12} is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

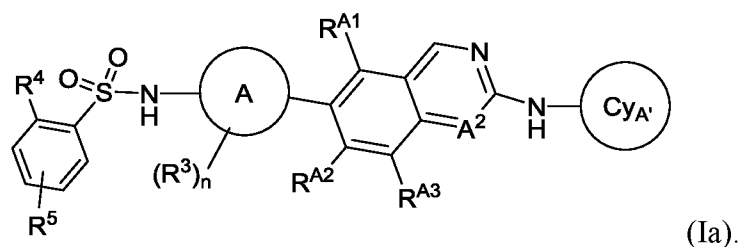
63. The compound of claim 57, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^5 is optionally substituted C_1 - C_4 alkyl.

64. The compound of claim 63, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^5 is methyl, ethyl, propyl, or butyl.

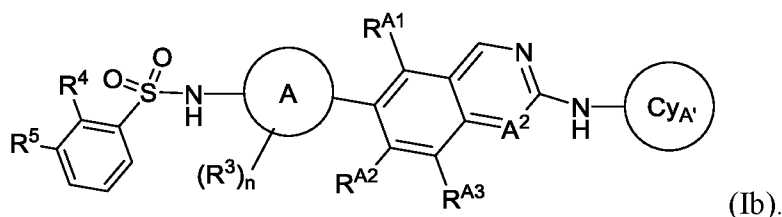
65. The compound of claim 57, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^5 is optionally substituted C_1 - C_4 fluoroalkyl.

66. The compound of claim 65, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^5 is $-CF_3$ or $-CH_2CF_3$.

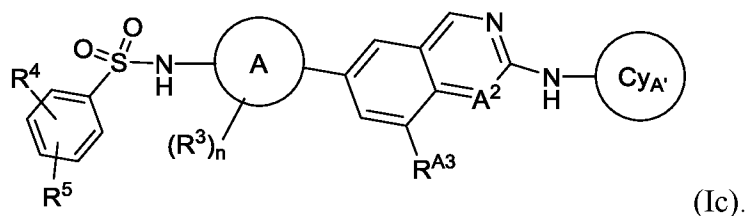
67. The compound of claim 1, or a pharmaceutically acceptable salt, or solvate thereof, wherein the compound has the structure of formula (Ia)



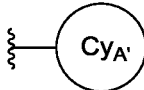
68. The compound of claim 1, or a pharmaceutically acceptable salt, or solvate thereof, wherein the compound has the structure of formula (Ib)

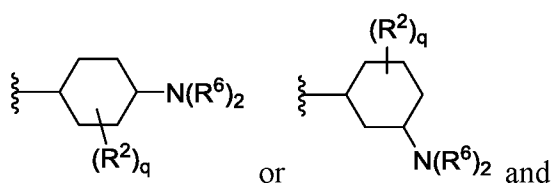


69. The compound of claim 1, or a pharmaceutically acceptable salt, or solvate thereof, wherein the compound has the structure of formula (Ic)



70. The compound of any one of claims 67-69, or a pharmaceutically acceptable salt, or

solvate thereof, wherein  is



q is 0 or 1.

71. The compound of claim 70, or a pharmaceutically acceptable salt, or solvate thereof, wherein each R^6 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, optionally substituted C_1 - C_4 fluoroalkyl, -X-optionally substituted C_1 - C_4 alkyl, -X-optionally substituted C_1 - C_4 heteroalkyl, or -X-optionally substituted C_1 - C_4 fluoroalkyl.

72. The compound of claim 71, or a pharmaceutically acceptable salt, or solvate thereof, wherein each R^6 is independently H.

73. The compound of any one of claims 67-72, or a pharmaceutically acceptable salt, or solvate thereof, wherein each R^2 is independently H, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 heteroalkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

74. The compound of any one of claims 67-73, or a pharmaceutically acceptable salt, or solvate thereof, wherein A^2 is N.

75. The compound of any one of claims 67-73, or a pharmaceutically acceptable salt, or solvate thereof, wherein A^2 is CR^A .

76. The compound of claim 75, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^A is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

77. The compound of claim 75, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^A is H.

78. The compound of any one of claims 67-77, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A1} is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

79. The compound of claim 78, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A1} is H.

80. The compound of any one of claims 67-79, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A2} is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

81. The compound of claim 80, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A2} is H.

82. The compound of any one of claims 67-81, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A3} is H, halogen, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, optionally substituted aryl, or $-OR^{10}$.

83. The compound of claim 82, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A3} is H, halogen, optionally substituted C_1 - C_4 alkyl, optionally substituted C_1 - C_4 fluoroalkyl, or $-OR^{10}$.

84. The compound of claim 82, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A3} is optionally substituted C_1 - C_4 alkyl.

85. The compound of claim 84, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A3} is methyl, ethyl, propyl, or butyl.

86. The compound of claim 85, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{A3} is ethyl.

87. The compound of any one of claims 67-86, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is phenylene.

88. The compound of any one of claims 67-86, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is a monocyclic 6-membered heteroarylene selected from pyridinylene, pyrimidinylene, pyrazinylene, and pyridazinylene.

89. The compound of claim 88, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is pyridinylene.

90. The compound of any one of claims 67-86, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is a monocyclic 5-membered heteroarylene selected from furanylene, thienylene, pyrrolylene, oxazolylene, thiazolylene, imidazolylene, pyrazolylene, triazolylene, tetrazolylene, isoxazolylene, isothiazolylene, oxadiazolylene, and thiadiazolylene.

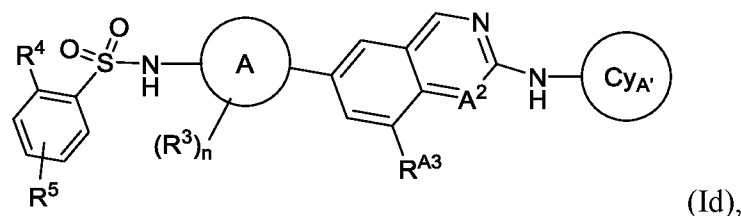
91. The compound of claim 90, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is pyrazolylene.

92. The compound of any one of claims 67-91, or a pharmaceutically acceptable salt, or solvate thereof, wherein each R^3 is independently H, $-OR^{11}$, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl; and n is 1, 2, or 3.

93. The compound of claim 92, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^{11} is H, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

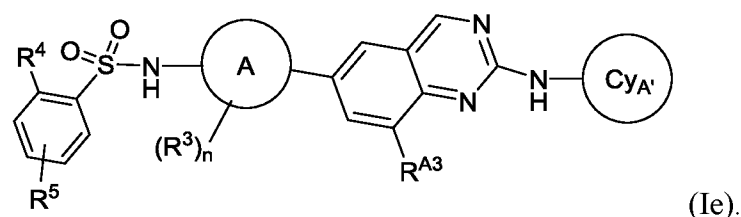
94. The compound of any one of claims 67-93, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^4 and R^5 are each independently H, halogen, $-CN$, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})_2$, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

95. The compound of claim 1, or a pharmaceutically acceptable salt, or solvate thereof, wherein the compound has the structure of formula (Id)

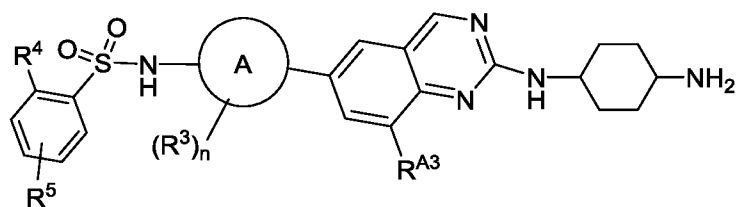


and R^{A3} is optionally substituted C_1 - C_4 alkyl.

96. The compound of claim 95, or a pharmaceutically acceptable salt, or solvate thereof, wherein the compound has the structure of formula (Ie)



97. The compound of claims 95, or 96, or a pharmaceutically acceptable salt, or solvate thereof, wherein the compound has the structure of formula (If)



98. The compound of any one of claims 95-97, or a pharmaceutically acceptable salt, or solvate thereof, wherein ring A is phenylene, pyridinylene, pyrazolylene, thiazolylene, imidazolylene, oxazolylene, or oxadiazolylene.

99. The compound of any one of claims 95-98, or a pharmaceutically acceptable salt, or solvate thereof, wherein R^4 and R^5 are each independently H, halogen, $-CN$, $-OR^{12}$, $-SR^{12}$, $-N(R^{12})_2$, optionally substituted C_1 - C_4 alkyl, or optionally substituted C_1 - C_4 fluoroalkyl.

100. The compound of claim 1, or a pharmaceutically acceptable salt, or solvate thereof, wherein the compound is a compound selected from:

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-1-methyl-1H-pyrazol-3-yl)-2-chlorobenzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-3-methylphenyl)-2-chlorobenzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-chlorobenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-4-methylpyridin-2-yl)-2-chlorobenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-4-methylpyridin-2-yl)-2-chlorobenzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-1-methyl-1H-pyrazol-3-yl)-2-chlorobenzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-(trifluoromethyl)benzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-(trifluoromethoxy)benzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2,5-dichlorobenzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-fluorobenzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)quinazolin-6-yl)-3-methylphenyl)-3-chlorobenzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-4-chlorobenzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)-2-methoxybenzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-(trifluoromethyl)phenyl)-2-chlorobenzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methylphenyl)benzenesulfonamide;

N-(5-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-6-methylpyridin-2-yl)-2-chlorobenzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-chlorophenyl)-2-chlorobenzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)phenyl)-2-chlorobenzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-3-methoxyphenyl)-2-chlorobenzenesulfonamide;

N-(6-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-5-methylpyridin-3-yl)-2-chlorobenzenesulfonamide;

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-2-fluoro-5-methylphenyl)-2-chlorobenzenesulfonamide; or

N-(4-(2-(((1r,4r)-4-aminocyclohexyl)amino)-8-ethylquinazolin-6-yl)-2,3-dimethylphenyl)-2-chlorobenzenesulfonamide.

101. The compound of any one of claims 1-100, or a pharmaceutically acceptable salt, or solvate thereof, wherein the compound or pharmaceutically acceptable salt, or solvate thereof, selectively binds to IRE1a at one or more binding sites.

102. The compound of claim 101, wherein the IRE1a comprises an RNase domain, a kinase domain, or any combination thereof.

103. The compound of claim 102, wherein the kinase domain is an auto-transphosphorylation kinase domain.

104. The compound of claim 102 or 103, wherein the kinase domain comprises an ATP-binding pocket.

105. The compound of any one of claims 101-104, wherein the kinase domain comprises an activation loop.

106. The compound of any one of claims 101-105, wherein at least one binding site is within the RNase domain.

107. The compound of any one of claims 101-106, where at least one binding site is within the kinase domain.

108. The compound of claim 107, wherein the at least one binding site is within the ATP-binding pocket of the kinase domain.

109. The compound of claim 107, wherein the at least one binding site is within the activation loop of the kinase domain.

110. The compound of any one of claims 101-109, wherein binding occurs at a first binding site.

111. The compound of claim 110, wherein the first binding site is located within the RNase domain, kinase domain, ATP-binding pocket, or activation loop.

112. The compound of any one of claims 110-111, wherein the first binding site comprises at least one amino acid residue of within amino acid residues 465-977 of SEQ ID NO: 1.

113. The compound of claim 112, wherein the first binding site comprises at least one amino acid residue within amino acid residues 568-833 of SEQ ID NO: 1.

114. The compound of claim 112, wherein the first binding site comprises at least one amino acid residue within amino acid residues 577-586, 597, 599, 626, 642-643, 645, 648, 688, 692-693, 695, or 711 of SEQ ID NO: 1.

115. The compound of claim 112, wherein the first binding site comprises at least one amino acid residue within amino acid residues 710-725 or 729-736 of SEQ ID NO: 1.

116. The compound of claim 112, wherein the first binding site comprises at least one amino acid residue within amino acid residues 835-963 of SEQ ID NO: 1.

117. The compound of any one of claims 110-116, wherein binding further occurs at a second binding site.

118. The compound of claim 117, wherein the second binding site is located within the RNase domain, the kinase domain, the ATP-binding pocket, or the activation loop.

119. The compound of claim 117, wherein the second binding site comprises at least one amino acid residue of within amino acid residues 465-977 of SEQ ID NO: 1.

120. The compound of claim 117, wherein the second binding site comprises at least one amino acid residue within amino acid residues 568-833 of SEQ ID NO: 1.

121. The compound of claim 117, wherein the second binding site comprises at least one amino acid residue within amino acid residues 577-586, 597, 599, 626, 642-643, 645, 648, 688, 692-693, 695, or 711 of SEQ ID NO: 1.

122. The compound of claim 117, wherein the second binding site comprises at least one amino acid residue within amino acid residues 710-725 or 729-736 of SEQ ID NO: 1.

123. The compound of claim 117, wherein the second binding site comprises at least one amino acid residue within amino acid residues 835-963 of SEQ ID NO: 1.

124. The compound of any one of claims 101-123, wherein binding occurs when the IRE1a is in a homo-dimerized conformation.

125. The compound of any one of claims 101-123, wherein binding occurs when the IRE1a is in an oligomerized conformation.

126. The compound of any one of claims 101-123, wherein binding occurs when the IRE1a is in a non-oligomerized or non-dimerized conformation.

127. The compound of any one of claims 101-126, wherein binding occurs when the IRE1a is in an ATP-bound state.

128. The compound of any one of claims 101-126, wherein binding occurs when the IRE1a is in a non-ATP-bound state.

129. The compound of any one of claims 101-128, wherein the compound selectively binds to a first IRE1a.

130. The compound of claim 129, wherein selectively binding to the first IRE1a blocks dimerization of the first IRE1a to a second IRE1a.

131. The compound of claim 129, wherein selectively binding to the first IRE1a blocks auto-transphosphorylation of the first IRE1a.

132. The compound of claim 129, wherein selectively binding to the first IRE1a blocks auto-transphosphorylation of a second IRE1a to which the first IRE1a is dimerized.

133. The compound of claim 129, wherein selectively binding to the first IRE1a blocks activation of the first IRE1a.

134. The compound of claim 129, wherein selectively binding to the first IRE1a blocks activation a second IRE1a to which the first IRE1a is dimerized.

135. The compound of claim 129, wherein selectively binding to the first IRE1a blocks kinase activity of the first IRE1a.

136. The compound of claim 129, wherein selectively binding to the first IRE1a blocks kinase activity of a second IRE1a to which the first IRE1a is dimerized.

137. The compound of claim 129, wherein selectively binding to the first IRE1a blocks RNase activity of the first IRE1a.

138. The compound of claim 129, wherein selectively binding to the first IRE1a blocks RNase activity of a second IRE1a to which the first IRE1a is dimerized.

139. A compound that selectively binds a first IRE1a at two or more sites, wherein when the compound is bound to the first IRE1a protein, the compound binds to an ATP-binding pocket of the first IRE1a and blocks the binding of ATP to the first IRE1a.

140. The compound of claim 139, wherein the ATP binding pocket is comprised within a kinase domain.

141. The compound of claim 139 or 140, wherein the ATP binding pocket is comprised within amino acid residues 465-977 of SEQ ID NO: 1

142. The compound of any one of claims 139-141, wherein the ATP binding pocket is comprised within amino acid residues 568-833 of SEQ ID NO: 1.

143. The compound of any one of claims 139-142, wherein the ATP binding pocket comprises one or more of amino acid residues 577-586, 597, 599, 626, 642-643, 645, 648, 688, 692-693, 695, or 711 of SEQ ID NO: 1.

144. A pharmaceutical composition comprising a compound according to any one of claims 1-143, or a pharmaceutically acceptable salt or solvate thereof.

145. The pharmaceutical composition of claim 144, comprising one or more pharmaceutically acceptable excipients.

146. A method for treating or ameliorating the effects of a disease associated with altered IRE1 signaling, the method comprising administering to a subject in need thereof a pharmaceutical composition, wherein the pharmaceutical composition comprises the compound of any one of claims 1-138.

147. The method of claim 146, wherein the disease is cancer.

148. The method of claim 147, wherein the cancer is a solid cancer or a hematologic cancer.

149. The method of claim 147, wherein the cancer is ovarian cancer, breast cancer, or triple negative breast cancer (TNBC).

150. A method for treating or ameliorating a cell proliferative disorder, the method comprising administering a pharmaceutical composition comprising a compound, or a pharmaceutically acceptable salt, or solvate thereof, that selectively binds to at least one amino acid residue of a IRE1 family protein comprising an RNase domain and kinase domain, wherein the pharmaceutical composition comprises the compound of any one of claims 1-143.

151. The method of claim 150, wherein the IRE1 family protein is IRE1a.

152. The method of claim 151, wherein the compound binds to an ATP-binding site of IRE1a.

153. The method of any one of claims 150-152, wherein the cell proliferative disorder is cancer.

154. The method of claim 153, wherein the cancer is a solid cancer or a hematologic cancer.

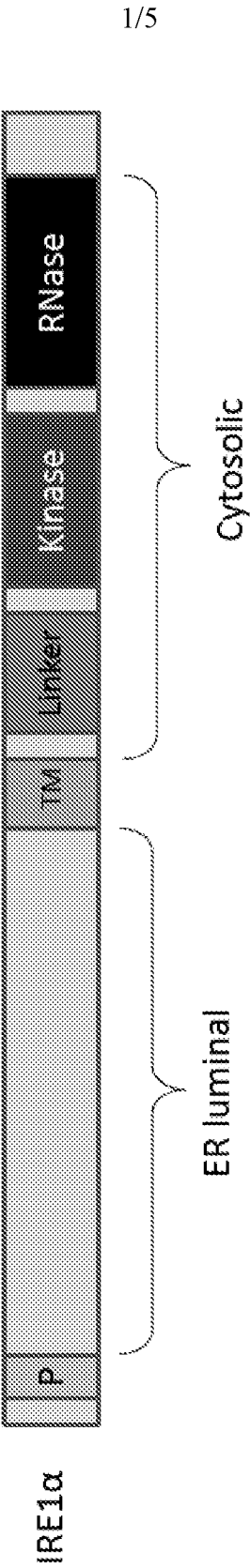


FIG. 1

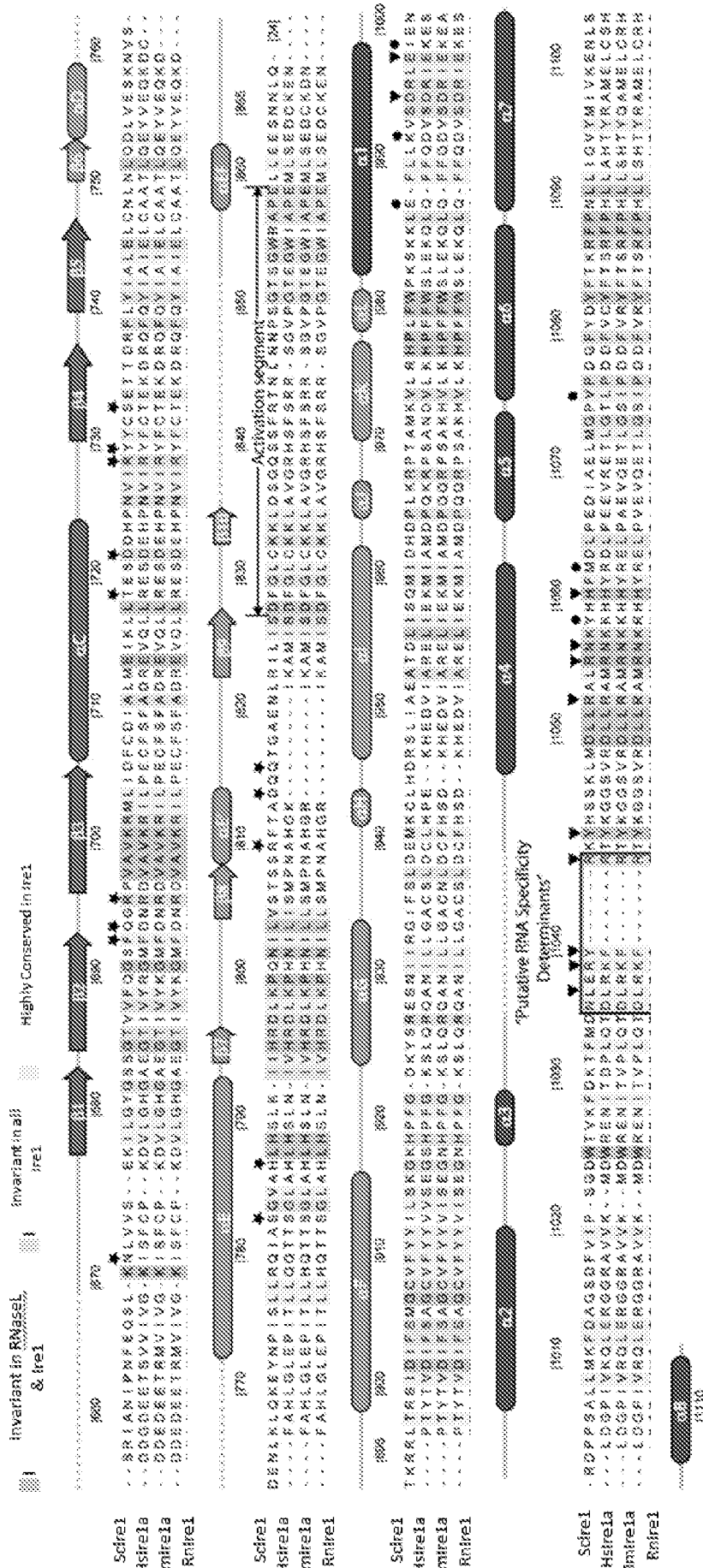


FIG. 2

- ★ Kinase domain dimer interface residues
- KEN domain dimer interface residues
- ▼ Putative Nuclease active site residues

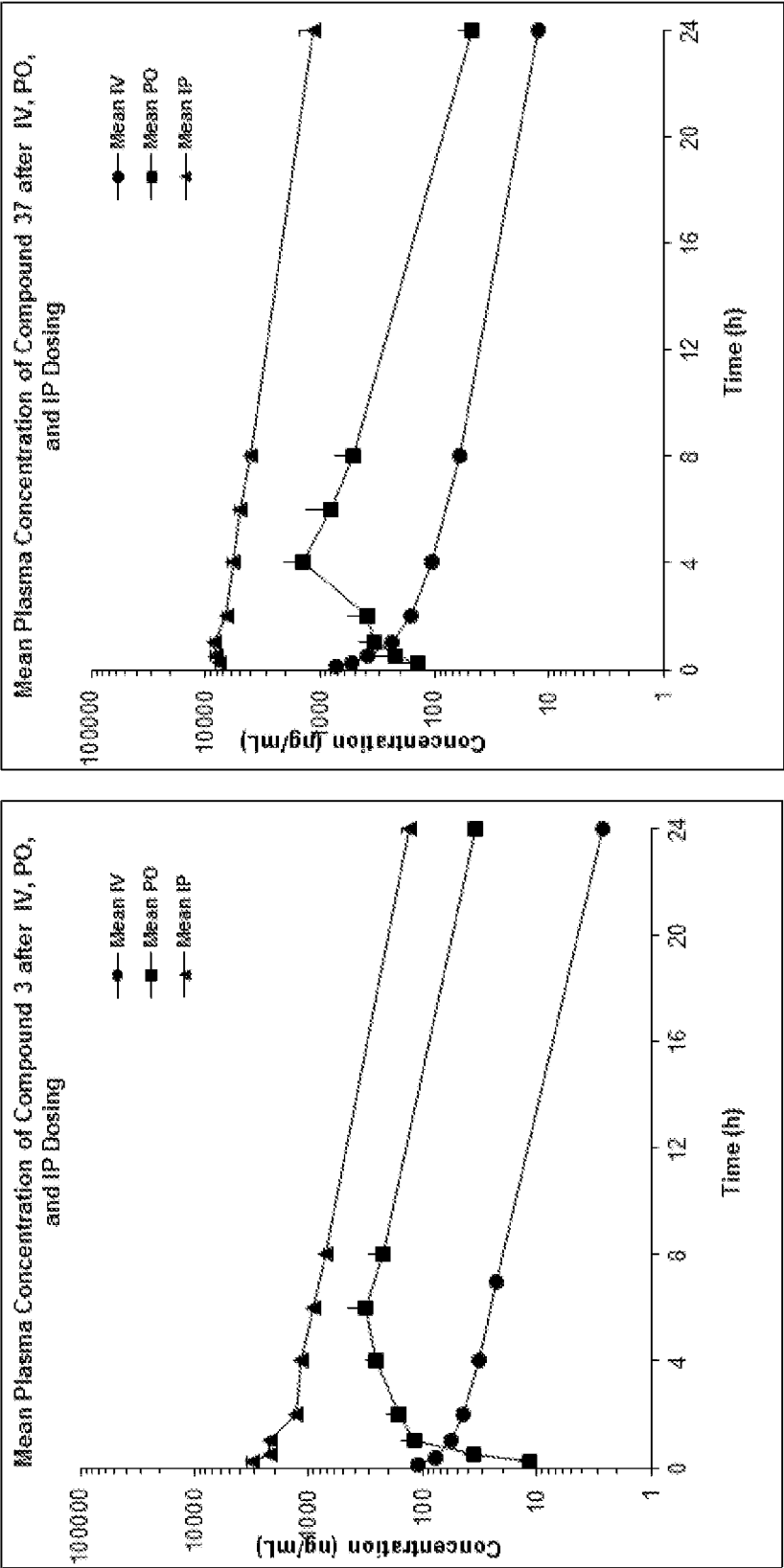
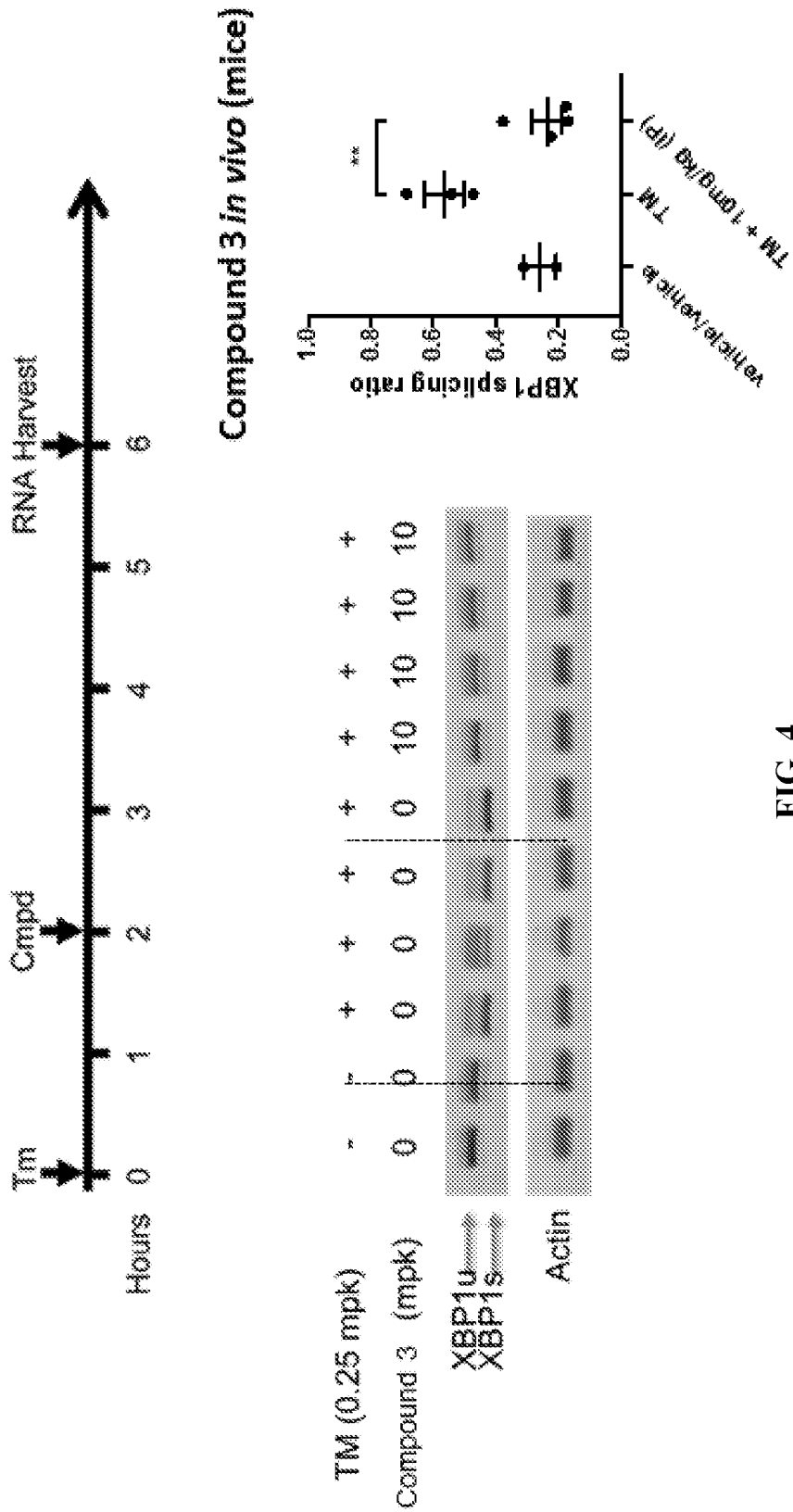


FIG. 3



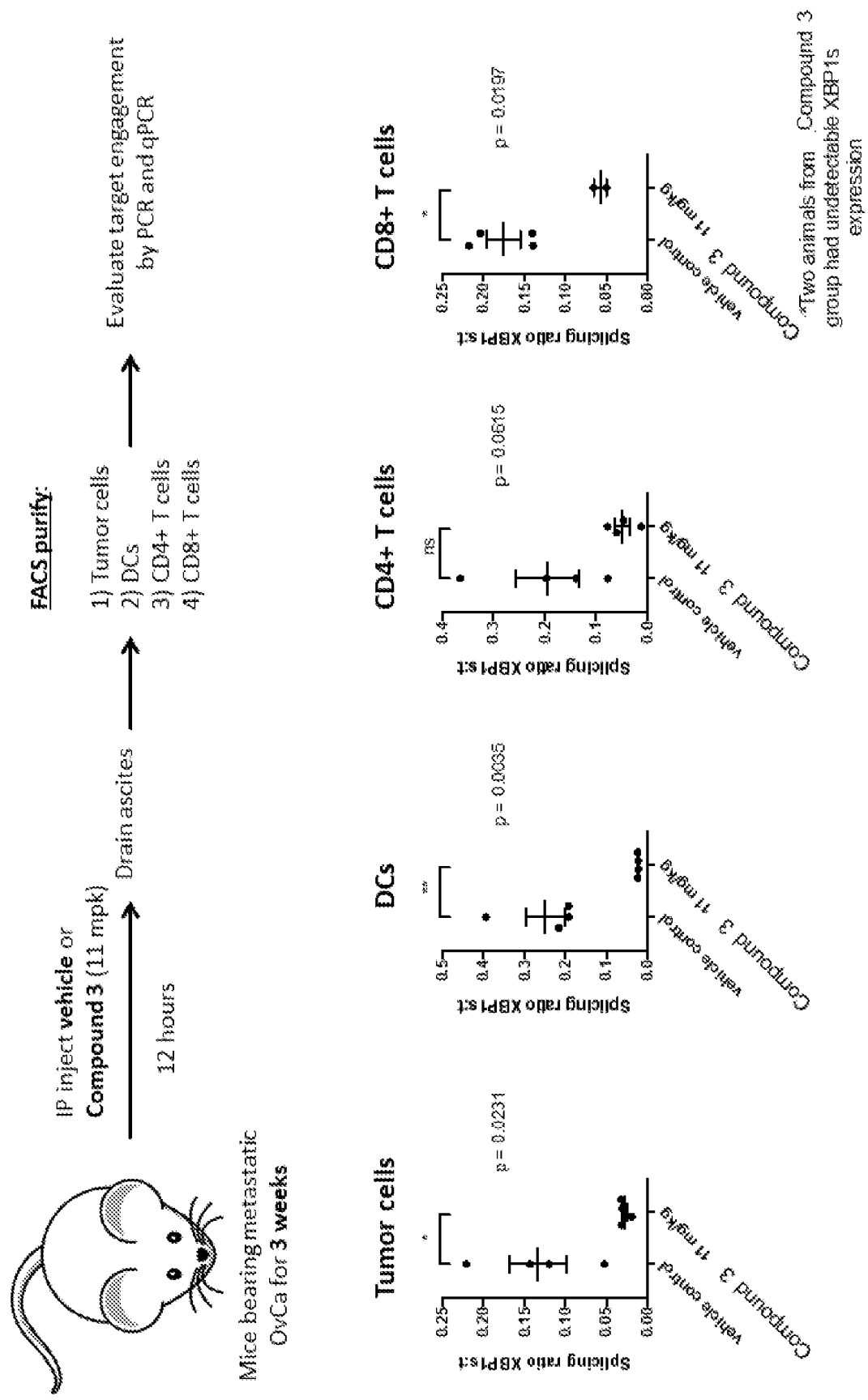


FIG. 5

A. CLASSIFICATION OF SUBJECT MATTER**C07D 403/04(2006.01)i, C07D 239/84(2006.01)i, A61K 31/517(2006.01)i, A61P 35/00(2006.01)i**

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D 403/04; C07H 21/04; A61K 31/7105; C07D 487/04; A61P 35/00; C07D 471/04; A61K 31/519; A61K 38/17; C12Q 1/68; C07D 239/84; A61K 31/517

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

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(Kipo internal), STN (Registry, Caplus) & Keywords: IRE1 protein, cancer, ATP binding pocket

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YANG, W. et al., "3D-QSAR and docking studies of 3-Pyridine heterocyclic derivatives as potent PI3K/mTOR inhibitors", Journal of Molecular Structure, 2013, pp. 107-116 See abstract; page 115; and table 5.	1-4, 67-72, 95-97, 100
A		139-141
X	WO 2011-047384 A2 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA et al.) 21 April 2011 See abstract; paragraph [0113]; and claim 1.	1-4, 67-72, 95-97, 100, 139, 140
Y		141
Y	US 2015-0190466 A1 (THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK) 09 July 2015 See paragraph [0322]; and SEQ ID NO: 132.	141
Y	US 8017331 B2 (PATTERSON, J. B. et al.) 13 September 2011 See column 8, lines 14-19; and SEQ ID NO:15.	141
X	WANG, L. et al., "Divergent allosteric control of the IRE1 α endoribonuclease using kinase inhibitors", Nat. Chem. Biol., 2012, Vol. 8, No. 12, pp. 982-989 See abstract; pages 982-984; and figure 1.	139, 140



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

17 September 2018 (17.09.2018)

Date of mailing of the international search report

17 September 2018 (17.09.2018)

Name and mailing address of the ISA/KR

International Application Division

Korean Intellectual Property Office

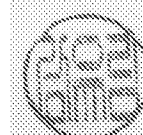
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2018/035465

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2015-0158874 A1 (CMG PHARMACEUTICAL CO., LTD.) 11 June 2015 See abstract; example 24; and claim 1.	1-4, 67-72, 95-97 , 100
PX	WO 2017-152117 A1 (CORNELL UNIVERSITY et al.) 08 September 2017 See abstract; paragraphs [0006], [0137]; tables 1-3; and claim 1.	1-4, 67-72, 95-97 , 100, 139-141

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 146-154
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 146-154 pertain to a method for treating a human body, and thus relate to a subject matter not required to search under PCT Article 17(2)(a)(i) and Rule 39.1(iv).
2. ☒ Claims Nos.: see below
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims 8, 11, 14, 15, 17, 19, 21-24, 26, 30, 32, 34, 35, 37, 38, 41-46, 48-56, 58-66, 76, 77, 79, 81, 83-86, 89, 91, 93, 102, 103, 108, 109, 111, 113-116, 118-123, 130-138, 145, 147-149, 151, 152, 154 refer to the multiple dependent claim which does not comply with PCT Rule 6.4(a).
3. ☒ Claims Nos.: see extra page
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of any additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Continuation of BOX NO. II

3. Claims Nos.:

5-7, 9, 10, 12, 13, 16, 18, 20, 25, 27-29, 31, 33, 36, 39, 40, 47, 57, 73-75, 78, 80, 82, 87, 88, 90, 92, 94, 98, 99, 101, 104-107, 110, 112, 117, 124-129, 142-144, 146, 150, 153

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2018/035465

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2011-047384 A2	21/04/2011	US 2012-0322814 A1 US 8980899 B2 WO 2011-047384 A9	20/12/2012 17/03/2015 21/04/2011
US 2015-0190466 A1	09/07/2015	US 9682123 B2	20/06/2017
US 8017331 B2	13/09/2011	EP 1943262 A1 EP 1943262 A4 EP 1943262 B1 JP 2009-514526 A JP 2013-048628 A US 2007-0105123 A1 US 2011-0287952 A1 US 8124343 B2 WO 2007-053151 A1	16/07/2008 19/01/2011 23/01/2013 09/04/2009 14/03/2013 10/05/2007 24/11/2011 28/02/2012 10/05/2007
US 2015-0158874 A1	11/06/2015	CN 104302647 A EP 2828258 A1 EP 2828258 A4 JP 2015-512896 A KR 10-1727211 B1 KR 10-2015-0005551 A US 2012-0238587 A1 US 2014-0113915 A1 US 8664230 B2 US 9422298 B2 WO 2013-141586 A1	21/01/2015 28/01/2015 12/08/2015 30/04/2015 14/04/2017 14/01/2015 20/09/2012 24/04/2014 04/03/2014 23/08/2016 26/09/2013
WO 2017-152117 A1	08/09/2017	US 2017-252350 A1 US 2017-253590 A1 WO 2017-152126 A1	07/09/2017 07/09/2017 08/09/2017