

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 May 2010 (14.05.2010)

PCT

(10) International Publication Number
WO 2010/054285 A2

(51) International Patent Classification:

C07D 495/12 (2006.01) C07D 491/02 (2006.01)
C07D 495/04 (2006.01) A61K 31/517 (2006.01)
C07D 495/02 (2006.01) A61P 35/00 (2006.01)
C07D 491/04 (2006.01)

(21) International Application Number:

PCT/US2009/063684

(22) International Filing Date:

9 November 2009 (09.11.2009)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

61/112,865 10 November 2008 (10.11.2008) US

(71) Applicant (for all designated States except US): NATIONAL HEALTH RESEARCH INSTITUTES; No. 35, Keyan Road, Zhunan Town, Miaoli County, 350 (TW).

(72) Inventors; and

(75) Inventors/Applicants (for US only): HSIEH, Hsing-Pang; No. 35, Keyan Road, Zhunan Town, Miaoli County, 35053 (TW). COUMAR, Selvaraj Mohane [IN/IN]; #239, 9th Cross, Dr. Radhakrishnan Nagar, Teacher's Colony, Pondicherry 605010 (IN). HSU, Tsu-An; No. 35, Keyan Road, Zhunan Town, Miaoli County, 350 (TW). LIN, Wen-Hsing; No. 35, Keyan Road, Zhunan Town, Miaoli County, 350 (TW). CHEN, Yi-Rong; No. 35, Keyan Road, Zhunan Town, Miaoli County, 350 (TW). CHAO, Yu-Sheng [US/US]; 28 Drinking Brook Road, Monmouth Junction, NJ 08852 (US).

(74) Agent: TSAO, Y. Rocky; Occhiuti Rohlicek & Tsao LLP, 10 Fawcett Street, Cambridge, MA 02138 (US).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))

Published:

- without international search report and to be republished upon receipt of that report (Rule 48.2(g))

(54) Title: FUSED BICYCLIC AND TRICYCLIC PYRIMIDINE COMPOUNDS AS TYROSINE KINASE INHIBITORS

(57) Abstract: Fused bicyclic or tricyclic compounds of formula (I) defined herein are disclosed. Also disclosed are a method for inhibiting EGFR kinase activity and a method for treating cancer with these compounds.



WO 2010/054285 A2

Fused Bicyclic and Tricyclic Pyrimidine Compounds as Tyrosine Kinase Inhibitors

CROSS-REFERENCE TO RELATED APPLICATION

This application claims the benefit of the priority of U.S. Provisional Patent Application No. 61/112,865, filed November 10, 2008. The content of the prior application is incorporated herein by its entirety.

5

BACKGROUND

Protein kinases play important roles in cellular signal pathways that regulate various cell functions such as differentiation, proliferation, migration, and apoptosis. Deregulation of protein kinases is implicated in a number of diseases including cancer. Thus protein kinases are attractive therapeutic targets in cancer treatment.

10

Epidermal growth factor receptor (EGFR) is a subfamily of four closely related receptor tyrosine kinases: EGFR, HER2, HER3, and HER4. Binding of EGF ligand to the extracellular domain of EGFR leads to activation of the intracellular protein-tyrosine kinase activity. As a result, autophosphorylation of several tyrosine residues in the C-terminal domain of EGFR occurs. (Kamath, S., Buolamwini, J.K., *Med. Res. Rev.* 2006, **26**, 569-594).

15

Deregulation in the EGFR signaling cascade has been implicated in the development of various cancers such as bladder, breast, colon, and lung cancer. Several EGFR kinase inhibitors, such as Gefitinib and Erlotinib, have been used for treating cancer, particularly Non-Small Cell Lung cancer (NSCLC). However, only 10-20% of the NSCLC patients respond to Gefitinib treatment, mainly due to drug resistance caused by T790M mutation in

20

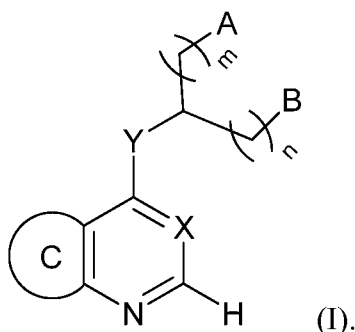
EGFR kinase. Thus, it is of great interest to develop EGFR kinase inhibitors, especially those which can inhibit activity of EGFR mutants (e.g., the T790M mutant), as anti-cancer drugs.

SUMMARY

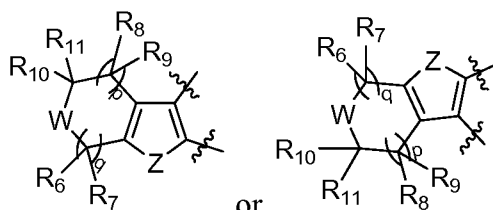
This invention is based on the unexpected discovery that certain fused bicyclic or tricyclic compounds can be used to inhibit activity of EGFR kinase (e.g., EGFR T790M mutant), which allows these compounds to be applied in treating cancer (e.g., NSCLC).

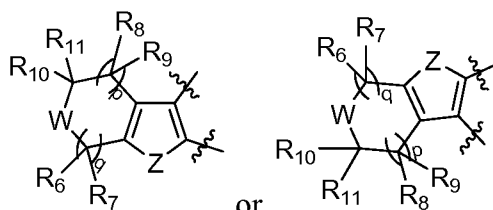
25

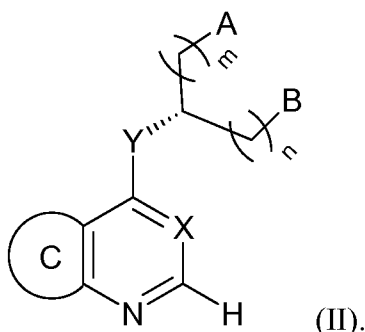
In one aspect, this invention relates to a fused bicyclic or tricyclic compound of formula (I):



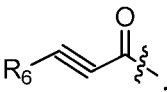
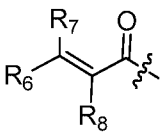
In formula (I), X is N or CR₁, in which R₁ is CN, CONH₂, halo, or H; Y is O, S, or NR₂, in which R₂ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; A is alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR₃, OC(O)R₃, C(O)R₃, C(O)OR₃, C(O)NR₃R₄, NR₃R₄, NHC(O)R₃, NHC(O)NR₃R₄, NHC(S)R₃, NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄, in which each of R₃ and R₄, independently, is H, alkyl, alkenyl, alkynyl, silyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R₃ and R₄, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl; B is aryl or heteroaryl; each of m and



n, independently, is 0, 1, or 2; and ring C is , in which p is 0, 1, or 2, q is 1 or 2, Z is O, S, or NH, W is CH₂ or NR₅, in which R₅ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, C(O)R_a, C(O)C(O)R_a, C(O)OR_a, C(O)NR_aR_b, or SO₂R_a, in which each of R_a and R_b, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_a and R_b, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, and each of R₆, R₇, R₈, R₉, R₁₀, and R₁₁, independently, is H, alkyl, or halo. In particular, this invention relates to a fused bicyclic or tricyclic compound of formula (II):



One subset of the above-described compounds includes those in which W is NR₅, R₅

being SO₂R_a, , or , in which each of R₆ and R₇, independently, is H, alkyl optionally substituted with alkylamino (e.g., dialkylamino), alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, C(O)R_c, C(O)OR_c, C(O)NR_cR_d, or CH₂NR_cR_d, in which each of R_c and R_d, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_c and R_d, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, and R₈ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl. In these compounds, A can be OR₃, R₃ being H, aryl, heteroaryl, or C₁₋₃ alkyl optionally substituted with aryl or heteroaryl or A can be C(O)OR₃; B can be phenyl; m can be 0 or 1; n can be 0; X can be N; Y can be NH; or Z can be S.

Another subset of the compounds includes those in which W is CH₂. In these compounds, A can be OR₃, R₃ being H, aryl, heteroaryl, or C₁₋₃ alkyl optionally substituted with aryl or heteroaryl, or A can be C(O)OR₃; B can be phenyl; m can be 0 or 1; n can be 0; X can be N; Y can be NH; or Z can be S.

The term “alkyl” refers to a straight or branched monovalent hydrocarbon containing 1-20 carbon atoms (e.g., C₁-C₁₀). Examples of alkyl include, but are not limited to, methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, and *t*-butyl. The term “alkenyl” refers to a straight or branched monovalent hydrocarbon containing 2-20 carbon atoms (e.g., C₂-C₁₀) and one or more double bonds. Examples of alkenyl include, but are not limited to, ethenyl, propenyl, and allyl. The term “alkynyl” refers to a straight or branched monovalent hydrocarbon containing 2-20 carbon atoms (e.g., C₂-C₁₀) and one or more triple bonds. Examples of alkynyl include, but are not limited to, ethynyl, 1-propynyl, 1- and 2-butynyl, and 1-methyl-2-butynyl. The term “alkylamino” refers to an -N(R)-alkyl in which R can be H, alkyl,

alkenyl, alkynyl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, or heteroaryl.

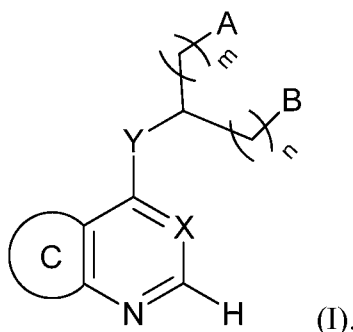
The term "cycloalkyl" refers to a monovalent saturated hydrocarbon ring system having 3 to 30 carbon atoms (e.g., C₃-C₁₂). Examples of cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. The term "cycloalkenyl" refers to a monovalent non-aromatic hydrocarbon ring system having 3 to 30 carbons (e.g., C₃-C₁₂) and one or more double bonds. Examples include cyclopentenyl, cyclohexenyl, and cycloheptenyl. The term "heterocycloalkyl" refers to a monovalent nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having one or more heteroatoms (such as O, N, S, or Se). Examples of heterocycloalkyl groups include, but are not limited to, piperazinyl, pyrrolidinyl, dioxanyl, morpholinyl, and tetrahydrofuranyl. The term "heterocycloalkenyl" refers to a monovalent nonaromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having one or more heteroatoms (such as O, N, S, or Se) and one or more double bonds.

The term "aryl" refers to a monovalent 6-carbon monocyclic, 10-carbon bicyclic, 14-carbon tricyclic aromatic ring system. Examples of aryl groups include, but are not limited to, phenyl, naphthyl, and anthracenyl. The term "heteroaryl" refers to a monovalent aromatic 5-8 membered monocyclic, 8-12 membered bicyclic, or 11-14 membered tricyclic ring system having one or more heteroatoms (such as O, N, S, or Se). Examples of heteroaryl groups include pyridyl, furyl, imidazolyl, benzimidazolyl, pyrimidinyl, thienyl, quinolinyl, indolyl, and thiazolyl.

Alkyl, alkenyl, alkynyl, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, alkylamino, aryl, and heteroaryl mentioned above include both substituted and unsubstituted moieties. Possible substituents on alkylamino, cycloalkyl, heterocycloalkyl, cycloalkenyl, heterocycloalkenyl, aryl, and heteroaryl include, but are not limited to, C₁-C₁₀ alkyl, C₂-C₁₀ alkenyl, C₂-C₁₀ alkynyl, C₃-C₂₀ cycloalkyl, C₃-C₂₀ cycloalkenyl, C₁-C₂₀ heterocycloalkyl, C₁-C₂₀ heterocycloalkenyl, C₁-C₁₀ alkoxy, aryl, aryloxy, heteroaryl, heteroaryloxy, amino, C₁-C₁₀ alkylamino, arylamino, hydroxy, halo, oxo (O=), thioxo (S=), thio, silyl, C₁-C₁₀ alkylthio, arylthio, C₁-C₁₀ alkylsulfonyl, arylsulfonyl, acylamino, aminoacyl, aminothioacyl, amidino, mercapto, amido, thioureido, thiocyanato, sulfonamido, guanidine, ureido, cyano, nitro, acyl, thioacyl, acyloxy, carbamido, carbamyl, carboxyl, and carboxylic ester. On the other hand, possible substituents on alkyl, alkenyl, or alkynyl include all of the above-recited substituents except C₁-C₁₀ alkyl. Cycloalkyl,

cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, aryl, and heteroaryl can also be fused with each other.

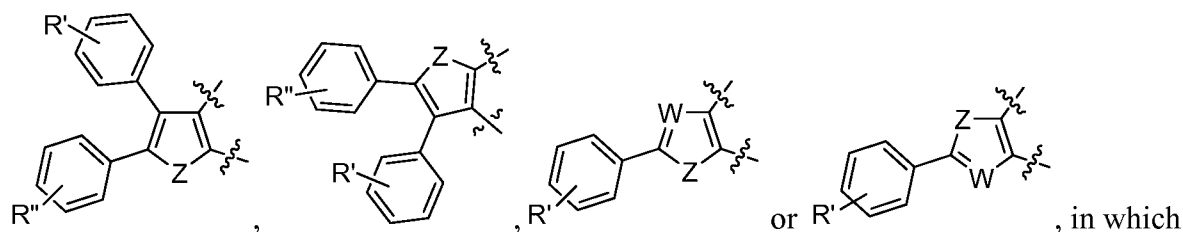
In another aspect, this invention relates to a fused bicyclic or tricyclic compound of formula (I):



In formula (I), X is N or CR₁, in which R₁ is CN, CONH₂, halo, or H; Y is O, S, or NR₂, in which R₂ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; A is alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR₃, OC(O)R₃, C(O)R₃, C(O)OR₃, C(O)NR₃R₄, NR₃R₄, NHC(O)R₃, NHC(O)NR₃R₄, NHC(S)R₃, NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄, in which each of R₃ and R₄, independently, is H, alkyl, alkenyl, alkynyl, silyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R₃ and R₄, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl; B is aryl or heteroaryl; each of m and n, independently, is 0, 1, or 2; and ring C is

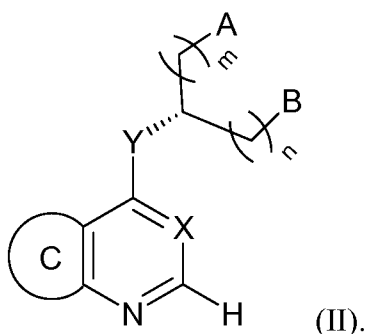
10

15

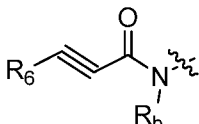
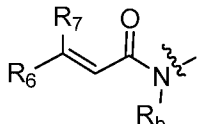


each of R' and R'', independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, nitro, cyano, OR_a, OR_aO, C(O)OR_a, C(O)NR_aR_b, NR_bC(O)R_a, NHC(O)NR_aR_b, NR_bC(S)R_a, NHSO₂R_a, or NR_aR_b, in which each of R_a and R_b, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_a and R_b, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, Z is O or NH, provided that at most one of R' and R'' is H, and W is N or CR₅, in which R₅ is alkenyl, alkynyl, aryl substituted with OR_a, OR_aO, or NR_bC(O)R_a, heteroaryl,

cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, nitro, C(O)OR_a, C(O)NR_aR_b, NR_bC(O)R_a, NHC(O)NR_aR_b, NR_bC(S)R_a, NHSO₂R_a, or NR_aR_b. In particular, the compound is of formula (II):



5 One subset of the compounds described immediately above includes those in which

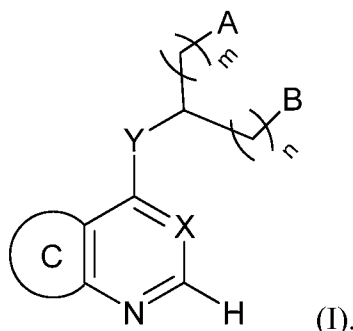
R' is  or , R₆ being H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, C(O)R_c, C(O)OR_c, C(O)NR_cR_d, or CH₂NR_cR_d, in which each of R_c and R_d, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_c and R_d, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, and R₇ being H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl. In these compounds, A can be OR₃, R₃ being H, aryl, heteroaryl, or C₁₋₃ alkyl optionally substituted with aryl or heteroaryl; B can be phenyl; m can be 1; n can be 0; X can be N; Y can be NH; or Z can be O.

10
15

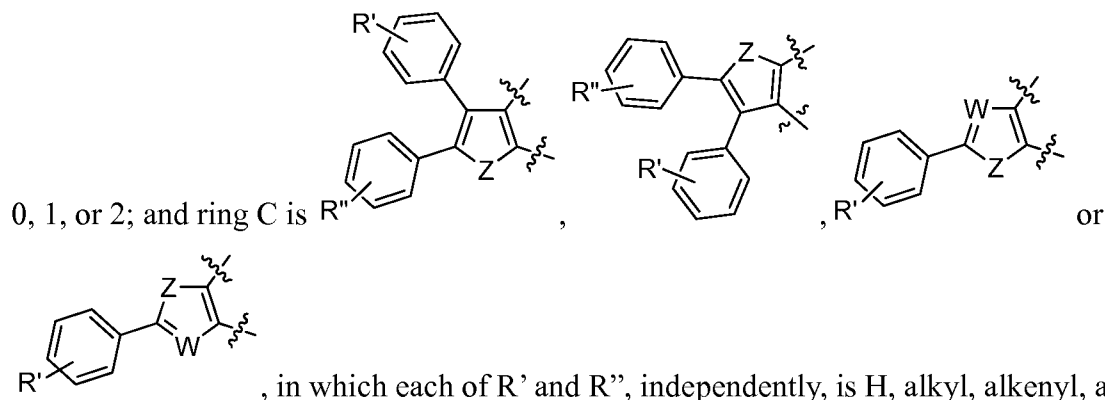
Another subset of the compounds includes those in which B is phenyl and n is 0. In these compounds, A can be OR₃, R₃ being H, aryl, heteroaryl, or C₁₋₃ alkyl optionally substituted with aryl or heteroaryl, or A can be C(O)OR₃; m can be 0 or 1; X can be N; Y can be NH; Z can be O; W can be CR₅, in which R₅ is halo; or each of R' and R'', independently, can be OR_a.

20

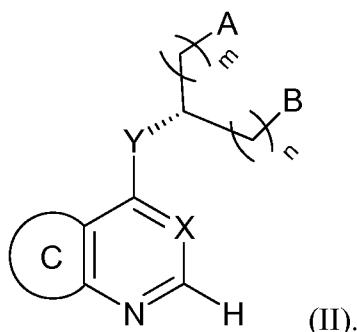
In still another aspect, this invention relates to a fused bicyclic or tricyclic compound of formula (I):



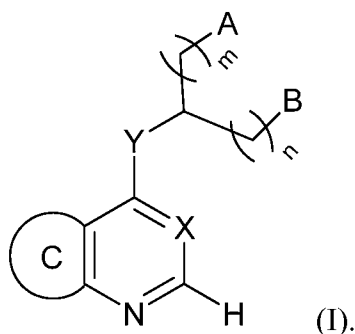
In formula (I), X is N or CR₁, in which R₁ is CN, CONH₂, halo, or H; Y is O, S, or NR₂, in which R₂ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; A is alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OC(O)R₃, C(O)R₃, C(O)OR₃, C(O)NR₃R₄, NR₃R₄, NHC(O)R₃, NHC(O)NR₃R₄, NHC(S)R₃, NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄, in which each of R₃ and R₄, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R₃ and R₄, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl; B is aryl or heteroaryl; each of m and n, independently, is



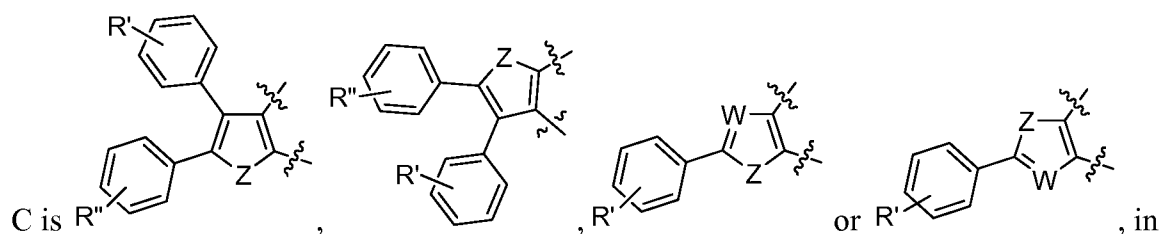
In particular, the compound is of formula (II):



In yet another aspect, this invention relates to a fused bicyclic or tricyclic compound of formula (I):

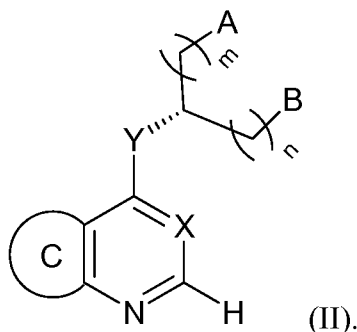


- 5 In formula (I), X is N or CR₁, in which R₁ is CN, CONH₂, halo, or H; Y is O, S, or NR₂, in which R₂ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; A is alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR₃, OC(O)R₃, C(O)R₃, C(O)OR₃, C(O)NR₃R₄, NR₃R₄, NHC(O)R₃, NHC(O)NR₃R₄, NHC(S)R₃,
 10 NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄, in which each of R₃ and R₄, independently, is H, alkyl, alkenyl, alkynyl, silyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R₃ and R₄, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl when X is N, and A is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl,
 15 heterocycloalkenyl, halo, cyano, nitro, OR₃, OC(O)R₃, C(O)R₃, C(O)OR₃, C(O)NR₃R₄, NR₃R₄, NHC(O)R₃, NHC(O)NR₃R₄, NHC(S)R₃, NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄ when X is CR₁; B is aryl or heteroaryl; each of m and n, independently, is 0, 1, or 2; and ring



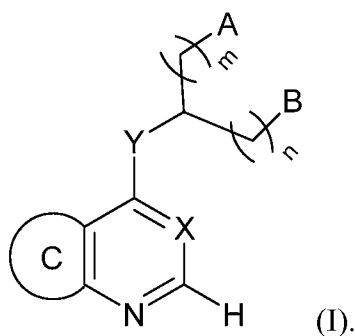
which each of R' and R'', independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl,

cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, nitro, cyano, OR_a , OR_aO , $C(O)OR_a$, $C(O)NR_aR_b$, $NR_bC(O)R_a$, $NHC(O)NR_aR_b$, $NR_bC(S)R_a$, $NHSO_2R_a$, or NR_aR_b , in which each of R_a and R_b , independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_a and R_b , together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, Z is S, and W is N or CR_5 , in which R_5 is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, nitro, $C(O)OR_a$, $C(O)NR_aR_b$, $NR_bC(O)R_a$, $NHC(O)NR_aR_b$, $NR_bC(S)R_a$, $NHSO_2R_a$, or NR_aR_b . In particular, the compound is of formula (II):



10

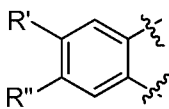
Further, this invention relates to a fused bicyclic or tricyclic compound of formula (I):

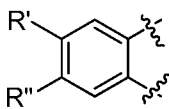


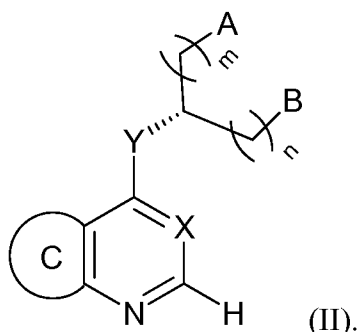
15

In formula (I), X is N or CR_1 , in which R_1 is CN, $CONH_2$, halo, or H; Y is O, S, or NR_2 , in which R_2 is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; A is alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR_3 , $OC(O)R_3$, $C(O)R_3$, $C(O)OR_3$, $C(O)NR_3R_4$, NR_3R_4 , $NHC(O)R_3$, $NHC(O)NR_3R_4$, $NHC(S)R_3$, $NHC(O)OR_3$, SO_2R_3 , SO_3R_3 , or $SO_2NR_3R_4$, in which each of R_3 and R_4 , independently, is H, alkyl, alkenyl, alkynyl, silyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_3 and R_4 , together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl; B is aryl or heteroaryl; each of m and

20

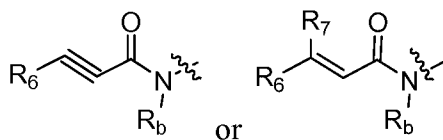


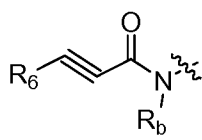
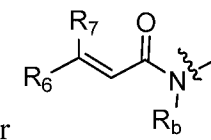
n, independently, is 0, 1, or 2; and ring C is , in which each of R' and R'', independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, nitro, cyano, OR_a, C(O)OR_a, C(O)NR_aR_b, NR_bC(O)R_a, NHC(O)NR_aR_b, NR_bC(S)R_a, NHSO₂R_a, or NR_aR_b, in which each of R_a and R_b, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_a and R_b, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, provided that at least one of R' and R'' is NR_bC(O)R_a, NHC(O)NR_aR_b, NR_bC(S)R_a, or NHSO₂R_a. In particular, the compound is of formula (II):



10

One subset of the compounds described immediately above includes those in which



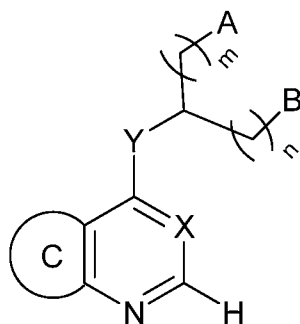
R' is  or , R₆ being H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, C(O)R_c, C(O)OR_c,

15

C(O)NR_cR_d, or CH₂NR_cR_d, in which each of R_c and R_d, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_c and R_d, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, and R₇ being H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl. In these compounds, A can be OR₃, R₃ being H, aryl, heteroaryl, or C₁₋₃ alkyl optionally substituted with aryl or heteroaryl, or A can be C(O)OR₃; B can be phenyl; m can be 0 or 1; or n can be 0.

20

In yet another aspect, this invention relates to a fused bicyclic or tricyclic compound of formula (I):

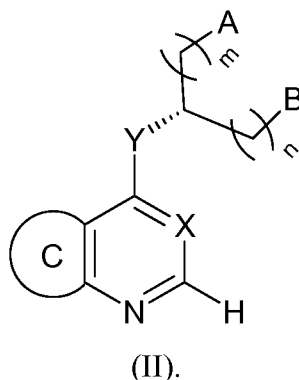


(I)

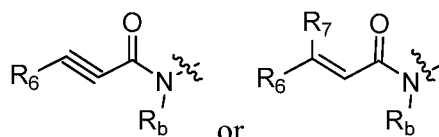
In formula (I), X is N or CR₁, in which R₁ is CN, CONH₂, halo, or H; Y is O, S, or NR₂, in which R₂ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl; A is alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR₃, OC(O)R₃, C(O)R₃, C(O)OR₃, C(O)NR₃R₄, NR₃R₄, NHC(O)R₃, NHC(O)NR₃R₄, NHC(S)R₃, NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄, in which each of R₃ and R₄, independently, is H, alkyl, alkenyl, alkynyl, silyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R₃ and R₄, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl when X is N, and A is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR₃, OC(O)R₃, C(O)R₃, C(O)OR₃, C(O)NR₃R₄, NR₃R₄, NHC(O)R₃, NHC(O)NR₃R₄, NHC(S)R₃, NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄ when X is CR₁; B is aryl or heteroaryl; each of m and n, independently, is 0, 1, or 2; and ring

C is , in which each of R' is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, nitro, cyano, OR_a, OR_aO, C(O)OR_a, C(O)NR_aR_b, NR_bC(O)R_a, NHC(O)NR_aR_b, NR_bC(S)R_a, NHSO₂R_a, or NR_aR_b, in which each of R_a and R_b, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_a and R_b, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, Z is O or S, and W is N or CR₅, in which R₅ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl,

heterocycloalkenyl, halo, nitro, C(O)OR_a, C(O)NR_aR_b, NR_bC(O)R_a, NHC(O)NR_aR_b, NR_bC(S)R_a, NHSO₂R_a, or NR_aR_b. In particular, the compound is of formula (II):



5 One subset of the compounds described immediately above includes those in which *m* is 1 and A is OR₃, R₃ being H, aryl, heteroaryl, or C₁₋₃ alkyl optionally substituted with aryl



or heteroaryl. In these compounds, R' is or , in which R₆ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, C(O)R_c, C(O)OR_c, C(O)NR_cR_d, or CH₂NR_cR_d, in which each of R_c and R_d, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_c and R_d, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, and R₇ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl.

15 The fused bicyclic or tricyclic compounds described above include the compounds themselves, as well as their salts, their solvates, and their prodrugs, if applicable. A salt, for example, can be formed between an anion and a positively charged group (e.g., amino) on a fused bicyclic or tricyclic compound. Suitable anions include chloride, bromide, iodide, sulfate, bisulfate, sulfamate, nitrate, phosphate, citrate, methanesulfonate, trifluoroacetate, glutamate, glucuronate, glutarate, malate, maleate, succinate, fumarate, tartrate, tosylate, salicylate, lactate, naphthalenesulfonate, and acetate. Likewise, a salt can also be formed between a cation and a negatively charged group (e.g., carboxylate) on a fused bicyclic or tricyclic compound. Suitable cations include sodium ion, potassium ion, magnesium ion, calcium ion, and an ammonium cation such as tetramethylammonium ion. The fused bicyclic or tricyclic compounds also include those salts containing quaternary nitrogen atoms. Examples of prodrugs include esters and other pharmaceutically acceptable derivatives,

which, upon administration to a subject, are capable of providing active fused bicyclic or tricyclic compounds.

This invention also relates to a method of inhibiting EGFR kinase (or other tyrosine kinases such as ERBB2 kinase) activity by contacting a cell expressing the protein kinase
5 with an effective amount of one or more of the fused bicyclic or tricyclic compounds described above. The cell can be a tumor cell or a cell that over-expresses the protein kinase.

In addition, this invention encompasses a method of treating an EGFR kinase-mediated disorder (or other tyrosine kinases- such as ERBB2 kinase-related disorder) such as cancer by administering to a subject in need thereof an effective amount of one or more of the
10 fused bicyclic or tricyclic compounds described above.

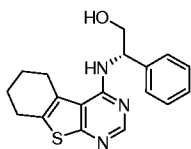
Also within the scope of this invention is a pharmaceutical composition containing one or more of the above-described fused bicyclic or tricyclic compounds for use in treating cancer (e.g., NSCLC), as well as this therapeutic use and use of the compounds for the manufacture of a medicament for treating cancer.

15 *(S)*-2-(5,6-dimethylthieno[2,3-*d*]pyrimidin-4-ylamino)-2-phenylethanol, *(S)*-2-(5-methylthieno[2,3-*d*]pyrimidin-4-ylamino)-2-phenylethanol, *(S)*-2-phenyl-2-(thieno[2,3-*d*]pyrimidin-4-ylamino)ethanol, and their analogs, as well as their therapeutic use as described above, are also contemplated.

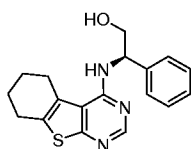
The details of one or more embodiments of the invention are set forth in the
20 description below. Other features, objects, and advantages of the invention will be apparent from the description and from the claims.

DETAILED DESCRIPTION

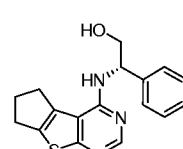
Shown below are exemplary compounds described herein:



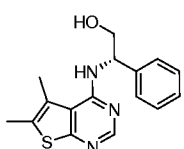
Compound 1



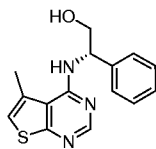
Compound 2



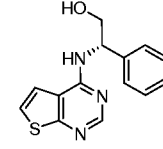
Compound 3



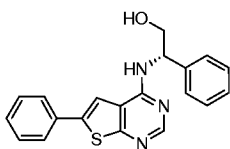
Compound 4



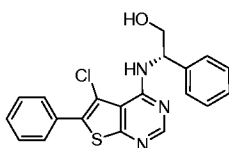
Compound 5



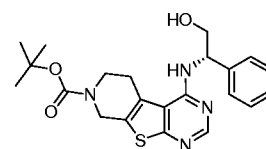
Compound 6



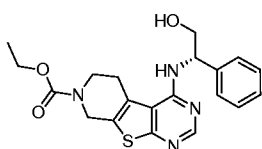
Compound 7



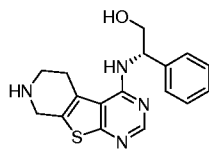
Compound 8



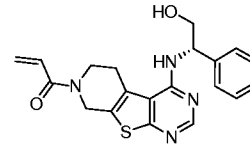
Compound 9



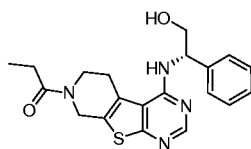
Compound 10



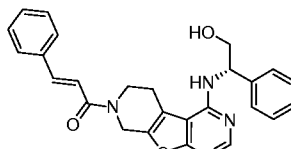
Compound 11



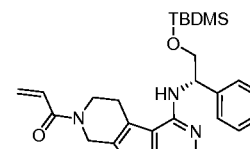
Compound 12



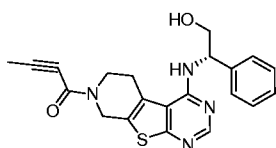
Compound 13



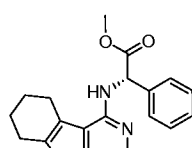
Compound 14



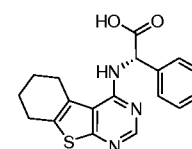
Compound 15



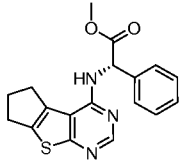
Compound 16



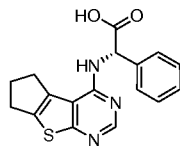
Compound 17



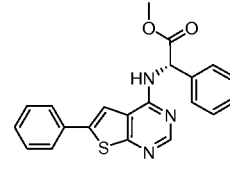
Compound 18



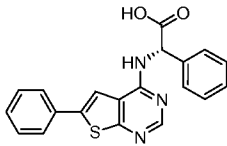
Compound 19



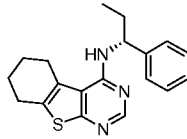
Compound 20



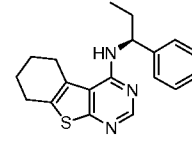
Compound 21



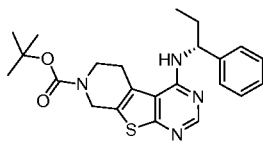
Compound 22



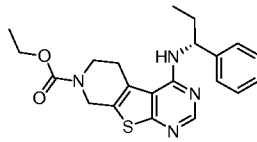
Compound 23



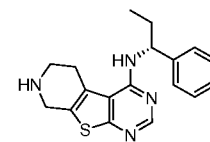
Compound 24



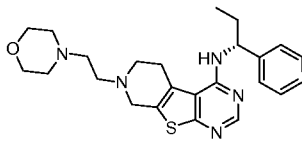
Compound 25



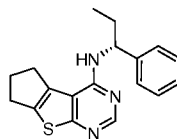
Compound 26



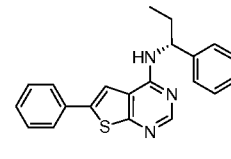
Compound 27



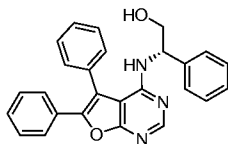
Compound 28



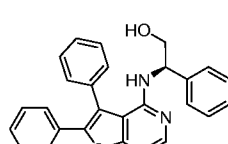
Compound 29



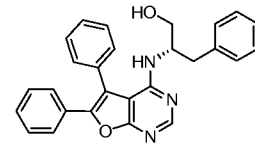
Compound 30



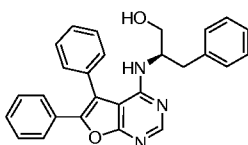
Compound 31



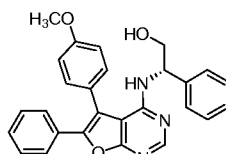
Compound 32



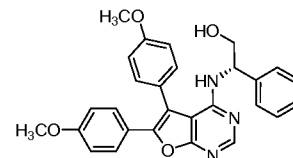
Compound 33



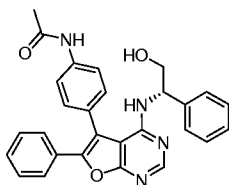
Compound 34



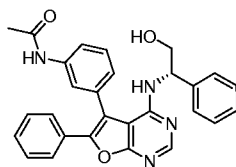
Compound 35



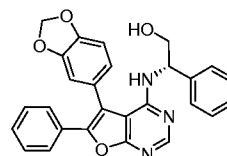
Compound 36



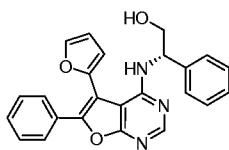
Compound 37



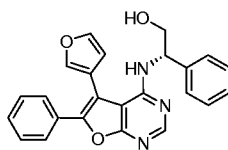
Compound 38



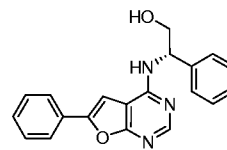
Compound 39



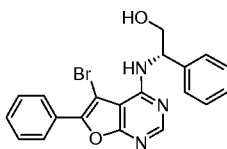
Compound 40



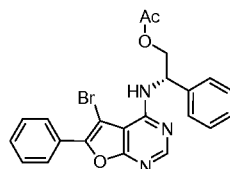
Compound 41



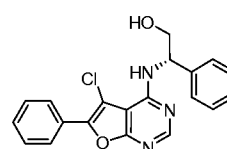
Compound 42



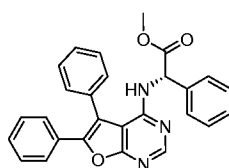
Compound 43



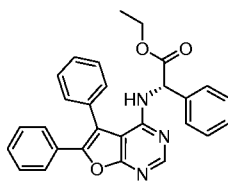
Compound 44



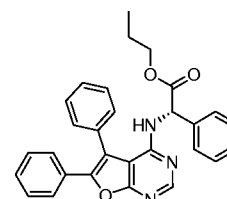
Compound 45



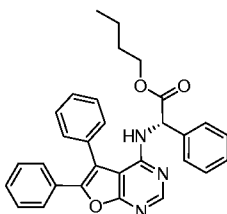
Compound 46



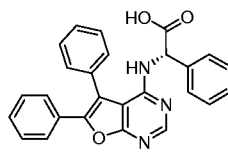
Compound 47



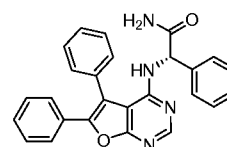
Compound 48



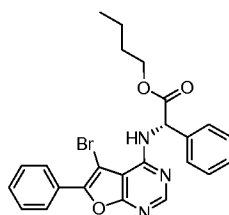
Compound 49



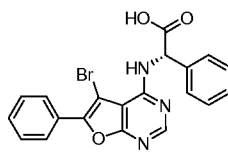
Compound 50



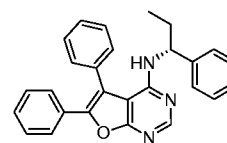
Compound 51



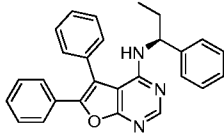
Compound 52



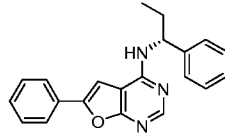
Compound 53



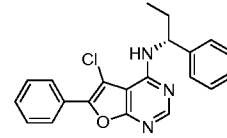
Compound 54



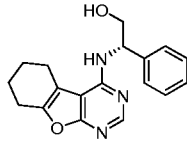
Compound 55



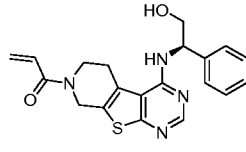
Compound 56



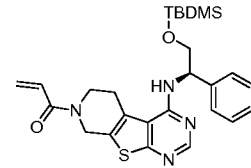
Compound 57



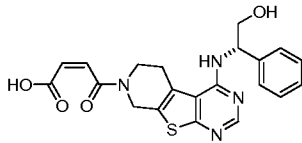
Compound 58



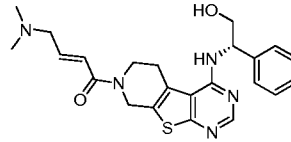
Compound 59



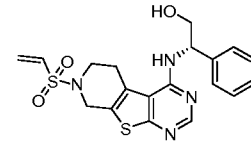
Compound 60



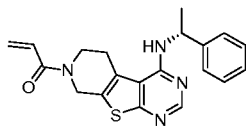
Compound 61



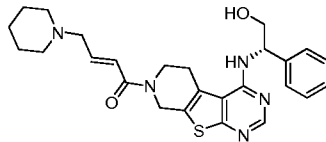
Compound 62



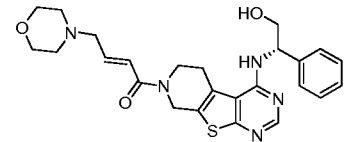
Compound 63



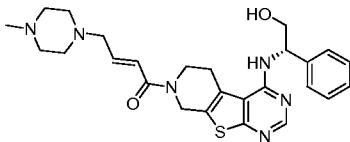
Compound 64



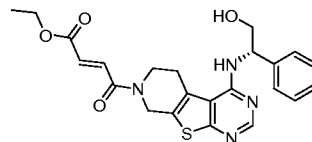
Compound 65



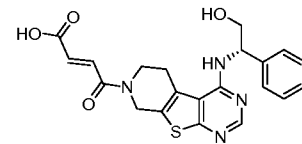
Compound 66



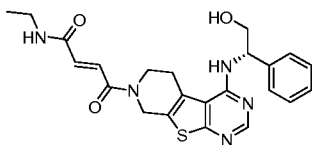
Compound 67



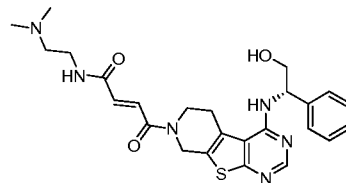
Compound 68



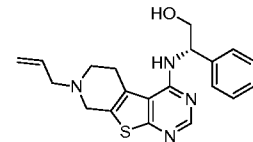
Compound 69



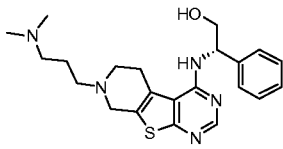
Compound 70



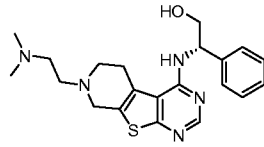
Compound 71



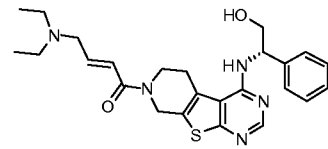
Compound 72



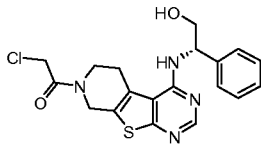
Compound 73



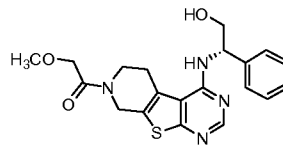
Compound 74



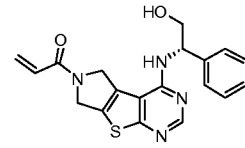
Compound 75



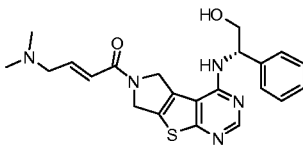
Compound 76



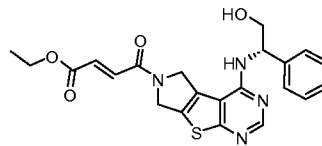
Compound 77



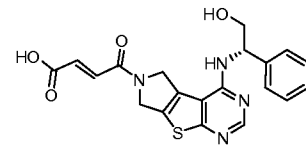
Compound 78



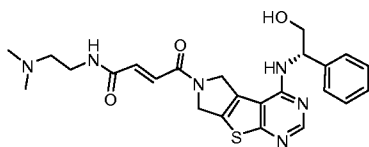
Compound 79



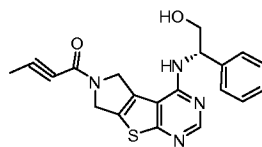
Compound 80



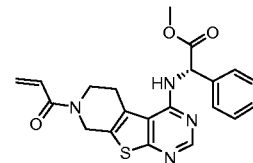
Compound 81



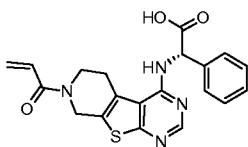
Compound 82



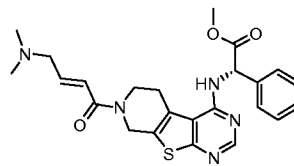
Compound 83



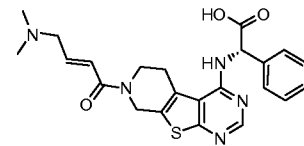
Compound 84



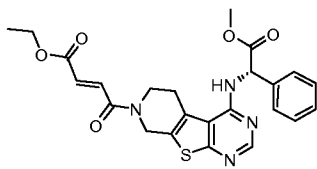
Compound 85



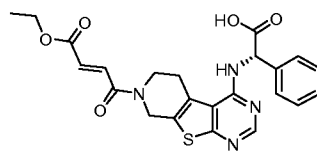
Compound 86



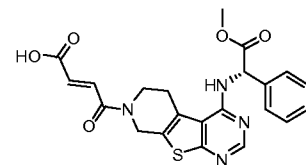
Compound 87



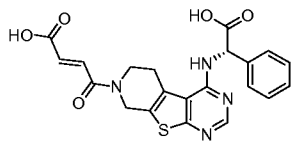
Compound 88



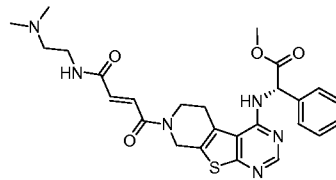
Compound 89



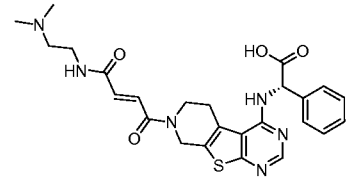
Compound 90



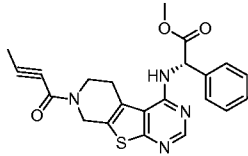
Compound 91



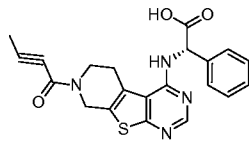
Compound 92



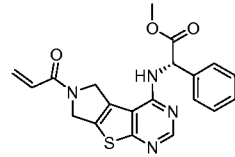
Compound 93



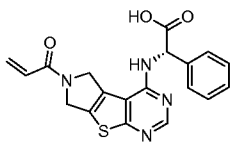
Compound 94



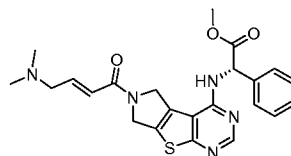
Compound 95



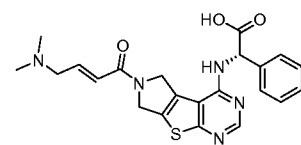
Compound 96



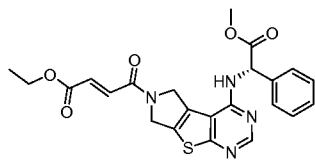
Compound 97



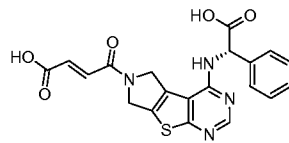
Compound 98



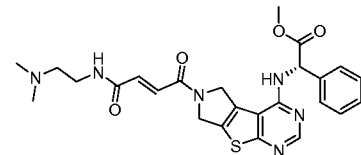
Compound 99



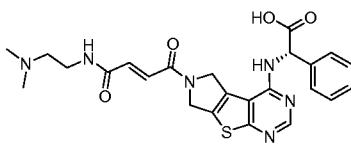
Compound 100



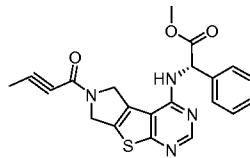
Compound 101



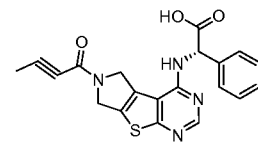
Compound 102



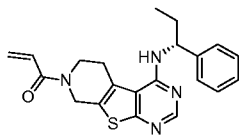
Compound 103



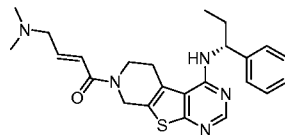
Compound 104



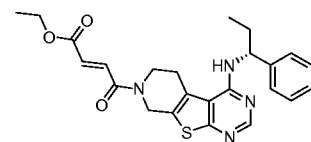
Compound 105



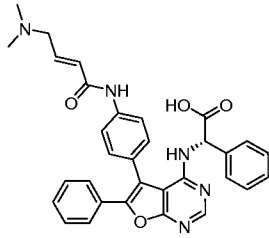
Compound 106



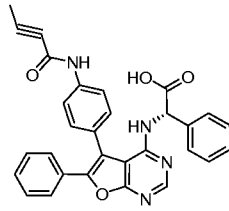
Compound 107



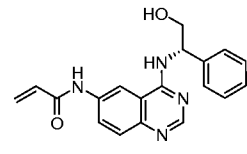
Compound 108



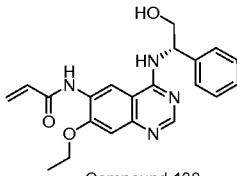
Compound 127



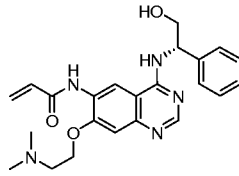
Compound 128



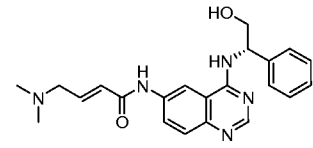
Compound 129



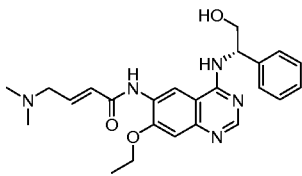
Compound 130



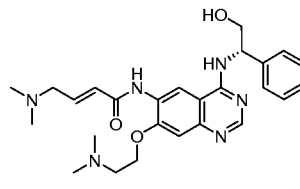
Compound 131



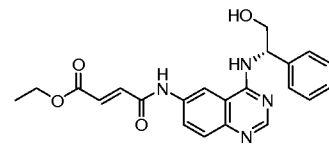
Compound 132



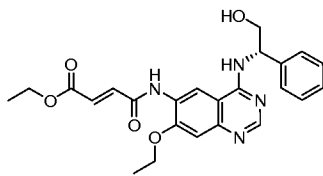
Compound 133



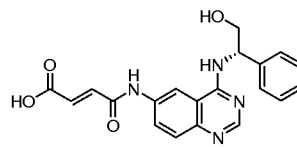
Compound 134



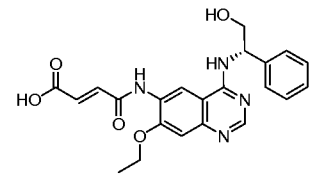
Compound 135



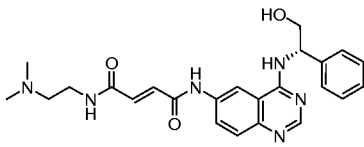
Compound 136



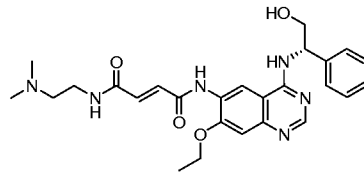
Compound 137



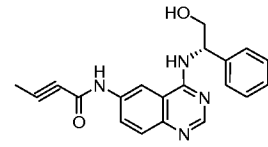
Compound 138



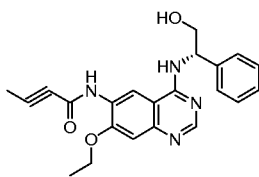
Compound 139



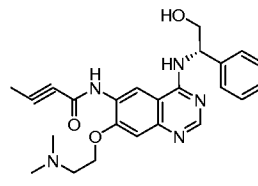
Compound 140



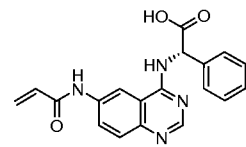
Compound 141



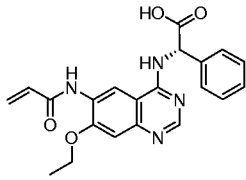
Compound 142



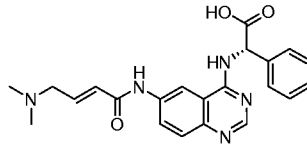
Compound 143



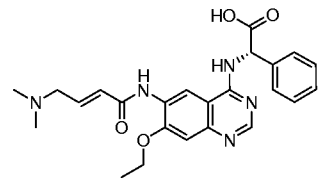
Compound 144



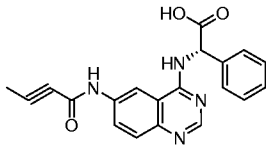
Compound 145



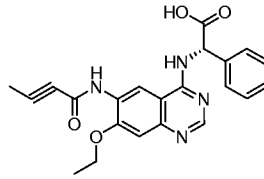
Compound 146



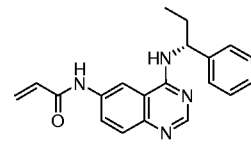
Compound 147



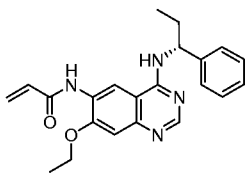
Compound 148



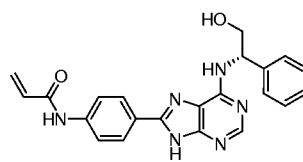
Compound 149



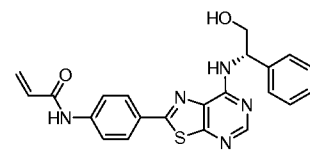
Compound 150



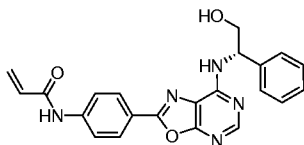
Compound 151



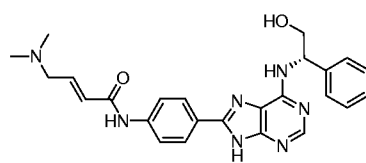
Compound 152



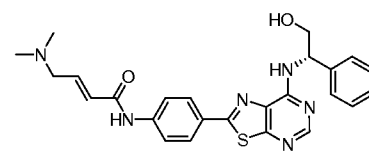
Compound 153



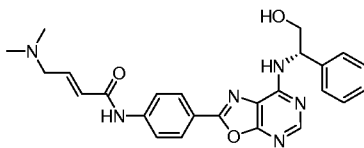
Compound 154



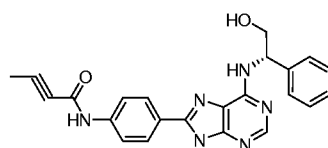
Compound 155



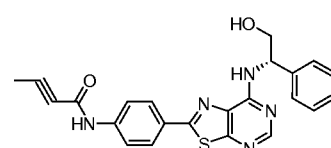
Compound 156



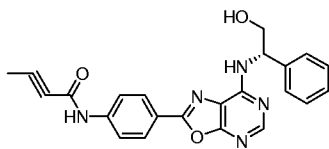
Compound 157



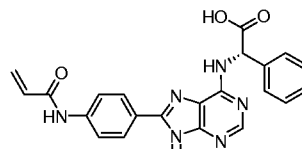
Compound 158



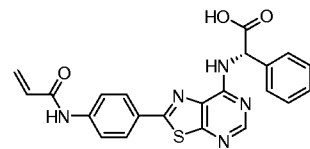
Compound 159



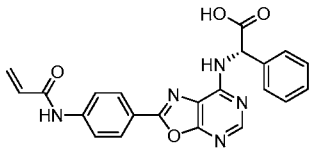
Compound 160



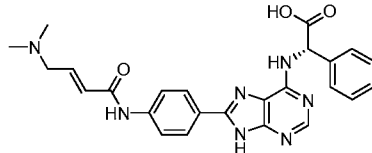
Compound 161



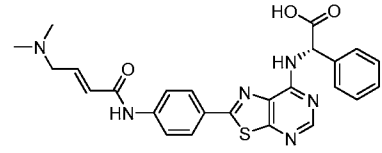
Compound 162



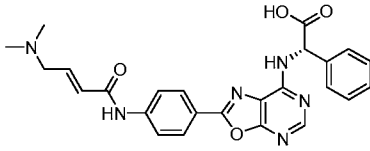
Compound 163



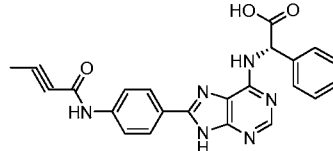
Compound 164



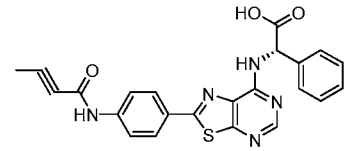
Compound 165



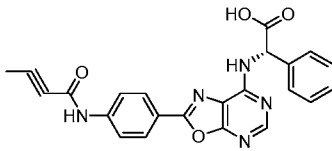
Compound 166



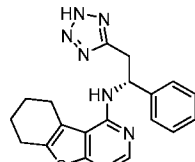
Compound 167



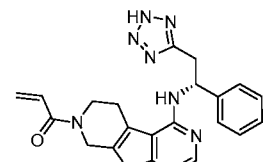
Compound 168



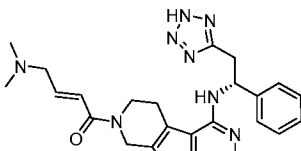
Compound 169



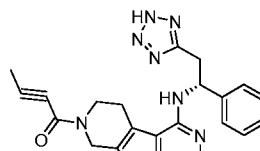
Compound 170



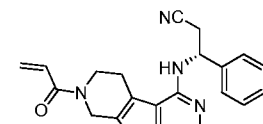
Compound 171



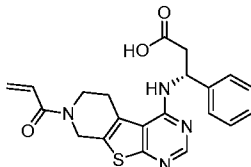
Compound 172



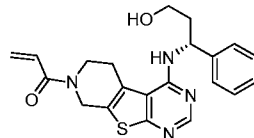
Compound 173



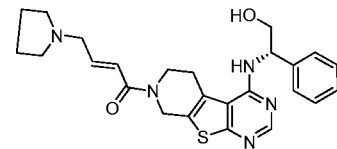
Compound 174



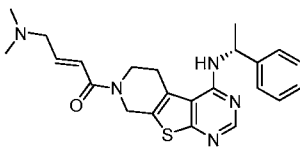
Compound 175



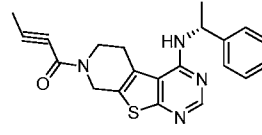
Compound 176



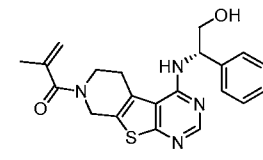
Compound 177



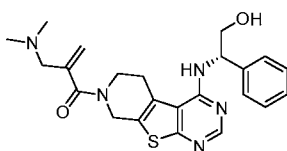
Compound 178



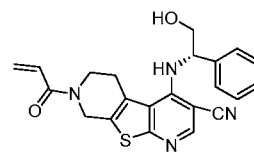
Compound 179



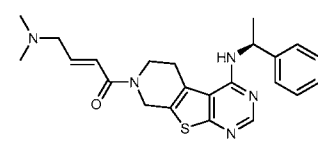
Compound 180



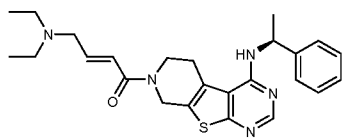
Compound 181



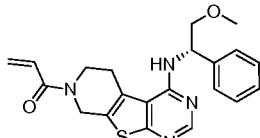
Compound 182



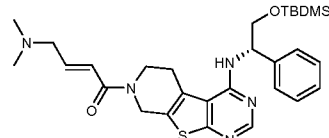
Compound 183



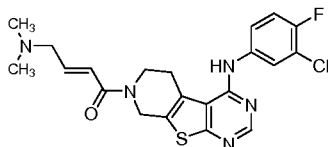
Compound 184



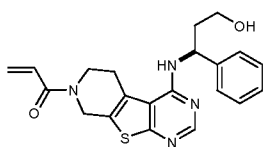
Compound 185



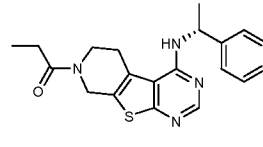
Compound 186



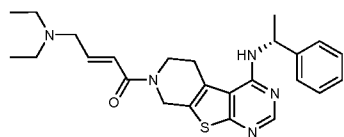
Compound 187



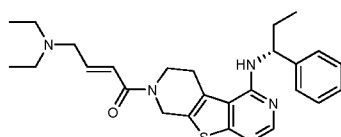
Compound 188



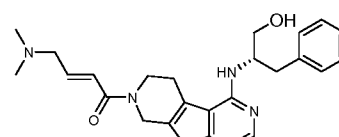
Compound 189



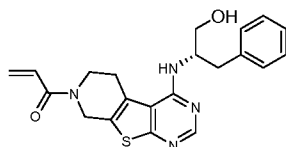
Compound 190



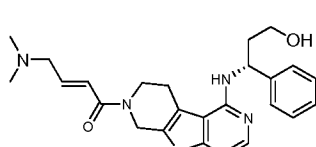
Compound 191



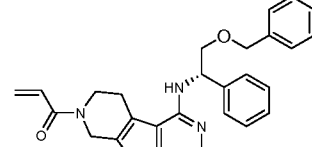
Compound 192



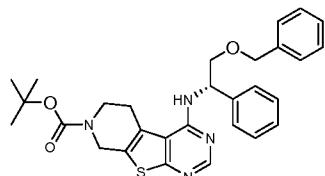
Compound 193



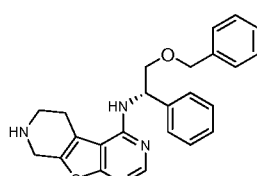
Compound 194



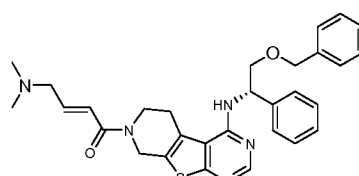
Compound 195



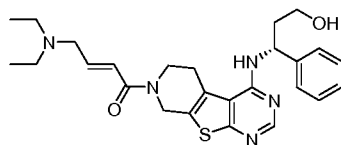
Compound 196



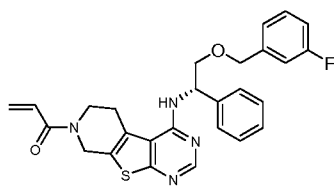
Compound 197



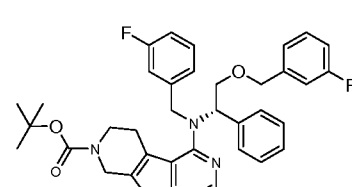
Compound 198



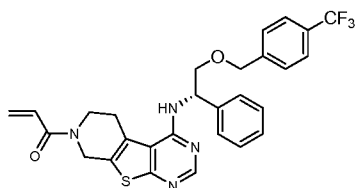
Compound 199



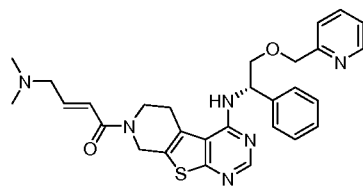
Compound 200



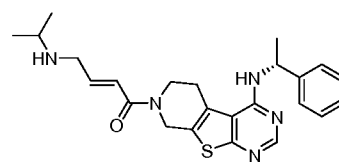
Compound 201



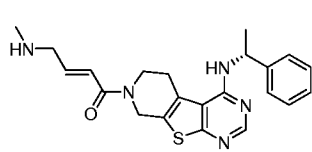
Compound 202



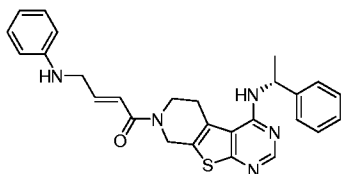
Compound 203



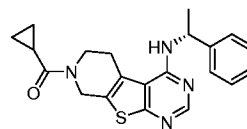
Compound 204



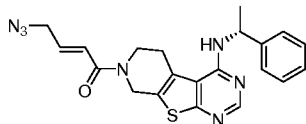
Compound 205



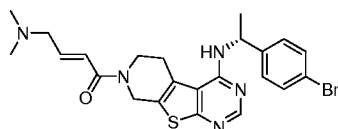
Compound 206



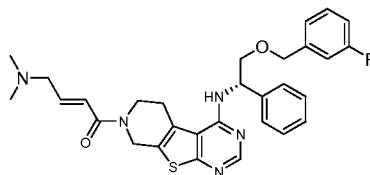
Compound 207



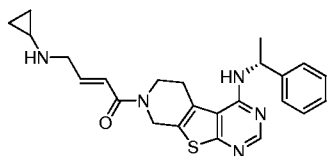
Compound 208



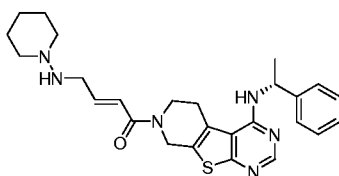
Compound 209



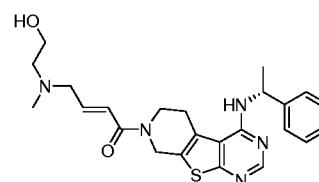
Compound 210



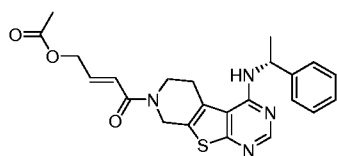
Compound 211



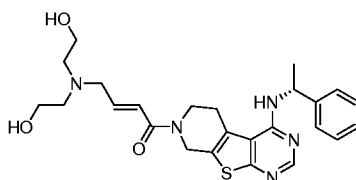
Compound 212



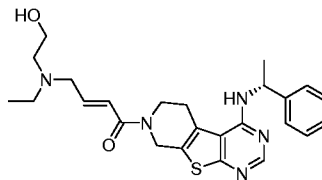
Compound 213



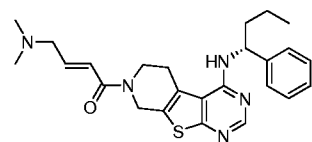
Compound 214



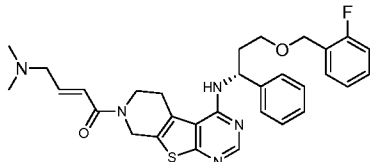
Compound 215



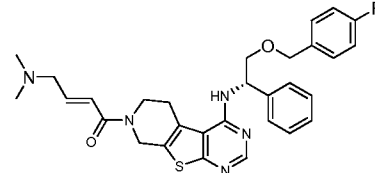
Compound 216



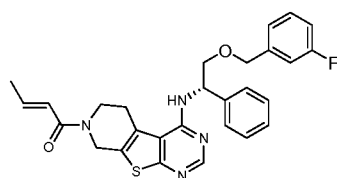
Compound 217



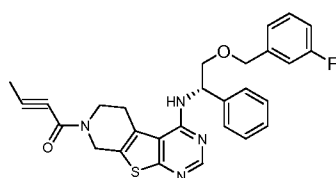
Compound 218



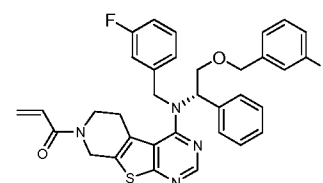
Compound 219



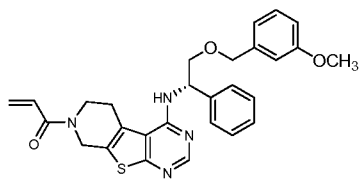
Compound 220



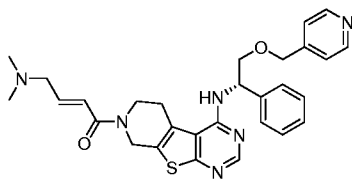
Compound 221



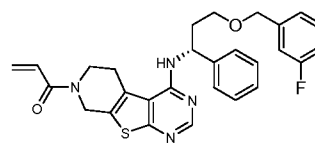
Compound 222



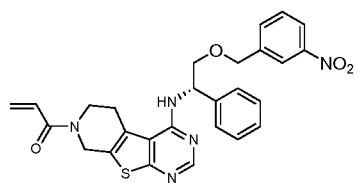
Compound 223



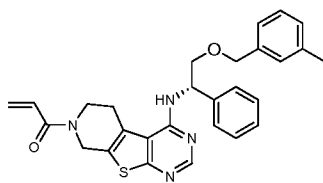
Compound 224



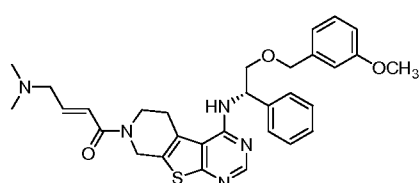
Compound 225



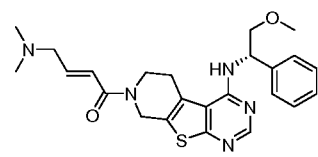
Compound 226



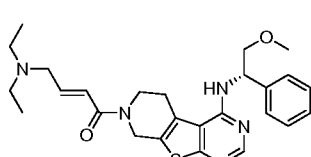
Compound 227



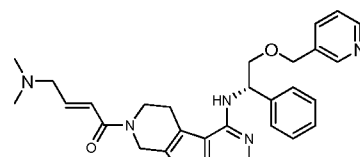
Compound 228



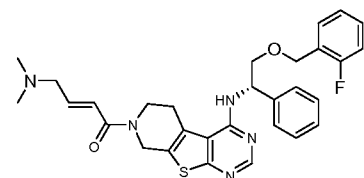
Compound 229



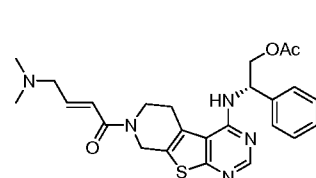
Compound 230



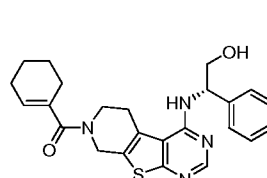
Compound 231



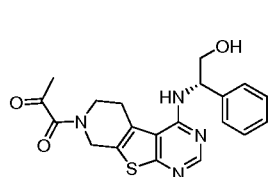
Compound 232



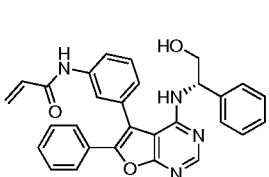
Compound 233



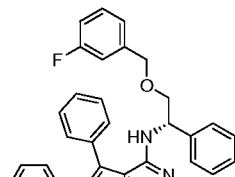
Compound 234



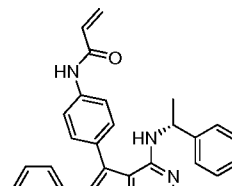
Compound 235



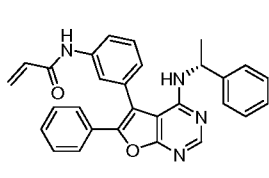
Compound 236



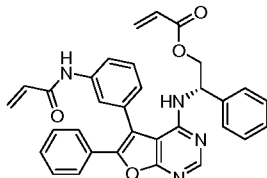
Compound 237



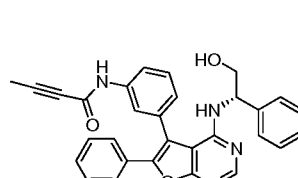
Compound 238



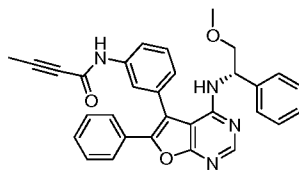
Compound 239



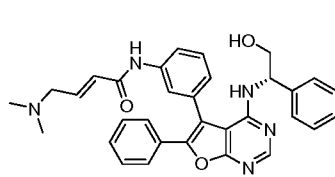
Compound 240



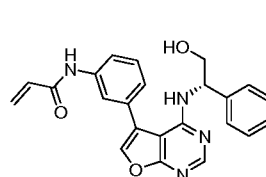
Compound 241



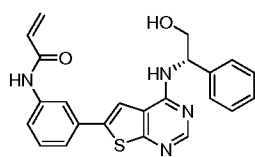
Compound 242



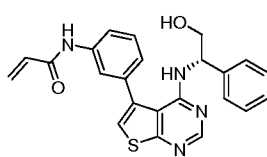
Compound 243



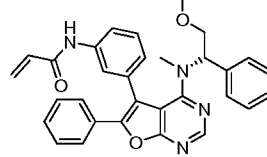
Compound 244



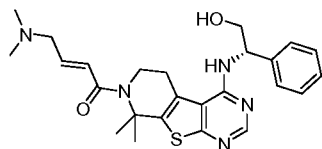
Compound 245



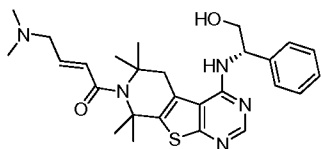
Compound 246



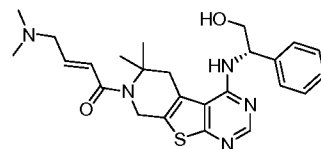
Compound 247



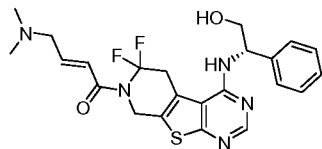
Compound 248



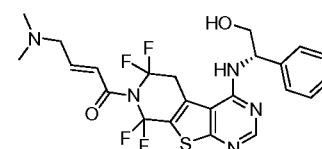
Compound 249



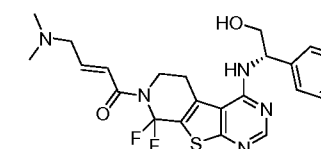
Compound 250



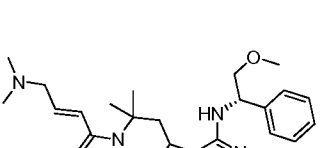
Compound 251



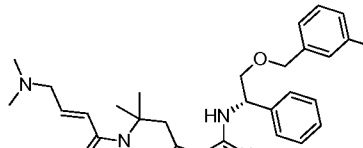
Compound 252



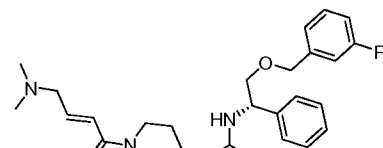
Compound 253



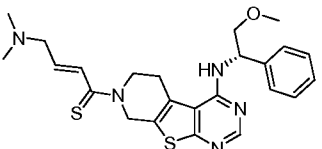
Compound 254



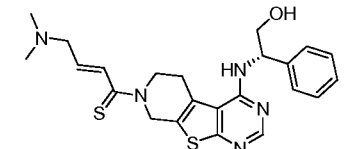
Compound 255



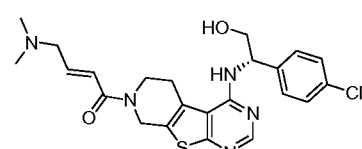
Compound 256



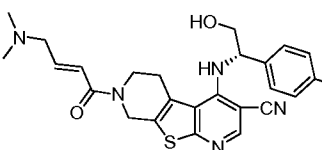
Compound 257



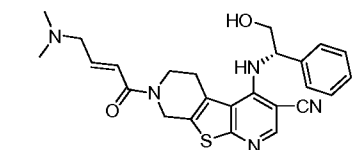
Compound 258



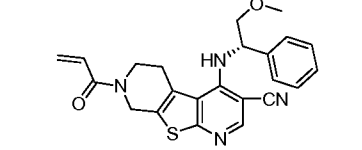
Compound 259



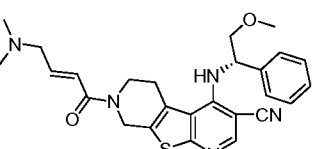
Compound 260



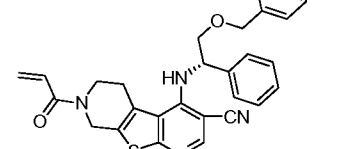
Compound 261



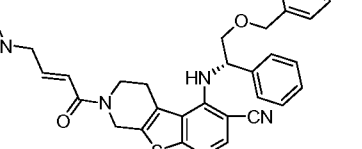
Compound 262



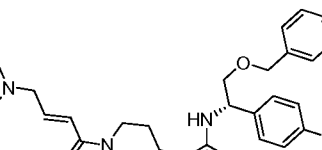
Compound 263



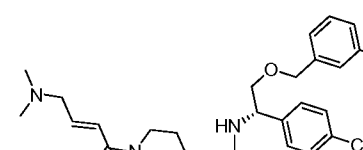
Compound 264



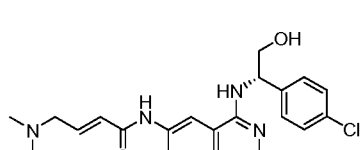
Compound 265



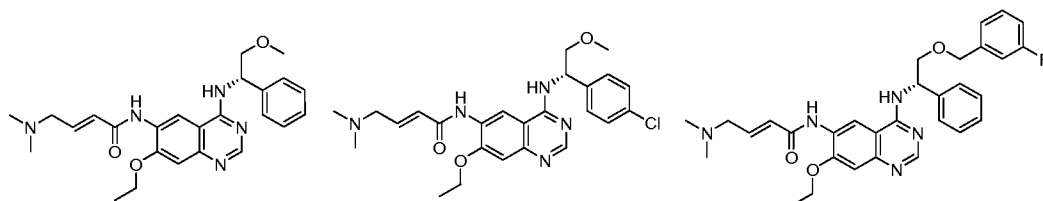
Compound 266



Compound 267



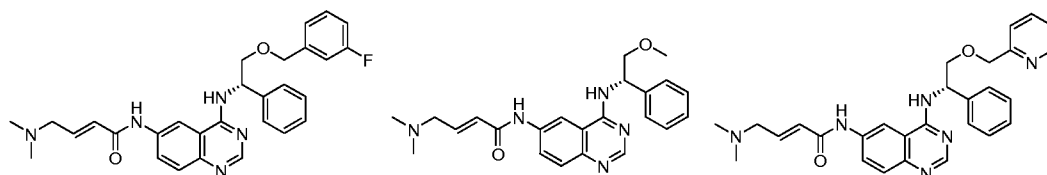
Compound 268



Compound 269

Compound 270

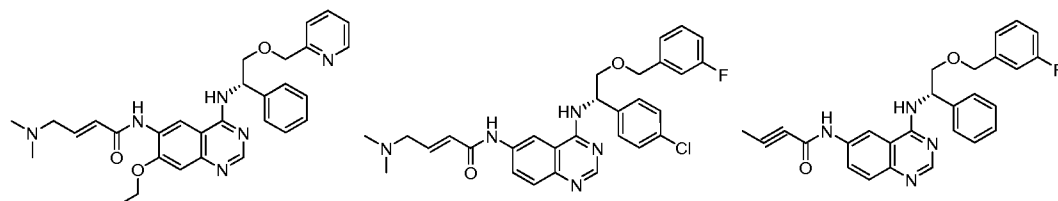
Compound 271



Compound 272

Compound 273

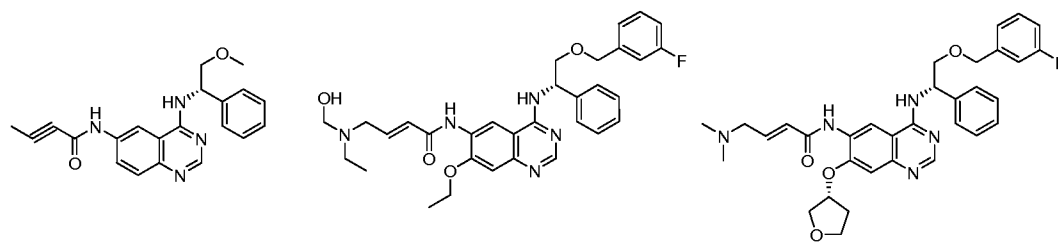
Compound 274



Compound 275

Compound 276

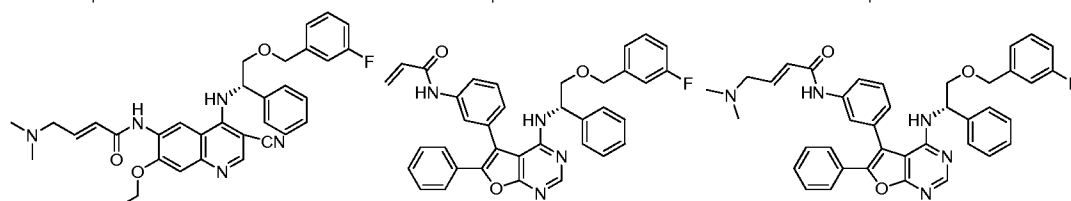
Compound 277



Compound 278

Compound 279

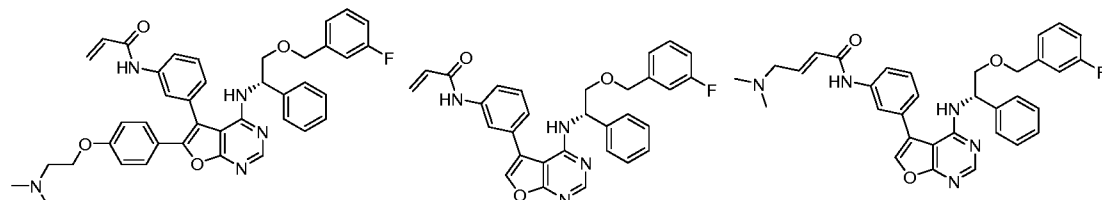
Compound 280



Compound 281

Compound 282

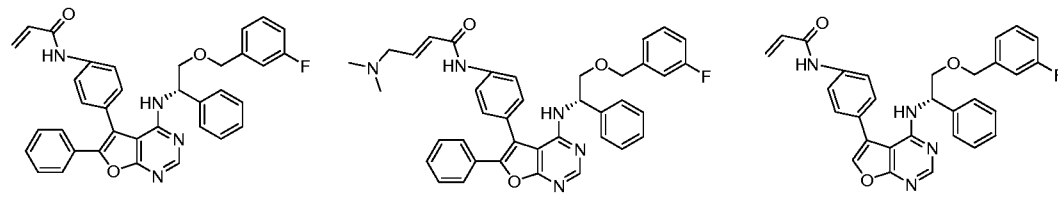
Compound 283



Compound 284

Compound 285

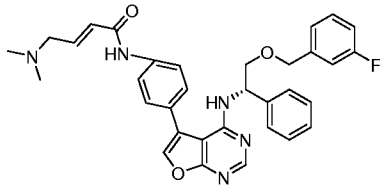
Compound 286



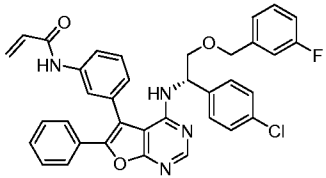
Compound 287

Compound 288

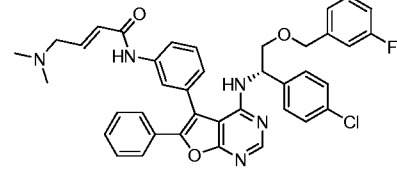
Compound 289



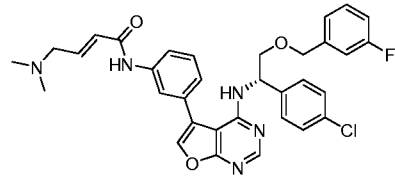
Compound 290



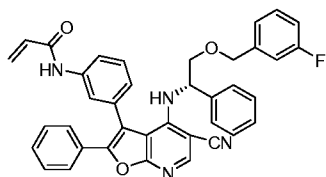
Compound 291



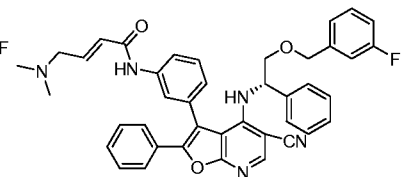
Compound 292



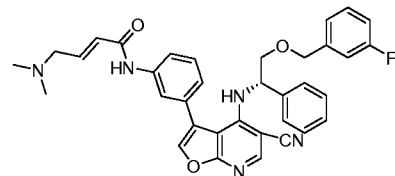
Compound 293



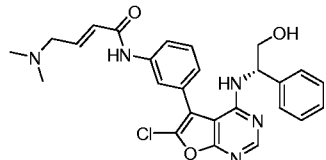
Compound 294



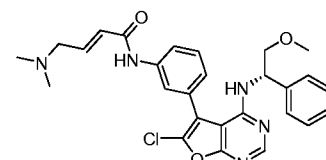
Compound 295



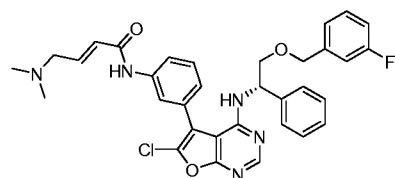
Compound 296



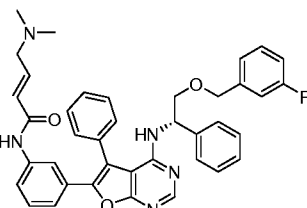
Compound 297



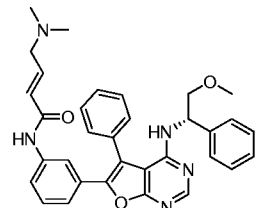
Compound 298



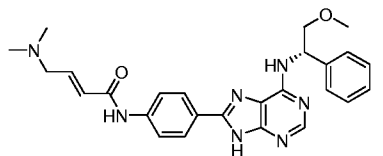
Compound 299



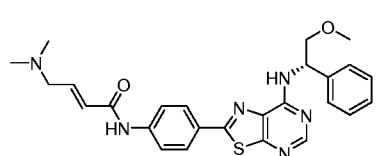
Compound 300



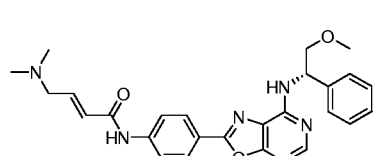
Compound 301



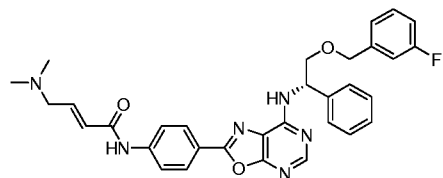
Compound 302



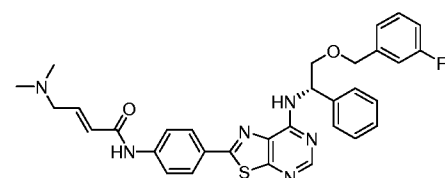
Compound 303



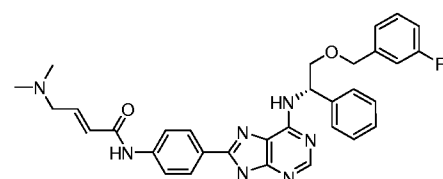
Compound 304



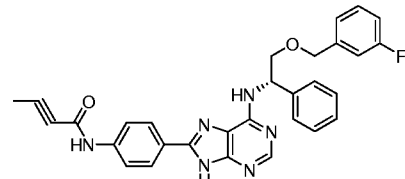
Compound 305



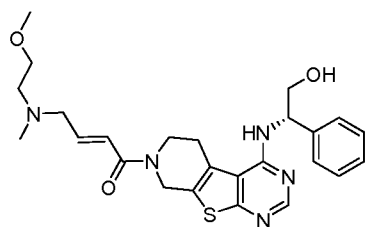
Compound 306



Compound 307



Compound 308

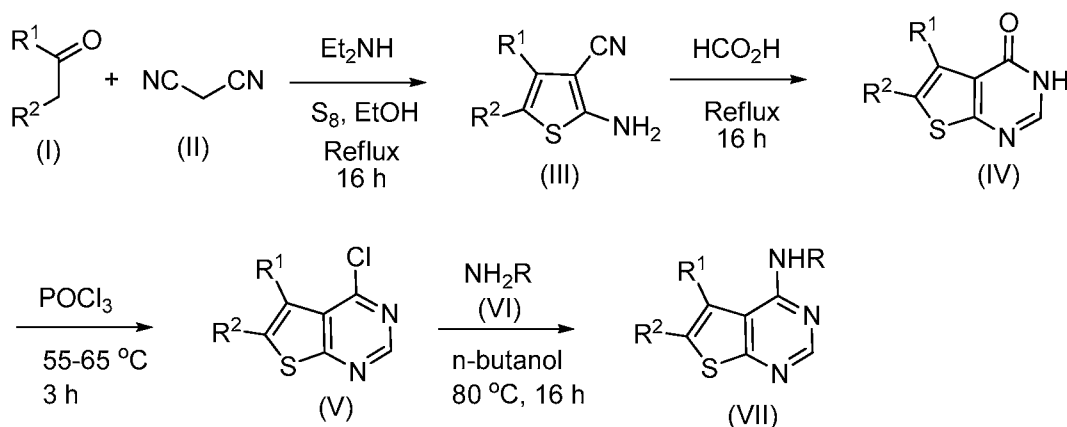


Compound 327

The fused bicyclic or tricyclic compounds of this invention can be prepared by conventional chemical transformations (including protecting group methodologies), e.g., those described in R. Larock, *Comprehensive Organic Transformations*, VCH Publishers (1989); T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, 3rd Ed., John Wiley and Sons (1999); L. Fieser and M. Fieser, *Fieser and Fieser's Reagents for Organic Synthesis*, John Wiley and Sons (1994); and L. Paquette, ed., *Encyclopedia of Reagents for Organic Synthesis*, John Wiley and Sons (1995) and subsequent editions thereof. Schemes 1-4 below show transformations for synthesizing compounds of this invention.

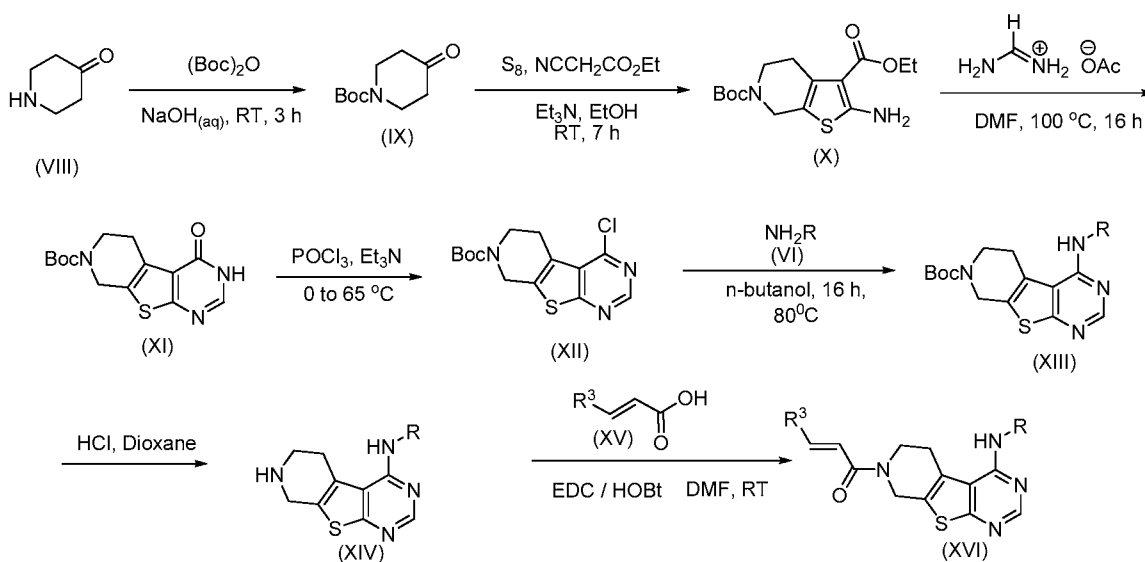
The route shown in Scheme 1 exemplifies the synthesis of thienopyrimidine compounds (VII) of the present invention. Triethylamine is added to a mixture of an appropriately substituted ketone (I), malanonitrile (II), and sulphur (S₈) in absolute ethanol. The resulting mixture is refluxed for 16 h, then concentrated. The residue is partitioned between water and ethyl acetate. The organic layer is concentrated and the residue is purified by silica gel chromatography to provide the thiophene compound (III). Subsequently, HCl is added to a mixture of the thiophene (III) and formic acid and the resulting mixture is refluxed for 16 h. Water is added and the precipitate formed is filtered to give the thienopyrimidinone (IV). A mixture of IV and POCl₃ is heated at 55-65°C for 3 h. Water is then added followed by sodium bicarbonate to neutralize the acid. The mixture is extracted with ethyl acetate and the separated organic layer is concentrated. The residue is purified by column chromatography to afford the chlorine-substituted thienopyrimidine (V). Heating V with an appropriate amine (VI) in *n*-butanol for 16 h then affords the desired substituted thienopyrimidine (VII).

Scheme 1



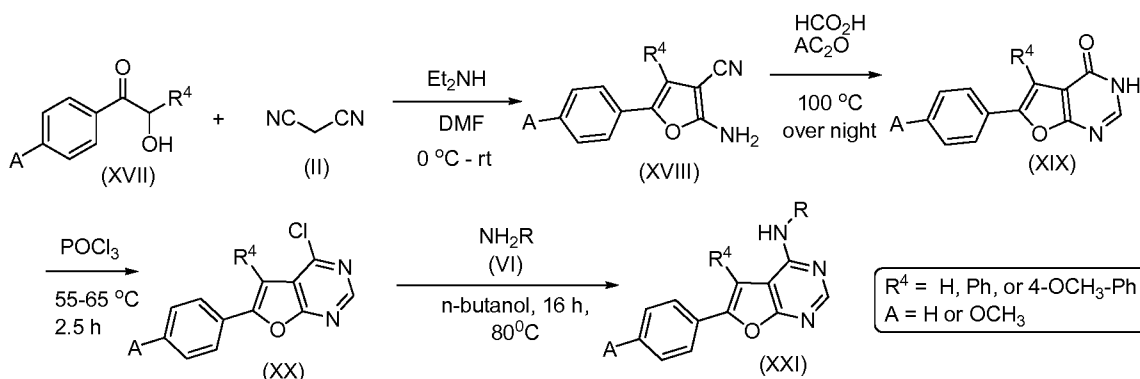
The thienopyrimidine compounds XVI of this invention can be synthesized by a
 5 slightly modified route as shown in Scheme 2. Piperidin-4-one (VIII) is protected with Boc
 under basic conditions, and the product is reacted with malononitrile and sulphur to form the
 thiophene ring. Cyclization of X with formamidine acetate in DMF at 100°C gives the
 thienopyrimidinone XI. Reaction of XI with POCl₃ provides the chlorine-substituted
 thienopyrimidine (XII), which is transformed into the substituted thienopyrimidine (XIII) by
 10 reacting with an appropriate amine (VI) in hot *n*-butanol. Removal of the Boc protecting
 group within XIII with HCl in dioxane for 16 h then affords the compound XIV. Amide
 coupling of XIV with an appropriate acid XV using HOBt and EDC in DMF, followed by
 standard work up yields the desired product XVI.

Scheme 2



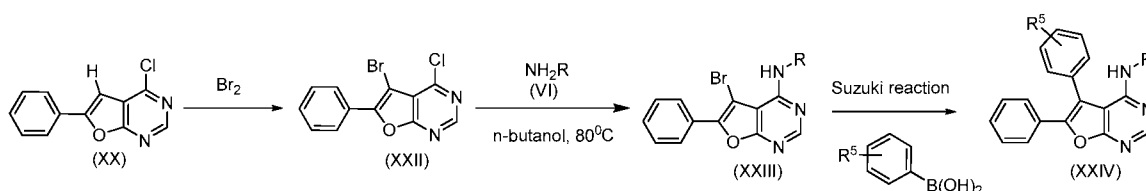
The route shown in Scheme 3 exemplifies the synthesis of furanopyrimidine
 5 compounds (XXI) of the present invention. Diethylamine is added dropwise over a period of
 30 min to a mixture of an appropriately substituted benzoin (XVII) and malanonitrile (II) in
 DMF at 0°C . The resulting mixture is allowed to stir for 16 h. Water is then added, and the
 precipitate thus formed is collected by filtration and crystallized from ethanol to give the
 substituted furan (XVIII). Acetic anhydride is added dropwise over a period of 30 min to a
 10 mixture of XVIII and formic acid at 0°C . The resulting mixture is heated at 100°C for 16 h.
 Water is then added and the precipitate formed is collected by filtration to afford the
 furanopyrimidinone (XIX). A mixture of XIX and POCl_3 is heated at 55 - 65°C for 3 h.
 Water is then added, followed by sodium bicarbonate. The resulting mixture is extracted
 with ethyl acetate. Concentration of the organic layer, followed purification of the residue by
 15 column chromatography, affords the chlorine-substituted furanopyrimidine (XX). Heating
 XX with an appropriate amine (VI) in hot *n*-butanol for 16 h affords the desired amino-
 substituted furanopyrimidine (XXI).

Scheme 3



The furanopyrimidine compounds of this invention can also be synthesized by
 5 alternative methods. Scheme 4 below exemplifies such an alternative synthetic route.
 Bromination of a chloro-substituted furanopyrimidine (XX) using *N*-bromosuccinimide
 (NBS) in DMF affords the bromo, chloro-substituted furanopyrimidine (XXII).
 Alternatively, the use of *N*-chlorosuccinimide (NCS) affords the corresponding dichloro
 derivative of XXII. Reaction of XXII with an appropriate amine (VI) by heating in *n*-butanol
 10 gives the bromo, amino-substituted furanopyrimidine (XXIII). The furanopyrimidine
 compound (XXIV) of this invention is then synthesized by reacting compound XXIII with an
 appropriate boronic acid under the standard Suzuki coupling conditions ($\text{Pd}(\text{OAc})_2$, PPh_3 , and
 sodium carbonate in a mixture of water and dioxane under refluxing conditions for 2-3 h).

Scheme 4



15

The fused bicyclic or tricyclic compounds of this invention can also be synthesized in
 manners similar to those outlined in Schemes 1-4 with necessary modifications as recognized
 by those skilled in the art.

20

A fused bicyclic or tricyclic compound thus synthesized can be further purified by
 flash column chromatography, high performance liquid chromatography, crystallization, or
 any other suitable methods.

The compounds mentioned herein may contain a non-aromatic double bond and one
 or more asymmetric centers. Thus, they can occur as racemates and racemic mixtures, single

enantiomers, individual diastereomers, diastereomeric mixtures, and cis- or trans- isomeric forms. All such isomeric forms are contemplated.

Also within the scope of this invention are (1) a pharmaceutical composition that contains an effective amount of at least one of the fused bicyclic or tricyclic compounds of this invention and a pharmaceutically acceptable carrier, and (2) a method for treating cancer by administering to a subject in need of this treatment an effective amount of such a fused bicyclic or tricyclic compound.

As used herein, the term “treating” refers to administering a fused bicyclic or tricyclic compound to a subject that has cancer, or has a symptom of or a predisposition toward it, with the purpose to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve, or affect cancer, the symptoms of or the predisposition toward cancer. The term “an effective amount” refers to the amount of the active agent that is required to confer the intended therapeutic effect in the subject. Effective amounts may vary, as recognized by those skilled in the art, depending on route of administration, excipient usage, and the possibility of co-usage with other agents.

Cancer that can be treated by the methods of the invention include both solid and haematological tumours of various organs. Examples of solid tumors include pancreatic cancer; bladder cancer; colorectal cancer; breast cancer, including metastatic breast cancer; prostate cancer, including androgen-dependent and androgen-independent prostate cancer; renal cancer, including, e.g., metastatic renal cell carcinoma; hepatocellular cancer; lung cancer, including, e.g., non-small cell lung cancer (NSCLC), bronchioloalveolar carcinoma (BAC), and adenocarcinoma of the lung; ovarian cancer, including, e.g., progressive epithelial or primary peritoneal cancer; cervical cancer; gastric cancer; esophageal cancer; head and neck cancer, including, e.g., squamous cell carcinoma of the head and neck; melanoma; neuroendocrine cancer, including metastatic neuroendocrine tumors; brain tumors, including, e.g., glioma, anaplastic oligodendroglioma, adult glioblastoma multiforme, and adult anaplastic astrocytoma; bone cancer; and soft tissue sarcoma. Examples of hematologic malignancy include acute myeloid leukemia (AML); chronic myelogenous leukemia (CML), including accelerated CML and CML blast phase (CML-BP); acute lymphoblastic leukemia (ALL); chronic lymphocytic leukemia (CLL); Hodgkin’s disease (HD); non-Hodgkin’s lymphoma (NHL), including follicular lymphoma and mantle cell lymphoma; B-cell lymphoma; T-cell lymphoma; multiple myeloma (MM); Waldenstrom’s macroglobulinemia; myelodysplastic syndromes (MDS), including refractory anemia (RA), refractory anemia with ringed siderblasts (RARS), (refractory anemia with excess blasts

(RAEB), and RAEB in transformation (RAEB-T); and myeloproliferative syndromes. Other cancer types, in which EGFR kinase activity is upregulated/dysregulated, are described in *Exp. Mol. Pathol.*, 2008, 84(2):79-89 and *Crit. Rev. Oncol. Hematol.*, 1995, 19, 183.

The compounds of this invention can be administered in conjunction with a
5 therapeutic agent selected from the group consisting of cytotoxic agents, radiotherapy, and immunotherapy. Non-limiting examples of cytotoxic agents suitable for use in combination with the protein kinase inhibitors of the invention include: antimetabolites, including, e.g., capecitabine, gemcitabine, 5-fluorouracil or 5-fluorouracil/ leucovorin, fludarabine, cytarabine, mercaptopurine, thioguanine, pentostatin, and methotrexate; topoisomerase
10 inhibitors, including, e.g., etoposide, teniposide, camptothecin, topotecan, irinotecan, doxorubicin, and daunorubicin; vinca alkaloids, including, e.g., vincristine and vinblastin; taxanes, including, e.g., paclitaxel and docetaxel; platinum agents, including, e.g., cisplatin, carboplatin, and oxaliplatin; antibiotics, including, e.g., actinomycin D, bleomycin, mitomycin C, adriamycin, daunorubicin, idarubicin, doxorubicin and pegylated liposomal
15 doxorubicin; alkylating agents such as melphalan, chlorambucil, busulfan, thiotepa, ifosfamide, carmustine, lomustine, semustine, streptozocin, decarbazine, and cyclophosphamide; thalidomide and related analogs, including, e.g., CC-5013 and CC-4047; protein tyrosine kinase inhibitors, including, e.g., imatinib mesylate and gefitinib; antibodies, including, e.g., trastuzumab, rituximab, cetuximab, and bevacizumab; mitoxantrone;
20 dexamethasone; prednisone; and temozolomide.

To practice the method of this invention, the above-described pharmaceutical composition can be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used
25 herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, and intracranial injection or infusion techniques.

A sterile injectable composition, e.g., a sterile injectable aqueous or oleaginous suspension, can be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as Tween 80) and suspending agents. The sterile
30 injectable preparation can also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that can be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium (e.g., synthetic mono- or

diglycerides). Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions can also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents. Other commonly used surfactants such as Tweens or Spans or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms can also be used for the purposes of formulation.

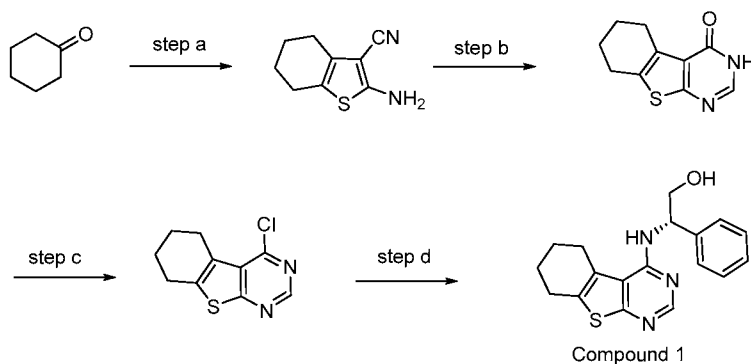
A composition for oral administration can be any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers that are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions or emulsions are administered orally, the active ingredient can be suspended or dissolved in an oily phase combined with emulsifying or suspending agents. If desired, certain sweetening, flavoring, or coloring agents can be added. A nasal aerosol or inhalation composition can be prepared according to techniques well known in the art of pharmaceutical formulation. A fused bicyclic or tricyclic compound-containing composition can also be administered in the form of suppositories for rectal administration.

The carrier in the pharmaceutical composition must be "acceptable" in the sense of being compatible with the active ingredient of the formulation (and preferably, capable of stabilizing it) and not deleterious to the subject to be treated. For example, one or more solubilizing agents, which form more soluble complexes with the fused bicyclic or tricyclic compounds, or more solubilizing agents, can be utilized as pharmaceutical carriers for delivery of the active compounds. Examples of other carriers include colloidal silicon dioxide, magnesium stearate, sodium lauryl sulfate, and D&C Yellow # 10.

Suitable *in vitro* assays can be used to preliminarily evaluate the efficacy of the fused bicyclic or tricyclic compounds of this invention in inhibiting activity of EGFR kinase. The compounds can further be examined for their efficacy in treating cancer *in vitro* and/or *in vivo*. For example, a compound can be tested for its efficacy in inhibiting cancer cell growth (e.g., a growth inhibition assay of HCC827 cells) or it can be administered to an animal (e.g., a mouse model) having cancer and its therapeutic effects are then assessed. Based on the results, an appropriate dosage range and administration route can also be determined.

Without further elaboration, it is believed that the above description has adequately enabled the present invention. The following examples are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever. All of the publications cited herein are hereby incorporated by reference in their entirety.

Example 1: Synthesis of *S*-2-phenyl-2-(5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-ylamino)-ethanol (Compound 1)



2-Amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl cyanide (step a): To a mixture of cyclohexanone (1.18 g), malononitrile (0.66 g), and sulphur (0.40 g) in absolute ethanol (3 ml) was added triethylamine (2 mL). After refluxed for 16 h, the reaction mixture was concentrated and the residue was partitioned between water and ethyl acetate. The organic layer was concentrated and the crude compound was purified by silica gel column chromatography using a mixture of hexanes:ethyl acetate (4:1), to give the title compound (0.94 g, 44%).

3,4,5,6,7,8-Hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-one (step b): To a mixture of 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-yl cyanide (0.9 g) and formic acid (10 mL) was added 0.1 mL conc. HCl. After refluxed for 16 h, the reaction mixture was cooled and water (20 mL) was added. The precipitate was collected by filtration and washed thoroughly with water and hexanes to give the title compound (0.8 g, 77%). ¹H NMR (300 MHz, CDCl₃): δ 7.91 (s, 1H), 3.03-3.00 (m, 2H), 2.80-2.77 (m, 2H), 1.89-1.83 (m, 4H).

4-Chloro-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine (step c): A mixture of 3,4,5,6,7,8-hexahydrobenzo[4,5]thieno[2,3-*d*]pyrimidin-4-one (0.8 g) and POCl₃ (10 mL) was heated at 55-65°C for 3 h. Water was then added followed by sodium bicarbonate. The resulting mixture was extracted with ethyl acetate. The organic layer was concentrated and the crude compound was purified by silica gel column chromatography using a mixture of

hexanes:ethyl acetate (20:1), to give the title compound (0.52 g, 60%). ¹H NMR (300 MHz, CDCl₃): δ 8.69 (s, 1H), 3.10-3.07 (m, 2H), 2.88-2.86 (m, 2H), 1.89-1.92 (m, 4H). LC-MS (ESI) *m/z* 225.3 (M+H).

S-2-Phenyl-2-(5,6,7,8-tetrahydro-benzo[4,5]thieno[2,3-*d*]pyrimidin-4-ylamino)-ethanol (Compound 1, step d): A mixture of 4-chloro-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-*d*]pyrimidine (1g) and *S*-2-amino-2-phenyl-ethanol (0.672 g, 1.1 eq) in *n*-butanol (1 mL) was heated at 80°C for 16 h. The reaction mixture was concentrated and the residue was partitioned between water and dichloromethane. The organic layer was washed with brine, dried over MgSO₄ and concentrated. The crude compound was purified by silica gel column chromatography using a mixture of dichloromethane:methanol (30:1), to give the title compound (0.88 g). ¹H NMR (400 MHz, CDCl₃): δ 8.20 (s, 1H), 7.25-7.36(m, 5H), 6.14 (d, 1H), 5.36 (dd, 1H, *J* = 9.6, 5.6 Hz), 3.93-4.02 (m, 2H), 2.81-2.99 (m, 2H), 2.74 (s, 2H), 1.80-1.96 (m, 4H). LC-MS (ESI) *m/z* 326.1 (M+H).

Example 2: Syntheses of Compounds 2-8, 17-24, 29, 30, 245, and 246

Compounds 2-8, 17-24, 29, 30, 245, and 246 were prepared in a manner similar to that described in Example 1. ¹H NMR and MS data of these compounds are listed below.

Compound 2: ¹H-NMR (400MHz, CDCl₃): δ 8.20 (s,1H), 7.25-7.34 (m, 5 H), 6.11 (d, 1 H, *J* = 6.4 Hz), 5.35-5.38 (m, 1 H), 3.93-3.99 (m, 2 H), 2.88-2.93 (m, 2 H), 2.73-2.76 (m, 2 H), 1.82-1.88 (m, 4 H). LC-MS (ESI) *m/z* 326.1 (M + 1).

Compound 3: ¹H-NMR (400 MHz, CDCl₃) δ 2.48-2.55 (m, 2H), 2.93-3.06 (m, 4H), 3.83 (brs, 1H), 4.00 (dd, 2H, *J* = 5.2, 5.2 Hz), 5.34 (ddd, 1H, *J* = 5.2, 5.2, 5.2 Hz), 5.80 (d, 1H, *J* = 6.0 Hz), 7.29-7.40 (m, 5H), 8.31 (s, 1H). ¹³C-NMR (75 MHz, CDCl₃) δ 27.9 (CH₂), 28.9 (CH₂), 29.4 (CH₂), 57.1 (CH), 67.2 (CH₂), 113.4 (C), 126.4 (CH), 127.8 (CH), 128.9 (CH), 134.3 (C), 139.1 (C), 139.6 (C), 152.5 (CH), 156.3 (C). HRMS (EI) calcd. for C₁₇H₁₇N₃OS (M⁺) 311.1092, found 311.1096.

Compound 4: LC-MS (ESI) *m/z* 300.0 (M+H)⁺.

Compound 5: LC-MS (ESI) *m/z* 286.0 (M+H)⁺.

Compound 6: LC-MS (ESI) *m/z* 272.0 (M+H)⁺.

Compound 7: LC-MS (ESI) *m/z* 348.0 (M+H)⁺.

Compound 8: LC-MS (ESI) *m/z* 382.3 (M+H)⁺.

Compound 17: ^1H NMR (400 MHz, CDCl_3): δ 8.30 (s, 1H), 7.445-7.48 (m, 1H), 7.31-7.37 (m, 4H), 6.41 (d, 1H, $J = 6.4$ Hz), 5.90 (d, 1H, 6.4 Hz), 3.74 (s, 3H), 3.00-3.04 (m, 2H), 2.77-2.80 (m, 2H), 1.18-1.95 (m, 4H). LC-MS (ESI) m/z 354.2 (M+H).

Compound 18: ^1H NMR (300 MHz, CDCl_3): δ 9.00 (s, 1H), 7.22~7.31 (m, 5H), 5.78 (s, 1H), 2.78~3.07 (m, 4H), 1.84~2.01 (m, 4H).

Compound 19: LC-MS (ESI) m/z 340.0 (M+H) $^+$.

Compound 20: LC-MS (ESI) m/z 326.0 (M+H) $^+$.

Compound 21: LC-MS (ESI) m/z 376.0 (M+H) $^+$.

Compound 22: LC-MS (ESI) m/z 362.0 (M+H) $^+$.

Compound 23: ^1H -NMR (400 MHz, CDCl_3) δ 0.94 (t, 3H, $J = 4.0$ Hz), 1.85-2.01 (m, 6H), 2.76-2.78 (m, 2H), 2.91-2.96 (m, 2H), 5.31 (q, 1H, $J = 4.0$ Hz), 5.56 (d, 1H, $J = 7.6$ Hz), 7.21-7.23 (m, 1H), 7.24--7.34 (m, 4H), 8.31 (s, 1H). HRMS (EI) calcd. for $\text{C}_{19}\text{H}_{21}\text{N}_3\text{S}$ (M $^+$) 323.1456, found 323.1452.

Compound 24: LC-MS (ESI) m/z 324.0 (M+H) $^+$.

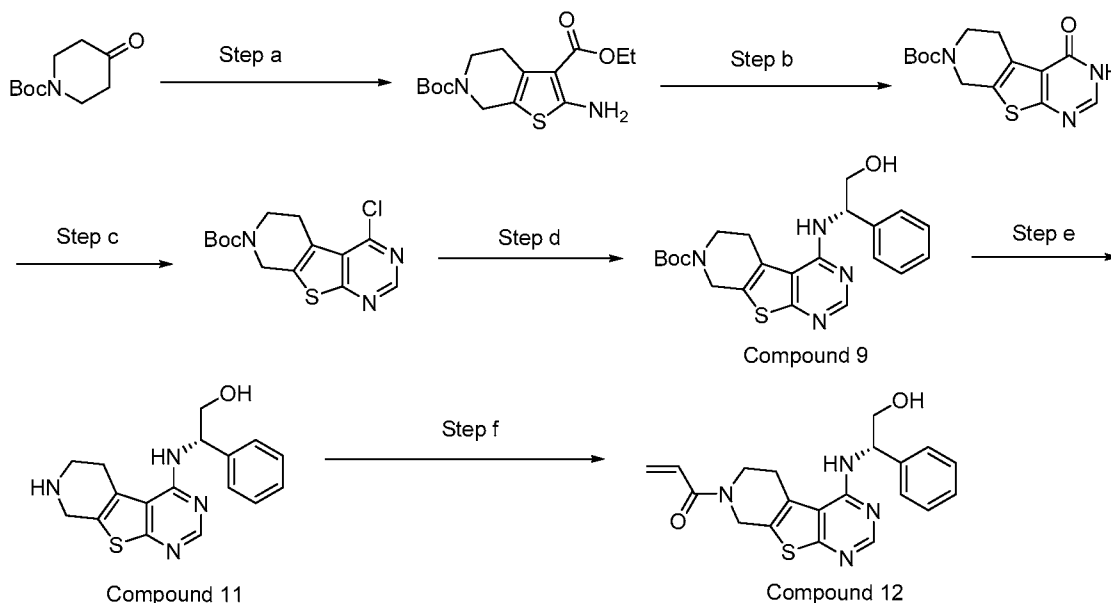
Compound 29: ^1H -NMR (300 MHz, CDCl_3) δ 0.93 (t, 3H, $J = 7.2$ Hz), 1.42 (s, 9H), 1.87-2.00 (m, 2H), 2.98-3.00 (m, 2H), 3.77-3.78 (m, 2H), 4.62 (s, 2H), 5.29 (td, 1H, $J = 7.2, 7.2$ Hz), 5.41 (d, 1H, $J = 7.2$ Hz), 7.22-7.33 (m, 5H), 8.33 (s, 1H). LCMS (ESI) m/z 425.1 [M+H] $^+$.

Compound 30: LC-MS (ESI) m/z 346.0 (M+H) $^+$.

Compound 245: ^1H NMR (400 MHz, CDCl_3): δ : 8.17 (s, 1H), 8.08 (br, 1H), 7.61 (s, 1H), 7.41-7.37 (m, 3H), 7.32-7.20 (m, 6H), 6.42 (dd, $J = 1.8, 17.0$ Hz, 1H), 6.34 (dd, $J = 9.6, 16.8$ Hz, 1H), 5.75 (dd, $J = 2.0, 9.6$ Hz, 1H), 5.43 (dd, $J = 4.0, 7.2$ Hz, 1H), 4.01 (dd, $J = 4.2, 11.8$ Hz, 1H), 3.94 (dd, $J = 7.4, 11.8$ Hz, 1H). LCMS: 417.0 (M+H).

Compound 246: ^1H NMR (400 MHz, CDCl_3): δ : 8.39 (s, 1H), 7.79 (d, $J = 8.4$ Hz, 1H), 7.71 (s, 1H), 7.44 (t, $J = 8.0$ Hz, 1H), 7.32 (s, 1H), 7.26-7.21 (m, 4H), 7.16 (s, 1H), 7.02 (dd, $J = 2.0, 7.6$ Hz, 1H), 6.45 (dd, $J = 1.4, 17.0$ Hz, 1H), 6.32 (dd, $J = 10.2, 17.0$ Hz, 1H), 5.94 (d, $J = 6.8$ Hz, 1H), 5.78 (dd, $J = 1.6, 10.0$ Hz, 1H), 5.32 (br, 1H), 3.81 (d, $J = 8.0$ Hz, 1H), 3.63 (d, $J = 6.8$ Hz, 1H). LCMS: 417.0 (M+H).

Example 3: Synthesis of 1-[4-(2-hydroxy-1-phenyl-ethylamino)-5,8-dihydro-6H-9-thia-1,3,7-triaza-fluorene-7-yl]-propanone (Compound 12)



2-Amino-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 6-tert-butyl ester

5 **3-ethyl ester** (step a). To a mixture of 4-oxo-piperidine-1-carboxylic acid tert-butyl ester (12.9 g), ethyl cyanoacetate (7.345 g), and sulphur (2.080 g) in absolute ethanol (50 mL) was added triethylamine (9 mL). After stirring for 16 h, the precipitate was collected by filtration and washed with ethanol to give the title compound (18.7 g, 88%). ¹H NMR (300 MHz, CDCl₃): δ 6.02 (s, 2H), 4.31 (s, 2H), 4.23 (q, 2H, *J* = 7.2 Hz), 3.58 (t, 2H, *J* = 6.0 Hz), 2.72-2.80 (brs, 2H), 1.44 (s, 9H), 1.30
10 (t, 3H, *J* = 7.2 Hz). LC-MS (ESI) *m/z* 327.0 (M+H).

4-Oxo-3,5,6,8-tetrahydro-4H-9-thia-1,3,7-triaza-fluorene-7-carboxylic acid tert-butyl ester (step b). A mixture of 2-amino-4,7-dihydro-5H-thieno[2,3-c]pyridine-3,6-dicarboxylic acid 6-tert-butyl ester 3-ethyl ester (18.5 g) and formamidine acetate (8.85 g) in DMF (100 mL) were heated at 100 °C for 16 h. The reaction mixture was cooled and concentrated. The residues was
15 partitioned between water and ethyl acetate. The organic layer was washed with water 3 times and concentrated to give the title compound (15.8 g, 90%). ¹H NMR (400 MHz, CDCl₃): δ 7.88 (s, 1H), 4.56-4.62 (brs, 2H), 3.62-3.70 (brs, 2H), 3.02-3.08 (brs, 2H), 1.42 (s, 9H). LC-MS (ESI) *m/z* 308.1 (M+H).

4-Chloro-5,8-dihydro-6H-9-thia-1,3,7-triaza-fluorene-7-carboxylic acid tert-butyl ester
20 (step c). To a of mixture of POCl₃ (30 mL) and triethylamine (50 mL) at 0 °C was added 4-oxo-3,5,6,8-tetrahydro-4H-9-thia-1,3,7-triaza-fluorene-7-carboxylic acid tert-butyl ester (10.0 g). The reaction mixture was heated at 60°C for 3 h. Water was then added, followed by sodium bicarbonate to neutralize the reaction mixture. The resulting mixture was extracted with dichloromethane. The

organic layer was concentrated and the crude compound was purified by silica gel column chromatography using a mixture of hexanes:ethyl acetate (10:1) to give the title compound (3.1 g, 25%). ¹H NMR (400 MHz, CDCl₃): δ 8.70 (s, 1H), 4.69 (s, 2H), 3.74 (t, 2H, *J* = 5.6 Hz), 3.14-3.18 (brs, 2H), 1.46 (s, 9H). LC-MS (ESI) *m/z* 326.0 (M+H).

5 **4-(2-Hydroxy-1-phenyl-ethylamino)-5,8-dihydro-6H-9-thia-1,3,7-triaza-fluorene-7-carboxylic acid tert-butyl ester** (Compound 9, step d). A mixture of 4-chloro-5,8-dihydro-6H-9-thia-1,3,7-triaza-fluorene-7-carboxylic acid tert-butyl ester (0.25 g) and *S*-2-amino-2-phenyl-ethanol (0.128 g) in *n*-butanol (1 mL) was refluxed for 8 h. The reaction mixture was concentrated and the residue was partitioned between water and dichloromethane. The organic layer was concentrated
10 and the crude compound was purified by silica gel column chromatography using a mixture of dichloromethane:methanol (20:1) to give the title compound (0.309 g, 95%). ¹H NMR (300 MHz, CDCl₃): δ 8.25 (s, 1H), 7.26-7.38 (m, 5H), 6.04 (d, 1H, *J* = 6.6 Hz), 5.36-5.43 (m, 1H), 4.62 (s, 2H), 3.97-4.02 (m, 2H), 3.72-3.81 (m, 2H), 2.90-3.08 (m, 2H), 1.46 (s, 9H). LC-MS (ESI) *m/z* 427.0 (M+H).

15 **2-Phenyl-2-(5,6,7,8-tetrahydro-9-thia-1,3,7-triaza-fluoren-4-ylamino)-ethanol** (Compound 11, step e). To a mixture of 4-(2-hydroxy-1-phenyl-ethylamino)-5,8-dihydro-6H-9-thia-1,3,7-triaza-fluorene-7-carboxylic acid tert-butyl ester (0.6 g) in dichloromethane (2 mL) at room temperature was added TFA (1 mL). The reaction mixture was stirred for 4 h, then neutralized by slow addition of sodium bicarbonate solution. The precipitate formed
20 was collected by filtration and washed with water then dichloromethane to give the title compound (0.350 g, 76%). ¹H NMR (400 MHz, CDCl₃): δ 8.28 (s, 1H), 7.26-7.38 (m, 5H), 6.04 (d, 1H, *J* = 6.4 Hz), 5.38 (d, 1H, *J* = 4.8 Hz), 4.01 (d, 2H, *J* = 7.6 Hz), 3.99 (d, 2H, *J* = 3.2 Hz), 3.20 (t, 2H, *J* = 4.4 Hz), 2.84-3.04 (m, 2H). LC-MS (ESI) *m/z* 327.1 (M+H).

25 **1-[4-(2-Hydroxy-1-phenyl-ethylamino)-5,8-dihydro-6H-9-thia-1,3,7-triaza-fluoren-7-yl]-propenone** (Compound 12, step f). A mixture of acrylic acid (3.6 mg) and EDCI (9.4 mg) in anhydrous DMF was stirred for 2 h and 2-phenyl-2-(5,6,7,8-tetrahydro-9-thia-1,3,7-triaza-fluoren-4-ylamino)-ethanol was then added. The resulting mixture was stirred for 16 h, then partitioned between water and ethyl acetate. The organic layer was dried over MgSO₄, concentrated. The residue was purified by silica gel column chromatography using a mixture of
30 dichloromethane:methanol (5:1) to give the title compound (8 mg, 44%). ¹H NMR (300 MHz, CD₃OD): δ 8.18 (s, 1H), 7.20-7.44 (m, 5H), 6.78-6.98 (m, 1H), 6.28 (d, 1H, *J* = 17.1 Hz), 5.78-5.84 (m, 1H), 5.39 (t, 1H, *J* = 5.1 Hz), 4.80-4.98 (m, 2H), 4.07 (t, 2H, *J* = 5.7 Hz), 3.82-3.98 (m, 2H), 3.20-3.38 (m, 2H). LC-MS (ESI) *m/z* 381.0 (M+H).

Example 4: Syntheses of Compounds 9-11, 13-16, 25-28, and 59-68, 75, 106, 107, 154, 176, 178, 180, 181, 183-235, and 327

Syntheses of Compounds 9 and 11 were described in Example 3. Compounds 10, 13-16, 25-28, and 59-68, 75, 106, 107, 154, 176, 178, 180, 181, 183-235, and 327 were prepared in a manner similar to that described in Example 3. ¹H NMR and MS data of these compounds are listed below.

Compound 10: ¹H NMR (400 MHz, CDCl₃): δ 8.31 (s, 1H), 7.29~7.39 (m, 5H), 6.00 (d, 1H, *J* = 6.4 Hz), 5.38~5.40 (m, 1H), 4.70 (s, 2H), 4.17 (q, 2H, *J* = 7.2 Hz), 4.00 (d, 2H, *J* = 4.0 Hz), 3.79~3.84 (m, 2H), 3.00~3.05 (m, 2H), 1.27 (t, 3H, *J* = 7.2 Hz).

Compound 13: ¹H-NMR (400 MHz, CD₃OD) δ 8.15 (s, 1H), 7.38-7.42 (m, 2H), 7.24-7.33 (m, 2H), 7.20-7.23 (m, 1H), 5.38-5.40 (m, 1H), 4.77-4.79 (m, 2H), 3.87-3.98 (m, 4H), 3.14-3.26 (m, 2H), 2.55 (q, 1.2H, *J* = 7.6 Hz), 2.48 (q, 0.8 H, *J* = 7.6 Hz), 1.17 (t, 1.8H, *J* = 7.6 Hz), 1.12 (t, 1.2H, *J* = 7.6 Hz); HRMS (EI) calcd. for C₂₀H₂₁N₄O₂S (M⁺) 382.1463, found 382.1466.

Compound 14: ¹H-NMR (300MHz, CDCl₃): δ 8.23 (s, 1H), 7.67 (d, 1H, *J* = 15.6 Hz), 7.47-7.52 (m, 2H), 7.24-7.27 (m, 8H), 6.91 (d, 1H, *J* = 15.6 Hz), 6.16 (s, 1H), 5.41 (s, 1H), 4.75-4.92 (m, 2H), 3.92-4.04 (m, 4H), 3.08 (br, 2H). LC-MS (ESI) *m/z* 457.1 (M+H).

Compound 15: ¹H NMR (300 MHz, CDCl₃): δ -0.16(s, 3H), -0.06 (s, 3H), 0.83 (s, 9H), 3.16 (m, 2H), 3.87~4.07 (m, 4H), 4.80~4.89 (m, 2H), 5.37~5.42 (m, 1H), 5.77 (d, 1H, *J* = 12 Hz), 6.34 (d, 1H, *J* = 18 Hz), 6.56~6.60 (m, 1H), 7.20~7.34 (m, 5H), 8.29 (s, 1H). LC-MS (ESI) *m/z* 495.2 (M+H).

Compound 16: ¹H-NMR (300 MHz, CDCl₃): δ 1.97~2.03 (m, 3H), 2.96~3.24 (m, 2H), 3.84~4.15 (m, 4H), 4.67~4.82 (m, 1H), 4.92 (s, 1H), 5.35~5.45 (m, 1H), 6.13~6.16 (m, 1H), 7.23~7.36 (m, 5H), 8.22 (s, 0.5H), 8.24 (s, 0.5 H); ¹³C-NMR (75 MHz, CDCl₃) δ 4.1 (CH₃), 25.7 (CH₂), 26.7 (CH₂), 29.6 (C), 38.4 (CH₂), 41.0 (CH₂), 43.7 (CH₂), 46.2 (CH₂), 56.5 (CH), 56.7 (CH), 66.4 (CH₂), 66.5 (CH₂), 72.4 (C), 72.5 (C), 90.1 (C), 91.3 (C), 115.3 (C), 115.4 (C), 124.0 (C), 124.9 (C), 126.4 (CH), 126.5 (C), 127.7 (C), 127.8 (CH), 128.6 (CH), 128.8 (C), 128.8 (C), 129.0 (C), 139.3 (C), 139.4 (C), 152.8 (C), 153.2 (CH), 153.3 (CH), 156.7 (C), 156.9 (C), 164.9 (C), 165.1 (C); HRMS (EI) calcd. for C₂₁H₂₀N₄O₂S (M⁺) 392.1307, found 392.1311.

Compound 25: ¹H-NMR (300 MHz, CDCl₃) δ 0.93 (t, 3H, *J* = 7.2 Hz), 1.42 (s, 9H), 1.87-2.00 (m, 2H), 2.98-3.00 (m, 2H), 3.77-3.78 (m, 2H), 4.62 (s, 2H), 5.29 (td, 1H, *J* = 7.2, 7.2 Hz), 5.41 (d, 1H, *J* = 7.2 Hz), 7.22-7.33 (m, 5H), 8.33 (s, 1H). LCMS (ESI) *m/z* 425.1

[M+H]⁺.

Compound 26: LC-MS (ESI) *m/z* 397.0 (M+H)⁺.

Compound 27: ¹H-NMR (400 MHz, CDCl₃) δ 0.93 (t, 3H, *J* = 7.6 Hz), 1.89-19.7 (m, 2H), 2.90-3.00 (m, 2H), 3.24 (t, 2H, 5.6 Hz), 4.04 (s, 2H), 5.30 (td, 1H, 7.2, 7.2 Hz), 5.46 (d, 1H, 7.2 Hz), 7.22-7.33 (m, 5H), 8.32 (s, 1H). LCMS (ESI) *m/z* 325.0 [M+H]⁺.

Compound 28: LC-MS (ESI) *m/z* 438.0 (M+H)⁺.

Compound 59: ¹H-NMR (400MHz, CD₃OD): δ 7.39~7.41 (m, 2H), 7.29~7.33 (m, 2H), 7.20~7.24 (m, 1H), 6.25~6.30 (m, 1H), 5.79~5.84 (m, 1H), 5.39 (dd, 1H, *J* = 5.2, 5.2 Hz), 4.90 (m, 2H), 3.94~4.04 (m, 2H), 3.89 (dd, 2H, *J* = 6.0, 11.2 Hz), 3.25~3.27 (m, 2H).

LC-MS (ESI) *m/z* 381.1 (M+H).

Compound 60: ¹H-NMR (400MHz, CDCl₃): δ -0.14 (s, 3H), -0.04 (s, 3H), 0.85 (s, 9H), 3.18~3.29 (m, 2H), 3.88~4.12 (m, 4H), 4.82~4.91 (m, 2H), 5.39~5.40 (m, 1H), 5.79 (d, 1H, *J* = 12 Hz), 6.36 (d, 1H, *J* = 18 Hz), 6.58~6.61 (m, 1H), 7.23~7.37 (m, 5H), 8.31 (s, 1H).

LC-MS (ESI) *m/z* 495.3(M+H).

Compound 61: ¹H-NMR (400MHz, CD₃OD): δ 8.12 (s, 1H), 7.32~7.43 (m, 3H), 7.28~7.30 (m, 2H), 7.19~7.23 (m, 1H), 6.16~6.32 (m, 2H), 5.38 (dd, 1H, *J* = 5.6, 5.6 Hz), 4.76~4.83 (m, 2H), 3.86~4.02 (m, 4H), 3.21~3.33 (m, 2H). LC-MS (ESI) *m/z* 425.2 (M+H).

Compound 62: ¹H NMR (400 MHz, CDCl₃): δ 8.30 (s, 1H), 7.28-7.40 (m, 5H), 6.80-6.98 (brs, 1H), 6.38-6.57 (m, 1H), 6.03 (d, 1H, *J* = 13.6 Hz), 5.39 (s, 1H), 4.86 (s, 1H), 4.78 (s, 1H), 4.00-4.12 (brs, 2H), 3.90-3.99 (brs, 2H), 3.01-3.20 (brs, 4H), 2.24 (s, 6H). LC-MS (ESI) *m/z* 438.2 (M+H).

Compound 63: ¹H NMR (400 MHz, CDCl₃): δ 8.32 (s, 1H), 7.28-7.39 (m, 5H), 6.44 (dd, 1H, *J* = 16.4, 9.6 Hz), 6.32 (d, 1H, *J* = 16.4 Hz), 6.02 (d, 1H, *J* = 4.8 Hz), 5.99 (d, 1H, *J* = 6.4 Hz), 5.41 (dd, 1H, *J* = 10.4, 4.8 Hz), 4.47 (s, 2H), 3.96-4.23 (m, 2H), 3.63 (t, 2H, *J* = 4.8 Hz), 3.04-3.18 (m, 2H). LC-MS (ESI) *m/z* 417.1 (M+H).

Compound 64: ¹H NMR (300 MHz, CD₃OD): δ 8.20 (s, 1H), 7.43 (d, 2H, *J* = 7.8 Hz), 7.31 (m, 2H), 7.21 (t, 1H, 6.9 Hz), 6.75-6.93 (m, 1H), 6.26 (d, 1H, *J* = 16.5 Hz), 5.81 (d, 1H, *J* = 10.8 Hz), 5.48 (q, 1H, *J* = 6.9 Hz), 4.78-5.01 (m, 2H), 3.91-4.05 (m, 2H), 3.01-3.22 (m, 2H), 1.61 (d, 3H, *J* = 7.2 Hz). LC-MS (ESI) *m/z* 365.1 (M+H).

Compound 65: ¹H-NMR (400MHz, CDCl₃): δ 8.25 (s, 0.5H), 8.24 (s, 0.5H), 7.23-7.33 (m, 5H), 6.81 (m, 1H), 6.35-6.46 (m, 1H), 6.05-6.12 (m, 2H), 5.37-5.38 (m, 1H), 4.81 (m, 1H), 4.74 (m, 1H), 3.88-3.98 (m, 4H), 3.07 (m, 4H), 2.35 (m, 4H), 1.54 (m, 4H), 1.39 (m, 2H). LC-MS (ESI) *m/z* 478.1 (M+H).

Compound 66: $^1\text{H-NMR}$ (400MHz, CDCl_3): δ 8.23 (s, 1H), 7.22-7.33 (m, 5H), 6.84-6.88 (m, 1H), 6.53 (t, 1H, $J = 16.2$ Hz), 6.04-6.09 (m, 1H), 5.36-5.38 (m, 1H), 4.81 (m, 1H), 4.74 (m, 1H), 4.79 (m, 1H), 3.88-3.97 (m, 4H), 3.60-3.67 (m, 4H), 3.10-3.11 (m, 4H), 2.42 (m, 4H). LC-MS (ESI) m/z 480.2 (M+H).

5 Compound 67: $^1\text{H-NMR}$ (400MHz, CDCl_3): δ 8.28 (s, 1H), 7.25-7.37 (m, 5H), 6.82-6.88 (m, 1H), 6.40-6.50 (m, 1H), 6.09 (d, 1H, $J = 1.6$ Hz), 5.35-5.40 (m, 1H), 4.76-4.88 (m, 2H), 3.89-4.03 (m, 4H), 3.13-3.16 (m, 4H), 2.60 (m, 8H), 2.28 (s, 3H). LC-MS (ESI) m/z 493.1 (M+H).

10 Compound 68: $^1\text{H-NMR}$ (300MHz, CDCl_3): δ 8.33 (s, 1H), 7.29-7.47 (m, 6H), 6.81 (dd, 1H, $J = 15.0, 15.0$ Hz), 5.99 dd, 1H, $J = 6.0, 15.0$ Hz), 5.39-5.42 (m, 1H), 4.90 (brs, 1H), 4.81 (brs, 1H), 4.26 (q, 1H, $J = 7.2$ Hz), 4.25 (q, 1H, $J = 7.2$ Hz), 3.92-4.08 (m, 4H), 3.05-3.16 (m, 2H), 1.31 (t, 1.5H, $J = 7.2$ Hz), 1.30 (t, 1.5H, $J = 7.2$ Hz), LC-MS (ESI) m/z 453.1 $[\text{M} + 1]^+$.

15 Compound 75: $^1\text{H-NMR}$ (300MHz, CDCl_3) δ 0.96-1.06 (m, 6H), 2.55-2.58 (m, 4H), 3.11-3.28 (m, 4H), 3.93-4.02 (m, 2H), 4.08-4.13 (m, 2H), 4.80-4.85 (m, 1H), 4.85-4.92 (m, 1H), 5.39-5.44 (m, 1H), 6.08 (s, 1H), 6.52 (dd, 1H, $J = 14.7, 15.6$ Hz), 6.90-6.97 (m, 1H), 7.27-7.41 (m, 5H), 8.32 (s, 1H). HRMS (EI) calcd. for $\text{C}_{25}\text{H}_{31}\text{N}_5\text{O}_2\text{S}$ (M^+) 465.2198, found 465.2195.

20 Compound 106: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 0.86-0.91 (t, 3H), 1.77-2.01 (m, 2H), 2.97-3.11 (m, 2H), 3.90-4.08 (m, 2H), 4.79-4.89 (m, 2H), 5.26-5.43 (m, H), 5.74-5.79 (m, H), 6.24-6.36 (m, H), 7.21-7.32 (m, 5H), 8.33 (s, H). LCMS-ESI (m/z): $[\text{M} + 1]^+$ 479.1.

25 Compound 107: $^1\text{H-NMR}$ (400MHz, CDCl_3): δ 0.95 (t, 3H, $J = 7.2$ Hz), 1.85~2.04 (m, 2H), 2.17 (s, 3H), 2.37 (s, 3H), 3.13~3.17 (m, 2H), 3.84~4.03 (m, 2H), 4.80~4.89 (m, 2H), 5.30~5.46 (m, 2H), 6.53 (dd, 1H, $J = 4.8, 14.4$ Hz), 7.25~7.36 (m, 5H), 8.37 (s, 1H). LCMS LCMS-ESI (m/z): 436.1 (M+H).

Compound 154: $^1\text{H NMR}$ (300 MHz, CDCl_3): δ : 8.45 (s, 1H), 8.34 (s, 1H), 7.86 (d, $J = 7.8$ Hz, 1H), 7.74 (br, 2H), 7.49-7.32 (m, 6H), 6.75 (br, 1H), 6.53 (d, $J = 16.8$ Hz, 1H), 6.35 (dd, $J = 1.5, 26.1$ Hz, 1H), 5.85 (d, $J = 10.2$ Hz, 1H), 4.11 (m, 3H). LCMS: 402.1 (M+H).

30 Compound 176: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.97-2.02 (m, H), 2.23-2.31 (m, H), 2.96-3.03 (m, H), 3.10-3.16 (m, H), 3.68-3.91 (m, 4H), 4.79-4.95 (m, 2H), 5.58-5.63 (m, H), 5.75-5.78 (m, H), 6.30-6.42 (m, H), 6.55-6.66 (m, H), 7.27-7.33 (m, 5H), 8.33 (s, H). LC-MS (ESI) m/z 395.1 (M+H).

Compound 178: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.23-1.27 (m, 3H), 2.17-2.27 (m, 6H), 3.03-3.11 (m, 4H), 3.93-4.05 (m, 2H), 4.80-4.93 (m, 2H), 5.32-5.40 (m, H), 5.52-5.53 (m, H), 6.43-6.54 (m, H), 7.27-7.38 (m, 5H), 8.39 (s, H). LC-MS (ESI) m/z 422.5 (M+H).

5 Compound 180: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.22 (1H, s), 7.36-7.24 (5H, m), 6.11 (1H, s), 5.41-5.37 (1H, m), 5.27 (1H, s), 5.10 (1H, s), 3.99-3.89 (4H, m), 3.14-3.02 (2H, m), 2.00-1.91 (5H, m).

Compound 181: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 0.83 (s, 15H), 2.17-2.18 (m, 6H), 3.06-3.09 (m, 4H), 3.89-4.11 (m, 4H), 4.86 (m, 2H), 5.41-5.43 (m, H), 5.43-5.44 (m, H), 6.37-6.41 (m, H), 7.23-7.36 (m, 5H), 8.30 (s, H).

10 Compound 183: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.25 (m, 3H), 2.05-2.27 (m, 4H), 3.03-3.11 (m, 4H), 3.93-4.05 (m, 2H), 4.80-4.94 (m, 2H), 5.29-5.54 (m, H), 6.43-6.52 (m, H), 7.27-7.38 (m, 5H), 8.37 (s, H). LC-MS (ESI) m/z 422.1 (M+H).

15 Compound 184: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.05-1.16 (m, 6H), 1.24-1.27 (m, 3H), 2.56-2.57 (m, 4H), 3.07 (m, 2H), 3.93-3.99 (m, 2H), 4.80-4.93 (m, 2H), 5.33-5.53 (m, 2H), 6.46-6.59 (m, H), 7.28-7.38 (m, 5H), 8.39 (s, H).

Compound 185: $^1\text{H-NMR}$ (300MHz, CDCl_3): δ 8.31 (s, 1H), 7.22~7.38 (m, 5H), 6.54~6.66 (m, 1H), 6.30~6.39 (m, 1H), 5.99~6.11 (m, 1H), 5.75~5.79 (m, 1H), 5.52 (m, 1H), 4.80~4.88 (m, 2H), 3.76~4.13 (m, 4H), 3.38 (s, 3H), 3.03~3.04 (m, 2H). LC-MS (ESI) m/z 395.1 (M+H).

20 Compound 186: $^1\text{H-NMR}$ (400MHz, CDCl_3): δ 8.29 (s, 0.5H), 8.28 (s, 0.5H), 7.23-7.31 (m, 5H), 6.88-6.92 (m, 1H), 6.51-6.59 (m, 1H), 6.29-6.36 (m, 1H), 5.38-5.40 (m, 1H), 4.81-4.88 (m, 2H), 3.86-4.05 (m, 4H), 3.17 (m, 4H), 2.32 (s, 6H), 0.83 (s, 9H), -0.11 (s, 3H), -0.20 (s, 3H); LC-MS (ESI) m/z 552.2 (M+H).

25 Compound 187: $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.52 (s, 1H), 7.82 (br, 1H), 7.42 (br, 1H), 7.17 (m, 1H), 6.92 (m, 2H), 6.52 (m, 1H), 4.90 (br d, 2H), 4.03 (br, 2H), 3.17 (br, 4H), 2.29 (s, 6H). LC-MS (ESI) m/z 446.0 (M+H)⁺.

30 Compound 188: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.97-2.05 (m, H), 2.24-2.30 (m, H), 2.97-3.01 (m, H), 3.09-3.15 (m, H), 3.65-3.99 (m, 4H), 4.85-4.91 (m, 2H), 5.58-5.62 (m, H), 5.76-5.79 (m, H), 6.30-6.38 (m, H), 7.26-7.39 (m, 5H), 8.34 (s, H). LC-MS (ESI) m/z 395.1 (M+H).

Compound 189: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.12-1.15 (m, 3H), 1.61-1.64 (m, 3H), 2.41-2.49 (m, 2H), 2.94-3.08 (m, 2H), 3.78-3.86 (m, H), 3.92-4.01 (m, H), 4.77-4.89 (m, 2H), 5.50-5.55 (m, H), 7.27-7.41 (m, 5H), 8.39 (s, H).

Compound 190: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.13-1.20 (m, 6H), 1.62-1.64 (m, 3H), 2.54-2.68 (m, 4H), 3.04-3.08 (m, 2H), 3.28-3.29 (m, 2H), 3.44-3.99 (m, 2H), 4.80-4.89 (m, 2H), 5.33-5.39 (m, H), 5.53 (m, H), 6.44-6.58 (m, H), 7.27-7.38 (m, 5H), 8.40 (s, H).

5 Compound 191: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 0.93-0.97 (t, 3H), 1.13-1.16 (m, 6H), 1.92-2.01 (m, 2H), 2.16-2.56 (m, 4H), 3.10-3.28 (m, 2H), 3.46-3.47 (m, 2H), 3.95-4.01 (m, 2H), 4.79-4.92 (m, 2H), 5.29-5.44 (m, 2H), 6.46-6.60 (m, H), 7.25-7.30 (m, 5H), 8.36 (s, H).

10 Compound 192: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 2.05-2.17 (m, 6H), 2.27-2.33 (m, H), 2.49-2.77 (m, H), 2.92-2.95 (m, H), 3.07-3.15 (m, 4H), 3.74-3.88 (m, 4H), 4.81-4.51 (m, H), 4.76-4.85 (m, 2H), 5.36-5.39 (m, H), 6.42-6.52 (m, H), 7.26-7.36 (m, 4H), 8.36 (s, H).
LCMS-ESI (m/z): 452.1 (M + H).

Compound 193: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 2.47-2.49 (m, H), 2.76-2.78 (m, H), 2.91-2.96 (m, H), 3.08-3.13 (m, H), 3.74-3.88 (m, 4H), 4.48-4.49 (m, H), 4.76-4.85 (m, 2H), 5.76-5.82 (m, H), 6.31-6.38 (m, H), 6.54-6.64 (m, H), 7.25-7.36 (m, 5H), 8.38 (s, H).

15 Compound 194: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.96-2.02 (m, 6H), 3.03-3.16 (m, 4H), 3.75-3.96 (m, 4H), 4.74-4.95 (m, 2H), 6.43-6.53 (m, H), 6.68-6.89 (m, 2H), 7.25-7.35 (m, 5H), 8.30 (s, H). LCMS-ESI (m/z): 452.1 (M + H).

20 Compound 195: $^1\text{H-NMR}$ (400MHz, CDCl_3): δ 8.30 (s, 1H), 7.22~7.31 (m, 10H), 6.57 (dd, 1H, $J = 10.8, 17.8$ Hz), 6.35 (dd, 1H, $J = 8.0, 17.6$ Hz), 6.15 (m, 1H), 5.77~5.79 (m, 1H), 5.51~5.52 (m, 1H), 4.78~4.88 (m, 2H), 4.52 (s, 2H), 3.77~3.95 (m, 4H), 2.94~3.00 (m, 2H). LC-MS (ESI) m/z 471.2 (M+H).

Compound 196: $^1\text{H-NMR}$ (400MHz, CDCl_3): δ 8.29 (s, 1H), 7.22~7.37 (m, 10H), 6.14 (d, 1H, $J = 6.8$ Hz), 5.52 (m, 1H), 4.63 (s, 2H), 4.52 (s, 2H), 3.71~3.89 (m, 4H), 2.93~2.94 (m, 2H), 1.49 (s, 9H). LC-MS (ESI) m/z 517.2 (M+H).

25 Compound 197: $^1\text{H-NMR}$ (300MHz, CDCl_3): δ 8.28 (s, 1H), 7.21~7.39 (m, 10H), 6.22 (d, 1H, $J = 6.6$ Hz), 5.52~5.55 (m, 1H), 4.52 (s, 2H), 4.04 (d, 2H, $J = 2.1$ Hz), 3.91 (dd, 1H, $J = 4.2, 9.6$ Hz), 3.82 (dd, 1H, $J = 4.8, 9.6$ Hz), 3.16 (dd, 2H, $J = 6.0, 6.0$ Hz), 2.88~2.90 (m, 2H). LC-MS (ESI) m/z 417.1 (M+H).

30 Compound 198: $^1\text{H-NMR}$ (300MHz, CDCl_3): δ 8.29 (s, 1H), 7.22~7.35 (m, 10H), 6.88 (m, 1H), 6.43~6.49 (m, 1H), 6.13 (m, 1H), 5.52 (m, 1H), 4.79~4.85 (m, 2H), 4.53 (s, 2H), 3.87~3.91 (m, 2H), 3.79 (m, 2H), 3.10~3.11 (m, 2H), 2.99 (m, 2H), 2.27 (m, 6H). LC-MS (ESI) m/z 528.2 (M+H).

Compound 199: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 0.87-0.94 (m, 6H), 2.27-2.40 (m, 2H), 2.56-2.57 (m, 4H), 2.99-3.26 (m, 4H), 3.64-4.16 (m, 4H), 4.65 (m, 2H), 5.53-5.59 (m, 2H), 6.93-6.98 (m, H), 7.25-7.36 (m, 5H), 8.36 (s, H).

Compound 200: $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.32 (s, 1H), 7.39-6.98 (m, 7H),
5 6.99 (m, 2H), 6.63 (dd, 1H, $J_1 = 9.3$ Hz, $J_2 = 16.2$ Hz), 6.37 (d, 1H, $J = 6.9$ Hz), 6.12 (d, NH),
5.79 (d, 1H, $J = 9.6$ Hz), 5.57 (br s, 1H), 4.84 (br, 2H), 4.53 (s, 2H), 3.89 (m, 2H), 3.06 (br,
2H). LC-MS (ESI) m/z 489.1 (M+H).

Compound 201: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.57 (s, 1H), 7.30 (m, 7H), 6.88 (m,
6H), 5.18 (m, 1H), 4.59 (m, 4H), 4.42 (br, 2H), 3.71 (br, 1H), 3.54 (br, 1H), 3.13 (br, 1H),
10 3.00 (br, 1H). LC-MS (ESI) m/z 643.2 (M+H).

Compound 202: $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.34 (s, 1H), 7.58 (d, 2H, $J = 8.4$
Hz), 7.37-7.25 (m, 7H), 6.99 (m, 2H), 6.59 (dd, 1H, $J_1 = 10.5$ Hz, $J_2 = 16.5$ Hz), 6.36 (d, 1H,
 $J = 16.5$ Hz), 6.09 (s, NH), 5.79 (dd, 1H, $J_1 = 1.8$ Hz, $J_2 = 11.1$ Hz), 5.60 (br s, 1H), 4.85 (m,
2H), 4.60 (m, 2H), 3.79 (m, 4H), 3.05 (br, 2H). LC-MS (ESI) m/z 539.2 (M+H).

Compound 203: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.52 (d, 1H, $J = 14.4$ Hz), 8.31 (s,
1H), 7.63 (m, 1H), 7.19-7.39 (m, 2H), 6.92 (br, 1H), 6.48 (br, 1H), 6.24 (br, 1H), 5.58 (s, 1H),
4.88 (m, 2H), 4.67 (s, 1H), 4.00 (m, 4H), 3.11 (m, 4H) 2.27 (s, 6H). LC-MS (ESI) m/z 529.3
(M+H).

Compound 204: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.60 (s, 6H), 1.54-1.56 (d, 3H),
20 2.94-2.96 (m, 3H), 3.39-3.43 (m, 4H), 3.77-3.87 (m, H), 4.70-4.85 (m, 2H), 6.43-6.60 (m, H
, 6.86-6.93 (m, H), 7.17-7.31 (m, 5H), 8.46 (s, H). LC-MS (ESI) m/z 436.2 (M+H).

Compound 205: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.52-1.54 (d, 3H), 2.28 (s, 3H),
3.21-3.48 (m, 4H), 3.91 (m, 2H), 5.39-5.44 (m, H), 6.46-6.48 (m, H), 6.65-6.72 (m, H), 7.16-
7.43 (m, 5H), 8.22 (s, H).

Compound 206: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.34-1.38 (m, 3H), 2.88-3.06 (m,
2H), 3.72-3.73 (m, 2H), 3.82-3.95 (m, 2H), 4.58 (m, H), 4.76-4.88 (m, H), 5.49-5.50 (m, H),
6.87-6.97 (m, H), 7.03-7.09 (m, H), 7.14-7.35 (m, 8H), 8.33 (s, H).

Compound 207: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 0.80-0.82 (m, 2H), 1.01-1.21 (m,
2H), 1.61-1.74 (m, 3H), 1.79-1.90 (m, H), 2.95-3.04 (m, 2H), 3.94-4.06 (m, 2H), 4.78-4.89
30 (m, 2H), 5.31-5.38 (m, H), 7.24-7.35 (m, 5H), 8.37 (s, H). LC-MS (ESI) m/z 379.1 (M+H).

Compound 208: $^1\text{H-NMR}$ (300MHz, CDCl_3): δ 8.39 (s, 1H), 7.27~7.36 (m, 5H),
6.85 (m, 1H), 6.54~6.61 (m, 1H), 5.51~5.53 (m, 1H), 5.28~5.37 (m, 1H), 4.79~4.89 (m, 2H),
3.92~4.05 (m, 4H), 3.05 (m, 2H), 1.61 (d, 3H, 6.6 Hz). LC-MS (ESI) m/z 420.2 (M+H).

Compound 209: $^1\text{H-NMR}$ (300MHz, CDCl_3): δ 8.35 (s, 1H), 7.43~7.45 (m, 2H), 7.24 (m, 2H), 6.86~6.91 (m, 1H), 6.40~6.53 (m, 1H), 5.44 (m, 1H), 5.22~5.29 (m, 1H), 4.78~4.85 (m, 2H), 3.91~4.10 (m, 2H), 3.03~3.09 (m, 4H), 2.25 (s, 6H), 1.57 (d, 3H, $J = 6.0$ Hz). LC-MS (ESI) m/z 502.1 (M+H).

5 Compound 210: $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.33 (s, 1H), 7.31 (m, 6H), 6.98 (m, 3H), 6.49 (br, m, 1H), 6.11 (br, s, 1H), 5.58 (s, 1H), 4.85 (d, 2H), 6.22 (s, 2H), 3.77 (br, 4H), 3.08 (m, 4H), 2.29 (s, 6H). LC-MS (ESI) m/z 546.0 (M+H).

10 Compound 211: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 0.35-0.44 (m, 4H), 1.58-1.60 (m, 4H), 3.0-3.02 (m, 2H), 3.40-3.48 (m, 2H), 3.88-3.94 (m, 2H), 4.75-4.84 (m, 2H), 5.48-5.50 (m, H), 6.37-6.47 (m, H), 6.94-6.95 (m, H), 7.24-7.34 (m, 5H), 8.35 (s, H). LC-MS (ESI) m/z 434.2(M+H).

Compound 212: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.23-1.32 (m, 6H), 1.43-1.60 (m, 4H), 2.15-2.23 (m, 3H), 2.89-2.98 (m, 2H), 3.05-3.13 (m, 2H), 3.91-3.97 (m, 2H), 4.78-4.84 (m, H), 6.40-6.51 (m, H), 6.90-6.92 (m, H), 7.25-7.36 (m, H), 7.25-7.36 (m, 4H), 8.38 (s, H).

15 Compound 213: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.39-1.48 (m, 3H), 2.15-2.25 (m, 3H), 2.45-2.57 (m, 2H), 2.85-2.89 (m, 2H), 3.04-3.26 (m, 2H), 3.74-3.91 (m, 2H), 4.51-4.59 (m, 2H), 6.64-6.56 (m, H), 6.86-6.91 (m, H), 7.17-7.36 (m, 5H), 8.32 (s, H).

20 Compound 214: $^1\text{H-NMR}$ (300MHz, CDCl_3): δ 8.38 (s, 1H), 7.23~7.36 (m, 5H), 6.85~6.88 (m, 1H), 6.45~6.54 (m, 1H), 5.50~5.51 (m, 1H), 5.27~5.32 (m, 1H), 4.73~4.88 (m, 4H), 3.88~3.98 (m, 2H), 3.01~3.90 (m, 2H), 2.11 (s, 3H), 1.60 (d, 3H, $J = 5.2$ Hz). LC-MS (ESI) m/z 437.2 (M+H).

25 Compound 215: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 1.24-1.28 (m, 3H), 2.70-2.73 (m, 4H), 3.04-3.07 (m, 2H), 3.40-3.47 (m, 2H), 3.65-3.66 (m, 4H), 3.86-3.99 (m, 2H), 4.77-4.87 (m, 2H), 5.49-5.55 (m, H), 6.64-6.70 (m, H), 6.88-6.92 (m, H), 7.26-7.40 (m, 5H), 8.38 (s, H).

Compound 216: $^1\text{H-NMR}$ (300 MHz, CDCl_3): δ 1.05-1.07 (m, 3H), 1.61-1.63 (m, 3H), 2.52-2.64 (m, 3H), 2.72-3.05 (m, 2H), 3.33-3.46 (m, 2H), 3.63-3.64 (m, 2H), 3.91-3.98 (m, 2H), 4.79-4.87 (m, 2H), 5.51-5.53 (m, H), 6.44-6.57 (m, H), 6.92-7.24 (m, H), 7.27-7.37 (m, 5H) 8.38 (s, H).

30 Compound 217: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 0.92-0.94 (m, 3H), 1.28-1.44 (m, 2H), 1.85-1.92 (m, 2H), 2.26-2.31 (m, 6H), 3.10-3.13 (m, 3H), 3.94-3.99 (m, 2H), 4.78-4.86 (m, 2H), 5.37-5.41 (m, H), 6.43-6.58 (m, H), 6.88-6.92 (m, H), 7.24-7.34 (m, 5H), 8.34 (s, H).

Compound 218: ^1H NMR (300 MHz, CDCl_3): δ 8.28 (s, 1H), 7.24 (m, 9H), 6.92 (m, 1H), 6.76(m, 1H), 6.45 (m, 1H), 5.65(m, 1H), 4.81 (m, 2H), 4.53 (s, 2H), 6.63 (m, 4H), 3.12 (d, 2H, $J = 5.7$ Hz), 2.95 (br, 2H), 2.28 (s, 6h), 2.06 (br, 2H). LC-MS (ESI) m/z 560.3 (M+H).

5 Compound 219: ^1H NMR (300 MHz, CDCl_3): δ 8.32 (s, 1H), 7.29 (m, 7H), 7.99 (m, 3H), 6.46 (br, 1 H), 6.10 (br, NH), 5.56 (br, 1H), 4.52 (d, 2H, $J = 3.9$ Hz), 4.51 (s, 2H), 3.83 (m, 4H), 3.09 (m, 4H), 2.34 (s, 6H). LC-MS (ESI) m/z 546.1 (M+H).

10 Compound 220: ^1H NMR (300 MHz, CDCl_3): δ 8.32 (s, 1H), 7.30 (m, 6H), 6.99 (m, 3H), 6.32 (br, NH), 6.12 (d, 1H), 5.57 (br, 1H), 4.86 (m, 2H), 4.53 (s, 2H), 3.88 (br, 4H), 3.05 (br, 2H), 1.93 (d, 3H, $J = 4.8$ Hz). LC-MS (ESI) m/z 503.2 (M+H).

Compound 221: ^1H NMR (300 MHz, CDCl_3): δ 8.33 (s, 1H), 7.33 (m, 7H), 6.95 (m, 3H), 6.10 (m, 1H), 5.57 (m, 1H), 4.98 (s, 1H), 4.84 (s, 1H), 4.52 (m, 2H), 4.09 (m, 1H), 3.96 (m, 1H), 3.87 (m, 2H), 3.05 (m, 4H), 2.07 (s, 3H). LC-MS (ESI) m/z 501.2 (M+H).

15 Compound 222: ^1H NMR (300 MHz, CDCl_3): δ 8.48 (s, 1H), 7.23 (m, 7H), 8.87 (m, 6H), 6.56 (m, 1H), 6.35 (d, 1H, $J = 16.8$ Hz), 7.75 (d, 1H, $J = 9.6$ Hz), 5.15 (m, 1H), 4.90 (m, 2H), 4.65 (br, 2H), 4.55 (br, 2H), 4.36 (br, 2H), 3.71 (br, 2H), 3.06 (br, 2H). LC-MS (ESI) m/z 598.3 (M+H).

20 Compound 223: ^1H -NMR (400 MHz, CDCl_3): δ 2.70-2.80 (m, 2H), 3.63-3.69 (m, 2H), 3.76 (s, 3H), 3.77-3.91 (m, 2H), 4.48 (s, 2H), 4.79-4.87 (m, 2H), 5.78-5.81 (m, H), 6.16-6.18 (m, H), 6.33-6.40 (m, H), 6.56-6.60 (m,H), 6.79-6.83 (m,4H), 7.24-7.37 (m, 5H), 8.31 (s, H).

25 Compound 224: ^1H NMR (300 MHz, CDCl_3): δ 8.53 (d, 2H, $J = 5.4$ Hz), 8.35 (s, 1H), 7.32 (m, 5H), 7.10 (br, 2H), 6.94 (br m, 1H), 6.55 (br m, 1H), 6.04 (br m, 1H), 5.63 (br s, 1H), 4.86 (br m, 2H), 4.57 (m, 4H), 3.99 (br m, 4H), 3.08 (br, 4H), 2.12 9br s, 6H). LC-MS (ESI) m/z 529.2 (M+H).

Compound 225: ^1H -NMR (300MHz, CDCl_3): δ 8.36 (s, 1H), 7.23-7.30 (m, 1H), 6.95-7.06 (m, 4H), 6.56-6.59 (m, 1H), 6.33 (d, 1H, $J = 17.4$ Hz), 5.73 (d, 1H, $J = 10.2$ Hz), 5.59 (m, 1H), 4.72-4.85 m, 2H), 4.49 (s, 2H), 3.71-3.96 (m, 6H), 2.97 (t, 2H, $J = 5.7$ Hz).

Compound 226: LC-MS (ESI) m/z 516.0 $[\text{M} + 1]^+$.

30 Compound 227: ^1H -NMR (400 MHz, CDCl_3): δ 2.30 (s, 3H), 3.02 (m, 2H), 3.83-3.98 (m, 4H), 4.53 (s, 2H), 4.79-4.89 (m, 2H), 5.54-5.78 (m, H), 5.80-6.16 (m, H), 6.33-6.39 (m, H), 6.59-6.63 (m, H), 7.02-7.38 (m, 9H), 8.32 (s, H). LC-MS (ESI) m/z 485.2(M+H).

Compound 228: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 2.27 (s, 6H), 2.99-3.11 (m, 4H), 3.71 (s, 3H), 3.85-4.02 (m, 4H), 4.52 (s, H), 4.80-4.87 (m, 2H), 6.12-6.14 (m, H), 6.44-6.53 (m, H), 6.83-6.93 (m, H), 7.24-7.36 (m, 9H), 8.31 (s, H).

Compound 229: $^1\text{H-NMR}$ (400 MHz, CDCl_3) δ 2.28 (m, 6H), 3.13 (m, 4H), 3.40 (s, 3H), 3.79 (m, 2H), 3.97~4.09 (m, 2H), 4.82~4.89 (m, 2H), 5.54 (m, 1H), 6.04~6.13 (m, 1H), 6.45~6.58 (m, 1H), 6.91~6.95 (m, 1H), 7.24~7.40 (m, 5H), 8.33 (s, 1H); LCMS-ESI (m/z): 452.0 $[\text{M}+\text{H}]^+$.

Compound 230: $^1\text{H-NMR}$ (300 MHz, CDCl_3) δ 1.06 (t, 6H, $J = 6.9$ Hz), 2.53~2.57 (m, 4H), 3.15 (m, 2H), 3.30 (m, 2H), 3.40 (s, 3H), 3.72~3.80 (m, 2H), 3.97~4.07 (m, 2H), 4.82~4.88 (m, 2H), 5.55 (m, 1H), 6.05~6.14 (m, 1H), 6.47~6.61 (m, 1H), 6.95~7.00 (m, 1H), 7.24~7.40 (m, 5H), 8.33 (s, 1H); LCMS-ESI (m/z): 480.0 $[\text{M}+\text{H}]^+$.

Compound 231: $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.54 (m, 2H), 8.42 (s, 1H), 7.53 (d, 1H, $J = 7.5$ Hz), 7.29 (m, 6H), 6.91 (br, 1H), 6.45 (m, 1H), 6.06 (br, NH), 5.59 (br, 1H), 4.84 (m, 2H), 4.51 (s, 2H), 3.83 (m, 4H), 3.11 (m, 4H), 2.29 (s, 6H). LC-MS (ESI) m/z 529.1 (M+H).

Compound 232: $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.29 (s, 1H), 7.25 (m, 9H), 6.92 (br m, 1H), 6.45 (m, 1H), 6.19 (br, 1H), 5.58 (br s, 1H), 4.85 (br m, 2H), 4.60 (br s, 2H), 3.89 (br m, 4H), 3.08 (br m, 4H), 2.28 (s, 6h), 2.28 (br s, 6H). LC-MS (ESI) m/z 546.1 (M+H).

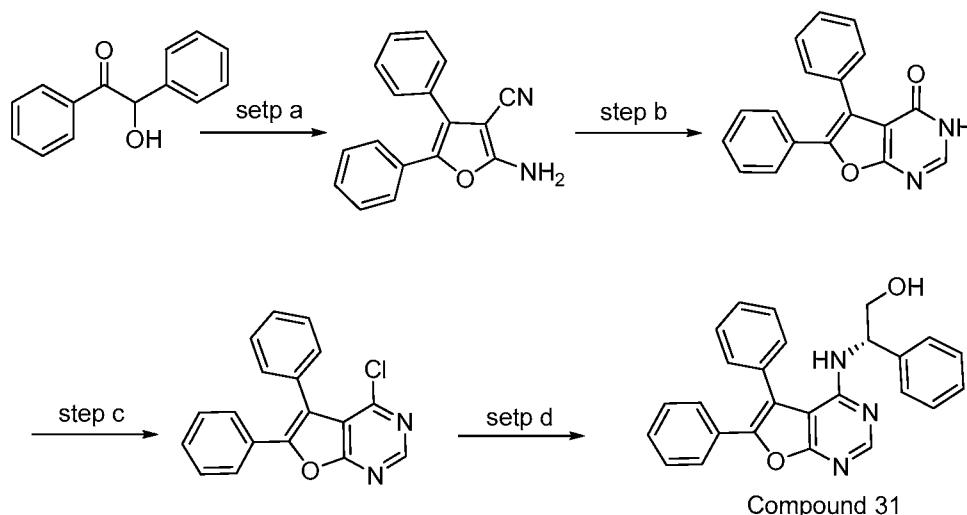
Compound 233: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.30 (s, H) 7.22-7.36 (m, 5H), 6.45-6.47(d, 1H), 5.44-5.41 (m, H), 4.09-3.89 (m, 4H), 3.26-3.29 (t, 2H), 3.06-3.09 (t, 2H), 0.82-0.84 (m, 15H).

Compound 234: $^1\text{H-NMR}$ (400 MHz, CDCl_3): δ 8.26 (1H, s), 7.36-7.03 (5H, m), 6.10 (1H, d, $J = 6.4\text{Hz}$), 5.90 (1H, t, $J = 3.6\text{Hz}$), 5.41(1H, q, $J = 4.0\text{Hz}$), 4.11-3.88 (4H, m), 3.15-3.01(2H, m) 2.99-2.13 (6H, m), 1.69-1.57 (4H, m).

Compound 235: $^1\text{H NMR}$ (400 MHz, CDCl_3): δ 8.30 (s, 1H), 7.28-7.38 (m, 5H), 5.99 (d, 1H, $J = 6.0$ Hz), 5.41 (t, 1H, $J = 4.8$ Hz), 4.79 (m, 2H), 3.96-4.02 (m, 2H), 3.82-3.85 (m, 2H), 3.09-3.16 (m, 2H), 2.48 (s, 1.8H), 2.45 (s, 1.2 H), LC-MS (ESI) m/z 397.0 $[\text{M}+\text{H}]^+$.

Compound 327: $^1\text{H NMR}$ (CDCl_3 , 400 MHz) δ 8.31 (s, 1H), 7.38 – 7.28 (m, 5H), 6.90 (d, $J = 10$ Hz, 1 H), 6.62 (t, $J = 16.8$ Hz, 1H), 6.02 (s, 1H), 5.39 (d, $J = 5.2$ Hz, 1H), 4.84 (d, $J = 16.8$ Hz, 2H), 4.00 (s, 3H), 3.93 (s, 2H), 3.62 (s, 1H), 3.47 (t, $J = 5$ Hz, 2H), 3.34 (d, $J = 5$ Hz, 4H), 3.23 (s, 2H), 2.57 (s, 2H), 2.31 (s, 3H). LCMS-ESI m/z 482.1 (M+H) $^+$.

Example 5: Synthesis of *S*-2-(5,6-diphenyl-furo[2,3-*d*]pyrimidin-4-ylamino)-2-phenyl-ethanol (Compound 31):



2-Amino-4,5-diphenylfuran-3-carbonitrile (step a): Diethylamine (13.8 g) was added dropwise over a period of 30 min to a mixture of benzoin (10 g) and malononitrile (3.8 g) in DMF (30 ml) at 0°C (the internal temperature should not exceed 40°C). After the resulting mixture was stirred at room temperature for 16 h, water (100 mL) was added. The resulting precipitate was filtered, washed with sufficient amount of water, then with hexanes, and dried. The solid was recrystallized from ethanol to provide yellowish-brown solid product of the title compound (6 g, 49%). ¹H NMR (300 MHz, CDCl₃): δ 7.47-7.34 (m, 8H), 7.28-7.18 (m, 2H), 4.94 (br, 2H). LC-MS (ESI) *m/z* 261.1 (M+H).

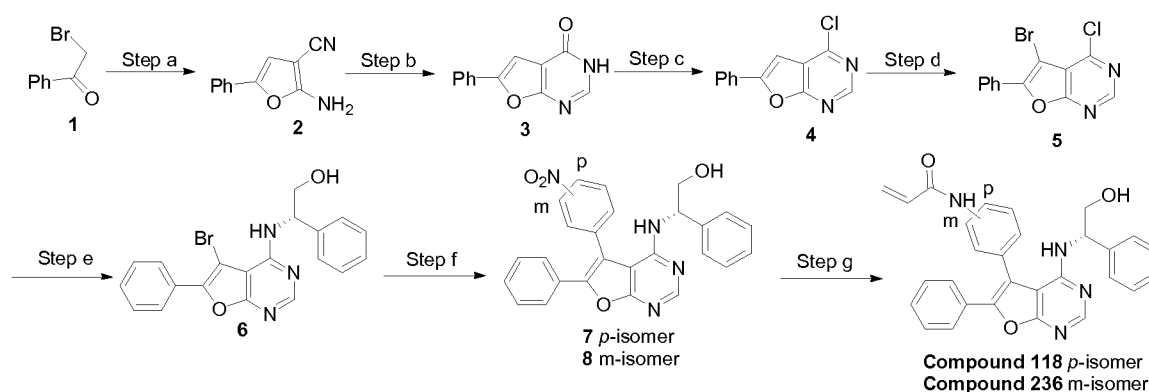
5,6-Diphenylfuro[2,3-*d*]pyrimidin-4(3*H*)-one (step b): A mixture of 2-amino-4,5-diphenylfuran-3-carbonitrile (2.0 g) and formic acid (24 mL) was cooled to 0°C and acetic anhydride (24 mL) was added dropwise. The resulting mixture was stirred for another 1 h and was then heated at 100°C for 16 h. The reaction mixture was cooled and water was added (40 mL). The precipitate was collected by filtration and washed thoroughly with water and hexanes to give the title compound (2.1 g, 95%). ¹H NMR (300 MHz, CDCl₃): δ 7.94 (s, 1H), 7.56-7.52 (m, 4H), 7.46-7.43 (m, 3H), 7.32-7.28 (m, 3H), 7.22 (s, 1H). LC-MS (ESI) *m/z* 289.1 (M+H).

4-Chloro-5,6-diphenylfuro[2,3-*d*]pyrimidine (step c): A mixture of 5,6-diphenylfuro[2,3-*d*]pyrimidin-4(3*H*)-one (3 g) and POCl₃ (30 mL) was heated at 55-65°C for 3 h. Water was then added followed by sodium bicarbonate. The resulting mixture was extracted with ethyl acetate. The organic layer was concentrated and the crude compound was purified by silica gel column chromatography using a mixture of hexanes:ethyl acetate

(95:5) to give the title compound as a white solid (2 g, 63%). ^1H NMR (300 MHz, CDCl_3): δ 8.77 (s, 1H), 7.61-7.58 (m, 2H), 7.52-7.46 (m, 5H), 7.35-7.32 (m, 3H). LC-MS (ESI) m/z 307.0 (M+H).

S-2-(5,6-Diphenyl-furo[2,3-*d*]pyrimidin-4-ylamino)-2-phenyl-ethanol (Compound 31, step d): A mixture of 4-chloro-5,6-diphenylfuro[2,3-*d*]pyrimidine (0.160 g) and *S*-2-amino-2-phenyl-ethanol (0.137 g, 2 eq) in *n*-butanol (5 mL) was heated at 80°C for 16 h. The reaction mixture was concentrated and the residue was partitioned between water and ethyl acetate. The organic layer was concentrated and the crude compound was purified by silica gel column chromatography using a mixture of dichloromethane:methanol (40:1) to give the title compound (0.140 g, 69%). ^1H NMR (300 MHz, CDCl_3): δ 8.31 (s, 1H), 7.50-7.47 (m, 2H), 7.45 (br s, 4H), 7.47-7.40 (m, 7H), 6.94 (m, 2H), 5.24(d, 1H, $J = 5.6\text{Hz}$), 5.16 (m, 1H), 3.72 (m, 2H). LC-MS (ESI) m/z 408.5 (M+H).

Example 6: Synthesis of *S*-N-(3-(4-(2-hydroxy-1-phenylethylamino)-6-phenylfuro[2,3-*d*]pyrimidin-5-yl)phenyl)acrylamide (Compound 236)



2-Amino-5-phenyl-furan-3-carbonitrile (2 from step a): 2 was prepared in 38% yield from 2-bromo acetophenone (1), similar to 2-amino-4,5-diphenylfuran-3-carbonitrile (see Example 5 above). ^1H NMR (300 MHz, CDCl_3) δ 7.50-7.47 (m, 2H), 7.39-7.33 (m, 2H), 7.27-7.25 (m, 1H), 6.54 (s, 1H), 4.86 (br, 2H). LCMS (ESI) m/z 185.0 (M+H) $^+$.

6-Phenyl-3H-furo[2,3-*d*]pyrimidin-4-one (3 from step b): 3 was prepared in 80% yield from 2, similar to 5,6-diphenylfuro[2,3-*d*]pyrimidin-4(3*H*)-one (see Example 5 above). ^1H NMR (300 MHz, CD_3OD) δ 9.00 (br, 1H), 8.36 (br, 1H), 7.67 (d, $J = 7.5\text{ Hz}$, 2H), 7.44-7.38 (m, 2H), 7.32-7.25 (m, 1H), 7.10 (s, 1H). LCMS (ESI) m/z 235.0 (M+Na) $^+$.

4-Chloro-6-phenyl-furo[2,3-*d*]pyrimidine (4 from step c): **4** was prepared in 94% yield from **3**, similar to 4-chloro-5,6-diphenylfuro[2,3-*d*]pyrimidine (see Example 5 above). ¹H NMR (300 MHz, CDCl₃) δ 8.75 (s, 1H), 7.93-7.89 (m, 2H), 7.55-7.26 (m, 3H), 7.09 (s, 1H). LCMS (ESI) *m/z* 231.0 (M+H)⁺.

5 **5-Bromo-4-chloro-6-phenyl-furo[2,3-*d*]pyrimidine (5 from step d):** *N*-Bromosuccinimide (1.16 g, 6.50 mmol) was added portion wise to 4-chloro-6-phenyl-furo[2,3-*d*]pyrimidine (**4**) (1.0 g, 4.33 mmol) in 20 mL DMF. After the resulting mixture was stirred at room temperature for 3 h, water (100 mL) was added. The resulting precipitate was filtered, washed with water, the crude compound was purified by silica gel column
10 chromatography using a mixture of ethyl acetate:*n*-hexane (1:10), to provide **5** (1.14 g, 85%). ¹H NMR (300 MHz, CDCl₃): δ 8.75 (s, 1H), 8.20-8.16 (m, 2H), 7.55-7.51 (m, 3H). LCMS (ESI) *m/z* 308.9 (M+H)⁺, 310.9 (M+2+H)⁺.

S-2-(5-Bromo-6-phenyl-furo[2,3-*d*]pyrimidin-4-ylamino)-2-phenyl-ethanol (6 from step e): 4-5-Bromo-4-chloro-6-phenyl-furo[2,3-*d*]pyrimidine (**5**) (0.2 g; 1 equiv) and
15 (*S*)-(+)-phenylglycinol (1.5 equiv) in *n*-butanol (5 mL) were heated at 80 °C for 16 h. The reaction mixture was concentrated and the residue was partitioned between water (50 mL) and ethyl acetate (3 × 50 mL). The organic layer was concentrated and the crude compound was purified by silica gel column chromatography using a mixture of
20 dichloromethane:methanol (40:1), to give 2-(5-bromo-6-phenyl-furo[2,3-*d*]pyrimidin-4-ylamino)-2-phenyl-ethanol (**6**) in 69% yield. ¹H NMR (300 MHz, CDCl₃): δ 8.30 (s, 1H), 8.07-8.02 (m, 2H), 7.51-7.30 (m, 8H), 6.89 (d, *J* = 6.9 Hz, 1H), 5.50-5.45 (m, 1H), 4.05 (d, *J* = 4.8 Hz, 2H), 3.39 (brs, 1H). LCMS (ESI) *m/z* 411.1 (M+H)⁺.

S-2-[5-(4-Nitro-phenyl)-6-phenyl-furo[2,3-*d*]pyrimidin-4-ylamino]-2-phenyl-ethanol (7 from step f): A mixture of **6** (410 mg, 1.0 mmol) and *p*-nitrobenzene boronic
25 acid (195 mg, 1.2 mmol), was dissolved in dioxane (2.0 mL) under nitrogen atmosphere. Added Pd(dppf)₂Cl₂ (4.2 mg, 0.05 mmol) and Na₂CO₃ solution (2 M, 1.0 mL) to this mixture and heated at 95 °C for 16 h under nitrogen. After completion, the reaction mixture was cooled to room temperature, added water and extracted with ethyl acetate (3 × 20 mL). Combined organics dried over NaSO₄, and concentrated under vacuum and the residue
30 obtained was purified over silica gel flash column chromatography using hexane:ethyl acetate = 1:1 to give **7** (346 mg, 77%). ¹H NMR (300 MHz, CDCl₃): δ 8.41 (s, 1H), 8.29 (d, *J* = 8.4 Hz, 2H), 7.67 (d, *J* = 8.4 Hz, 2H), 7.50-7.47 (m, 2H), 7.34-7.26 (m, 6H), 7.09-7.05 (m, 2H),

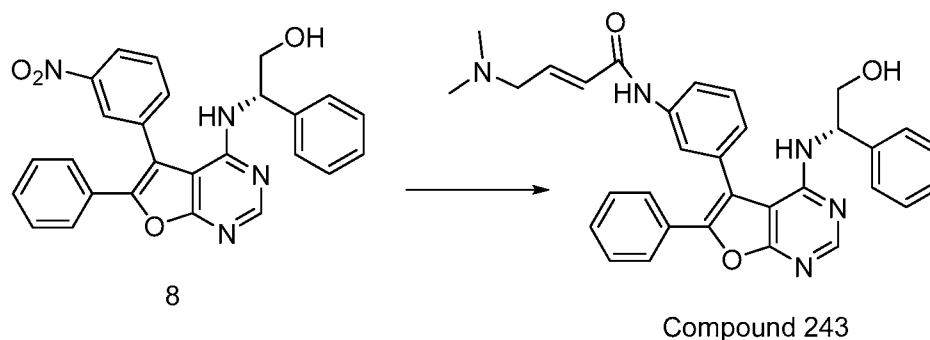
5.23 (dd, $J = 10.2, 5.4$ Hz, 1H), 5.16 (d, $J = 5.4$ Hz, 1H), 3.88-3.84 (m, 2H), 3.31 (t, $J = 5.4$ Hz, 1H). LC-MS (ESI) m/z 453.1 (M+H)⁺.

S-2-[5-(3-Nitro-phenyl)-6-phenyl-furo[2,3-*d*]pyrimidin-4-ylamino]-2-phenyl-ethanol (8 from step f): **8** was synthesized in 75% yield from **6**, in a manner similar to **7** using *m*-nitrobenzene boronic acid. ¹H NMR (300 MHz, CDCl₃): δ 8.41 (s, 2H), 8.30 (ddd, $J = 8.1, 1.2, 1.2$ Hz, 1H), 7.82 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.65 (dd, $J = 8.1, 7.8$ Hz, 1H), 7.50-7.47 (m, 2H), 7.34-7.26 (m, 6H), 7.11-7.07 (m, 2H), 5.27-5.20 (m, 2H), 3.88-3.84 (m, 2H), 3.31 (t, $J = 5.4$ Hz, 1H). LC-MS (ESI) m/z 453.1 (M+H)⁺.

S-N-{4-[4-(2-Hydroxy-1-phenyl-ethylamino)-6-phenyl-furo[2,3-*d*]pyrimidin-5-yl]-phenyl}-acrylamide (Compound 118 from step g): A mixture of **7** (136 mg, 0.3 mmol) and 5% Pd/C (10 mg) in EtOH (3 mL) was hydrogenated at atmospheric pressure for 16 h. Filtered the reaction mixture over celite, removed solvents under vacuum to give 2-[5-(4-amino-phenyl)-6-phenyl-furo[2,3-*d*]pyrimidin-4-ylamino]-2-phenyl-ethanol. To a mixture of the above compound and pyridine (0.05 mL, 0.6 mmol) in a solution of ether (3 mL), was added acryloyl chloride (0.03 mL, 0.33 mmol) and stirred the reaction mixture at room temperature for 16 h. Added water, and extracted with ethyl acetate (3 × 20 mL). Combined organics dried over MgSO₄, concentrated under vacuum and the residue purified over silica gel flash column chromatography using hexane:ethyl acetate = 2:3 to give Compound 118 (29 mg, 20%). ¹H NMR (300 MHz, CDCl₃) δ 8.33 (s, 1H), 8.00 (brs, 1H), 7.80-7.71 (m, 2H), 7.57 (d, $J = 8.4$ Hz, 2H), 7.47-7.44 (m, 3H), 7.30-7.19 (m, 5H), 7.07 (d, $J = 8.4$ Hz, 2H), 6.50 (d, $J = 16.8$ Hz, 1H), 6.32 (dd, $J = 16.8, 10.2$ Hz, 1H), 5.83 (d, $J = 10.2$ Hz, 1H), 5.45 (d, $J = 6.3$ Hz, 1H), 5.20-5.18 (m, 1H), 3.86-3.73 (m, 2H). LCMS (ESI) m/z 477.1 (M+H).

S-N-{3-[4-(2-Hydroxy-1-phenyl-ethylamino)-6-phenyl-furo[2,3-*d*]pyrimidin-5-yl]-phenyl}-acrylamide (Compound 236 from step g): Compound 236 was synthesized in 25% yield from **8**, in a manner similar to Compound 118. ¹H NMR (300 MHz, CDCl₃): δ 8.58 (brs, 1H), 8.27 (s, 1H), 7.79-7.64 (m, 2H), 7.49-7.46 (m, 2H), 7.40 (t, $J = 7.5$ Hz, 1H), 7.27-7.20 (m, 8H), 7.05-7.02 (d, $J = 7.5$ Hz, 2H), 6.46 (d, $J = 16.8$ Hz, 1H), 6.28 (dd, $J = 16.8, 10.2$ Hz, 1H), 5.73 (d, $J = 10.2$ Hz, 1H), 5.64 (d, $J = 6.0$ Hz, 1H), 5.30 (brs, 1H), 3.86 (dd, $J = 11.4, 2.7$ Hz, 1H), 3.69 (dd, $J = 11.4, 6.9$ Hz, 1H). HRMS (EI) calcd. for C₂₉H₂₄N₄O₃ 476.1848, found 476.1843.

Example 7: Synthesis of (*S,E*)-4-(dimethylamino)-*N*-(3-(4-(2-hydroxy-1-phenylethylamino)-6-phenylfuro[2,3-*d*]pyrimidin-5-yl)phenyl)but-2-enamide (Compound 243)



5 A mixture of **8** (1g, 0.002 mmol, see Example 6 above) and 5% Pd/C (10 mg) in MeOH (10 mL) was hydrogenated at 3atmospheric pressure for 8 h. Filtered the reaction mixture over celite, removed solvents under vacuum to give *S*-2-[5-(3-amino-phenyl)-6-phenyl-furo[2,3-*d*]pyrimidin-4-ylamino]-2-phenyl-ethanol. To a mixture of the above compound in DCM (5 mL), was added 4-bromocrotonic acid (422 mg, 2.55 mmol), EDCI
10 (490 mg, 2.55 mmol) and stirred the reaction mixture for 8 h. Then added *N,N*-dimethylamine (1.18ml, 23.2mmol) and continued stirring for 8 h at room temperature. Added water to the reaction mixture and extracted with dichloromethane (3 × 20 mL). Combined organics dried over MgSO₄, concentrated under vacuum and the residue purified over silica gel flash column chromatography using dichloromethane:methanol (20:1) to give
15 Compound 243 (370 mg, 30%).

¹H NMR (300 MHz, CDCl₃): δ 8.32 (s, 1H), 8.20 (brs, 1H), 7.78-7.73 (m, 2H), 7.54-7.51 (m, 2H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.27-7.18 (m, 7H), 7.05-7.02 (m, 2H), 6.94 (dt, *J* = 15.9, 6.0Hz, 1H), 6.14 (d, *J* = 15.9, 1H), 5.67 (d, *J* = 6.6 Hz, 1H), 5.34 (brs, 1H), 3.87 (dd, *J* = 11.4, 2.7 Hz, 1H), 3.67 (dd, *J* = 11.4, 6.9 Hz, 1H), 2.71 (brs, 1H), 2.25 (s, 6H). LC-MS
20 (ESI) *m/z* 534.1 (M+H).

Example 8: Syntheses of Compounds 32-58, 237-242, 244, and 247

Compounds 32-58, 237-242, 244, and 247 were prepared in a manner described in Example 5, 6, or 7. ¹H NMR and MS data of these compounds are listed below.

25 Compound 32: ¹H NMR (300 MHz, CDCl₃): δ 8.39 (s, 1H), 7.58-7.26 (m, 13H), 6.99 (m, 2H), 5.35(d, 1H, *J* = 6.3 Hz), 5.26 (m, 1H), 3.80 (m, 2H). LC-MS (ESI) *m/z* 408.1 (M+H).

Compound 33: LC-MS (ESI) *m/z* 422.1 (M+H)⁺.

Compound 34: LC-MS (ESI) m/z 422.2 (M+H)⁺.

Compound 35: ¹H NMR (300 MHz, CDCl₃): δ 8.37 (s, 1H), 7.58 (m, 2H), 7.35-7.26 (m, 8H), 5.19 (dd, 1H, $J_1 = 5.7$ Hz, $J_2 = 10.5$ Hz), 3.86 (s, 3H), 3.80 (dd, 2H, $J_1 = 4.5$ Hz, $J_2 = 10.8$ Hz). LC-MS (ESI) m/z 438.7 (M+H).

5 Compound 36: ¹H NMR (300 MHz, CDCl₃): δ 8.35 (s, 1H), 7.50 (m, 2H), 7.33-7.26 (m, 7H), 7.03 (m, 2H), 6.81 (m, 2H), 5.31 (d, 1H, $J = 5.7$ Hz), 5.17 (dd, 1H, $J_1 = 5.4$ Hz, $J_2 = 10.2$ Hz), 3.85 (s, 3H), 3.81 (m, 2H), 3.76 (s, 3H). LC-MS (ESI) m/z 468.4 (M+H).

10 Compound 37: ¹H NMR (300 MHz, CDCl₃): δ 8.35 (s, 1H), 7.57 (m, 3H), 7.45 (d, 2H, $J = 7.5$ Hz), 7.32-7.26 (m, 6H), 7.07 (m, 3H), 5.41 (d, 1H, $J = 6.3$ Hz), 5.20 (dd, 1H, $J_1 = 6.3$ Hz, $J_2 = 9.3$ Hz), 3.78 (m, 2H), 2.25 (s, 3H). LC-MS (ESI) m/z 465.7 (M+H).

Compound 38: ¹H NMR (300 MHz, CDCl₃): δ 8.28 (s, 1H), 7.65 (m, 2H), 7.49 (m, 2H), 7.40 (t, 1H, $J = 8.4$ Hz), 7.26-7.15 (m, 7H), 7.05 (m, 2H), 5.61 (d, 1H, $J = 6.0$ Hz), 5.30 (br, 1H), 3.84 (m, 1H), 3.70 (dd, 1H, $J_1 = 6.3$ Hz, $J_2 = 10.8$ Hz), 2.14 (s, 3H). LC-MS (ESI) m/z 465.7 (M+H).

15 Compound 39: ¹H NMR (300 MHz, CDCl₃): δ 8.36 (s, 1H), 7.59 (m, 2H), 7.49 (m, 2H), 7.36-7.26 (m, 7H), 7.10 (m, 2H), 6.05 (s, 2H), 5.46 (d, 1H, $J = 5.1$ Hz), 5.21 (dd, 1H, $J_1 = 5.4$ Hz, $J_2 = 10.5$ Hz), 3.85 (d, 2H, $J = 6.8$ Hz). LC-MS (ESI) m/z 452.6 (M+H).

20 Compound 40: ¹H NMR (300 MHz, CDCl₃): δ 8.38 (s, 1H), 7.28 (m, 2H), 7.42-7.26 (m, 8H), 6.88 (d, 1H, $J = 6.0$ Hz), 6.49 (m, 2H), 5.35 (dd, 1H, $J_1 = 3.9$ Hz, $J_2 = 15$ Hz), 3.99 (dd, 2H, $J_1 = 7.5$ Hz, $J_2 = 11.4$ Hz). LC-MS (ESI) m/z 398.6 (M+H).

Compound 41: ¹H NMR (300 MHz, CDCl₃): δ 8.36 (s, 1H), 7.68 (m, 2H), 7.62 (m, 2H), 7.38-7.28 (m, 6H), 7.26 (m, 2H), 6.54 (m, 1H), 5.75 (d, 1H, $J = 6.3$ Hz), 5.30 (q, 1H, $J = 5.4$ Hz), 3.89 (m, 2H). LC-MS (ESI) m/z 398.7 (M+H).

25 Compound 42: ¹H NMR (300 MHz, CDCl₃): δ 8.35 (s, 1H), 7.78 (m, 2H), 7.46-7.33 (m, 8H), 6.87 (s, 1H), 5.38 (d, 1H, $J = 5.7$ Hz), 4.08 (d, 2H, $J = 5.1$ Hz). LC-MS (ESI) m/z 332.6 (M+H).

Compound 43: ¹H NMR (300 MHz, CDCl₃): δ 8.32 (s, 1H), 8.06 (m, 2H), 7.52-7.26 (m, 8H), 6.90 (d, 1H, $J = 7.2$ Hz), 5.48 (m, 1H), 4.05 (m, 2H). LC-MS (ESI) m/z 411.1 (M+H).

30 Compound 44: ¹H NMR (300 MHz, CDCl₃): δ 8.35 (s, 1H), 8.07 (m, 2H), 7.52-7.26 (m, 8H), 5.79 (m, 1H), 4.57 (dd, 1H, $J_1 = 7.2$ Hz, $J_2 = 11.7$ Hz), 4.45 (dd, 1H, $J_1 = 4.8$ Hz, $J_2 = 11.4$ Hz). LC-MS (ESI) m/z 452.0 (M+H).

Compound 45: ¹H NMR (300 MHz, CDCl₃): δ 8.35 (s, 1H), 8.06 (m, 2H), 7.53-7.26

(m, 8H), 6.65 (d, 1H, $J = 7.2$ Hz), 5.48 (m, 1H), 4.07 (m, 2H), 3.03 (br, 1H). LC-MS (ESI) m/z 366.5 (M+H).

Compound 46: ^1H NMR (300 MHz, CDCl_3): δ 8.40 (s, 1H), 7.60-7.57 (m, 6H), 7.33-7.21 (m, 9H), 5.84 (d, 1H, $J = 9.0$ Hz), 5.71 (d, 1H, $J = 6.6$ Hz), 3.68 (s, 3H). LC-MS (ESI) m/z 436.2 (M+H).

Compound 47: LC-MS (ESI) m/z 450.6 (M+H)⁺.

Compound 48: LC-MS (ESI) m/z 464.2 (M+H)⁺.

Compound 49: LC-MS (ESI) m/z 478.2 (M+H)⁺.

Compound 50: ^1H NMR (300 MHz, $\text{CDCl}_3 + \text{CD}_3\text{OD}$): δ 8.19 (s, 1H), 7.44-7.42 (m, 7H), 7.24-7.17 (m, 8H), 5.55 (s, 1H). LC-MS (ESI) m/z 422.1 (M+H).

Compound 51: LC-MS (ESI) m/z 421.2 (M+H)⁺.

Compound 52: LC-MS (ESI) m/z 480.0 (M+H)⁺.

Compound 53: LC-MS (ESI) m/z 424.0 (M+H)⁺.

Compound 54: LC-MS (ESI) m/z 406.5 (M+H)⁺.

Compound 55: LC-MS (ESI) m/z 406.6 (M+H)⁺.

Compound 56: ^1H NMR (300 MHz, CDCl_3): δ 8.36 (s, 1H), 7.32 (d, 2H, $J = 7.8$ Hz), 7.42-7.24 (m, 8H), 6.83 (s, 1H), 5.73 (br, 1H), 5.21 (d, 1H, $J = 7.2$ Hz), 1.99 (m, 2H), 1.00 (t, 3H, $J = 7.5$ Hz). LC-MS (ESI) m/z 330.1 (M+H)⁺.

Compound 57: ^1H NMR (300 MHz, CDCl_3): δ 8.35 (s, 1H), 8.03 (m, 2H), 7.51-7.44 (m, 2H), 7.42-7.34 (m, 5H), 7.31-7.34 (m, 1H), 6.17 (d, 1H, $J = 7.8$ Hz), 6.35 (q, 1H, $J = 7.8$ Hz), 2.01 (m, 2H), 0.99 (t, 3H, $J = 7.5$ Hz). LC-MS (ESI) m/z 363.9 (M+H)⁺.

Compound 58: LC-MS (ESI) m/z 310.1 (M+H)⁺.

Compound 237: ^1H NMR (300 MHz, CDCl_3): δ 8.34 (s, 1H), 7.53 (m, 4H), 7.41 (m, 3H), 7.27 (m, 7H), 7.15 (m, 2H), 6.96 (m, 1H), 6.85 (d, 1H, $J = 7.5$ Hz), 6.77 (d, $J = 9.6$ Hz), 5.55 (m, 1H), 5.46 (m, 1H), 4.34 (d, 2H, $J = 5.4$ Hz), 3.67 (m, 1H), 3.54 (m, 1H). LC-MS (ESI) m/z 516.2 (M+H).

Compound 238: ^1H NMR (300 MHz, CDCl_3): δ 8.38 (s, 1H), 7.85-7.70 (m, 3H), 7.75-7.44 (m, 3H), 7.29-7.20 (m, 6H), 7.12 (d, $J = 6.9$ Hz, 2H), 6.52 (d, $J = 16.8$ Hz, 1H), 6.34 (dd, $J = 16.8, 9.9$ Hz, 1H), 5.85 (d, $J = 9.9$ Hz, 1H), 5.87-5.82 (m, 1H), 4.99 (d, $J = 7.8$ Hz, 1H), 1.38 (d, $J = 6.9$ Hz, 3H). LC-MS (ESI) m/z 461.2 (M+H).

Compound 239: ^1H NMR (300 MHz, CDCl_3): δ 8.38 (s, 1H), 7.96-7.91 (m, 1H), 7.55-7.47 (m, 5H), 7.29-7.18 (m, 6H), 7.12 (d, $J = 6.6$ Hz, 2H), 6.46 (d, $J = 16.8$ Hz, 1H),

6.23 (dd, $J = 16.8, 10.2$ Hz, 1H), 5.80 (d, $J = 10.2$ Hz, 1H), 5.36-5.28 (m, 1H), 5.04 (d, $J = 7.5$ Hz, 1H), 1.38 (d, $J = 6.6$ Hz, 3H). LC-MS (ESI) m/z 461.2 (M+H).

Compound 240: ^1H NMR (300 MHz, CDCl_3): δ 8.36 (s, 1H), 8.11 (brs, 1H), 7.57-7.47 (m, 4H), 7.30-7.21 (m, 8H), 7.08-7.06 (m, 2H), 6.47 (d, $J = 16.8$ Hz, 1H), 6.28 (dd, $J = 16.8, 8.1$ Hz, 2H), 5.99 (dd, $J = 16.8, 10.2$ Hz, 1H), 5.82-5.77 (m, 2H), 5.33 (d, $J = 8.4$ Hz, 1H), 4.50 (brs, 1H), 4.30-4.20 (m, 1H). LC-MS (ESI) m/z 531.0 (M+H).

Compound 241: ^1H NMR (300 MHz, CDCl_3): δ 8.37 (s, 1H), 7.67-7.64 (m, 2H), 7.56-7.52 (m, 3H), 7.42 (t, $J = 7.8$ Hz, 1H), 7.29-7.22 (m, 7H), 7.07-7.04 (m, 2H), 5.48-5.47 (m, 1H), 5.30-5.29 (m, 1H), 3.88-3.75 (m, 3H), 2.01 (s, 3H). LC-MS (ESI) m/z 489.1 (M+H).

Compound 242: ^1H NMR (300 MHz, CDCl_3): δ 8.35 (s, 1H), 7.76-7.73 (m, 2H), 7.61-7.21 (m, 11H), 7.06-7.03 (m, 2H), 5.54-5.53 (m, 1H), 5.00-4.97 (m, 1H), 4.04-4.02 (m, 2H), 3.49 (s, 3H), 2.28 (s, 3H). LC-MS (ESI) m/z 503.1 (M+H).

Compound 244: ^1H NMR (300 MHz, CDCl_3): δ 8.24 (s, 1H), 8.04 (s, 1H), 7.65 (d, $J = 8.4$ Hz, 1H), 7.50-7.29 (m, 9H), 7.00 (brs, 1H), 6.48 (d, $J = 16.8$ Hz, 1H), 6.38 (dd, $J = 16.8, 9.6$ Hz, 1H), 5.78 (d, $J = 9.6$ Hz, 1H), 5.38 (brs, 1H), 4.03-3.97 (m, 2H), 2.32 (s, 1H). LC-MS (ESI) m/z 401.0 (M+H).

Compound 247: ^1H -NMR (400 MHz, CDCl_3): δ 2.24 (s, 3H), 3.44 (s, 3H), 3.79-3.83 (m, H), 3.99-4.01 (m, H), 5.77-5.80 (d, H), 6.19-6.30 (m, H), 6.39-6.47 (d, 2H), 7.03-7.48 (m, 10H), 8.46 (s, H).

Example 9: Inhibiting EGFR kinase activity

The EGFR kinase assay was carried out in a 96-well plate at 37 °C for 60 min with a 50 μl mixture including the following components: 50 ng GST-EGFR-KD^{WT} proteins, 25 mM Tris-HCl, pH 7.5, 4 mM MnCl_2 , 2 mM DTT, 10 mM MgCl_2 , 0.1 mg/ml bovine serum albumin, 10 μM poly(Glu,Tyr) 4:1, 0.5 mM Na_3VO_4 , 5 μM ATP and a test compound. Following incubation, 50 μl Kinase-Glo Plus Reagent (Promega) was added and the mixture was further incubated at 25 °C for 20 min. A 70 μl aliquot of each reaction mixture was transferred to a black microtiter plate and the luminescence was measured on Wallac Vector 1420 multilabel counter (PerkinElmer).

GST-EGFR-KD^{WT} protein expression and purification were done in a manner as set forth in Analytical Biochemistry 377 (2008) 89–94.

Compounds 1-68, 75, 106, 107, 118, 154, 176, 178, 180, 181, 183-247, and 327 were tested in this assay. Unexpectedly, Compounds 1, 7, 8, 15, 18, 20, 22, 23, 31, 35, 38-43, 45, 61, 154, 181, 188, 192, 204, 206, 238-240, 242, and 247 showed IC₅₀ values (i.e., the concentration of a test compound at which activity of 50% of EGFR is inhibited) between 101 nM and 0.9 μM; Compounds 36, 37, 63, 118, 186, 220, 230, and 244 showed IC₅₀ values between 60 and 100 nM; and Compounds 12, 50, 53, 62, 64-67, 75, 106, 107, 176, 178, 185, 187, 190, 191, 193-195, 198-200, 202, 203, 205, 208-219, 223, 224, 226-229, 231-233, 236, 241, 243, 245, 246, and 327 and showed IC₅₀ values lower than 59 nM.

10 Example 10: In vitro anticancer activity

HCC827 cell viability was examined by the MTS assay (Promega, Madison, WI, USA). 1000 HCC827 cells in 100 μl RPMI1640 with 10 % FBS medium were seeded in each well of a 96-well plate. After 96-h incubation with a test compound, the cells were further incubated with 20 μl of a MTS/PMS mixture (MTS/PMS ratio: 20:1) in each well of the 96-well plate for 2 h at 37 °C in a humidified incubator with 5% CO₂ to allow viable cells to convert the tetrazolium salt (MTS) into formazan. The amount/concentration of formazan, which indicates the number of live cells, was determined by measuring its absorbance at 490 nm using a PerkinElmer Victor2 plate reader (PerkinElmer, Shelton, CT, USA).

20 Based on the test results in Example 9, only Compounds 1, 3-5, 7-8, 12, 15, 23, 31, 35, 37-51, 53, 54, 56, 62-68, 75, 106, 107, 118, 176, 178, 181, 185-188, 190-195, 198, 200, 202-206, 208-219, 223, 224, 226-232, 236, 238, 239, 241, and 243-246 were tested in this assay. Unexpectedly, Compounds 3, 4, 15, 23, 31, 40, 42, 44, 46, 47, 54, 56, 118, 186, 188, 193, 206, and 244 showed IC₅₀ values (i.e., the concentration of a test compound which causes 50% of the cell death) between 301 nM and 999 nM; Compounds 1, 35, 37-39, 41, 63, 202, and 245 showed IC₅₀ values between 100 nM and 300 nM; and Compounds 12, 62, 64-68, 75, 106, 107, 176, 178, 181, 185, 187, 190-192, 194, 195, 198, 200, 203-205, and 208-219, 223, 224, 226-232, 236, 238, 239, 241, 243, and 246 showed IC₅₀ values between 1 nM, and 99 nM.

30

Example 11: Double mutant EGFR kinase assay

GST-EGFR-KD^{L858RT/790M} containing the EGFR kinase catalytic domain (residues from 696 to 1022 and with L858R/T790M) were expressed in Sf9 insect cells transfected

with the baculovirus containing pBac-PAK8-GST-EGFR-KD^{L858RT/790M} plasmid. GST-EGFR-KD^{L858RT/790M} protein expression and purification were done in a manner similar to that reported earlier (Analytical Biochemistry 377 (2008) 89–94).

The EGFR^{L858RT/790M} Kinase-Glo assays were carried out in 96-well plates at
5 37 °C for 60 min in a final volume of 50 µL including the following components: 200 ng
GST-EGFR-KD^{L858R/T790M} proteins, 25 mM HEPES, pH 7.4, 4 mM MnCl₂, 2 mM DTT, 10
mM MgCl₂, 0.1 mg/ml bovine serum albumin, 10 µM poly(Glu,Tyr) 4:1, 0.5 mM Na₃VO₄, 1
µM ATP, and a test compound. Following incubation, 50 µL Kinase-Glo Plus Reagent
(Promega) was added and the mixture was incubated at 25 °C for 20 min. A
10 70 µL aliquot of each reaction mixture was transferred to a black microtiter plate and the
luminescence was measured on Wallac Vector 1420 multilabel counter (PerkinElmer).

Compounds 9, 11-16, 36, 59-68, 75, 106, 107, 118, 154, 176, 178, 180, 181, and 183-
236, 238-241, 243, 245-247, and 327 were tested in this assay. Unexpectedly, Compounds
63-67, 75, 106, 178, 188, 190, 191, 193, 198, 203, 205, 211, 215, 228, 232, 239, and 241
15 showed IC₅₀ values (i.e., the concentration of a test compound at which activity of 50% of
mutant EGFR is inhibited) between 500 nM and 2.5 µM; and Compounds 12, 62, 176, 185,
187, 195, 200, 202, 210, 223, 226, 227, 236, 240, and 243 showed IC₅₀ values between 10
nM and 499 nM.

20 Example 12: In vivo anticancer activity

In vivo efficacy of the compounds of this invention was assessed using lung cancer
xenograft mice (injected with HCC827), as described in Cancer Research 2004, 64, 4621-
4628.

HCC827 cells were injected via s.c. in nude mice to form lung cancer xenograft mice.
25 Mice bearing tumor with a size of ~100 mm³ were randomly assigned to two groups: a
vehicle control group (10 mice), and a treatment group (21 mice). Of the treated mice, 21
received Compound 62 at a daily dosage of 5 mg/kg and 15 mg/kg via IV injection through
the tail veins for 5 days/week for 2 consecutive weeks (days 1-5 and 8-12).

Unexpected, at the dosage of 5 and 15 mg/kg, Compound 62 suppressed tumor
30 growth significantly ($p < 0.05$), indicating its potent in vivo anti-cancer activity. Upon
treatment with this compound, the tumor size was 39% (5 mg/kg) or 23% (15 mg/kg) of that
of the vehicle controls at the end of the observation period on the 22nd day post treatment.

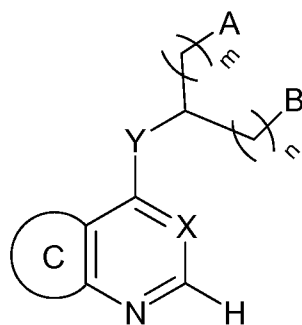
OTHER EMBODIMENTS

All of the features disclosed in this specification may be combined in any combination. Each feature disclosed in this specification may be replaced by an alternative feature serving the same, equivalent, or similar purpose. Thus, unless expressly stated
5 otherwise, each feature disclosed is only an example of a generic series of equivalent or similar features.

From the above description, one skilled in the art can easily ascertain the essential characteristics of the present invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various
10 usages and conditions. Thus, other embodiments are also within the scope of the following claims.

WHAT IS CLAIMED IS:

1. A compound of formula (I):



(I)

wherein

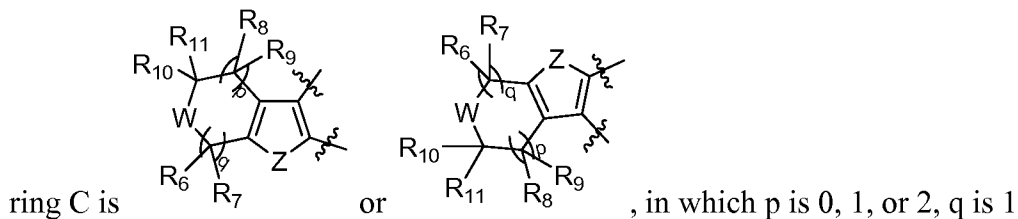
X is N or CR₁, in which R₁ is CN, CONH₂, halo, or H;

Y is O, S, or NR₂, in which R₂ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

A is alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR₃, OC(O)R₃, C(O)R₃, C(O)OR₃, C(O)NR₃R₄, NR₃R₄, NHC(O)R₃, NHC(O)NR₃R₄, NHC(S)R₃, NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄, in which each of R₃ and R₄, independently, is H, alkyl, alkenyl, alkynyl, silyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R₃ and R₄, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl;

B is aryl or heteroaryl;

each of m and n, independent, is 0, 1, or 2; and

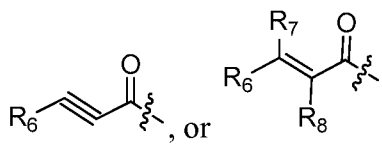
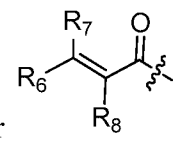


or

, in which p is 0, 1, or 2, q is 1 or 2, Z is O, S, or NH, W is CH₂ or NR₅, in which R₅ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, C(O)R_a, C(O)C(O)R_a, C(O)OR_a, C(O)NR_aR_b, or SO₂R_a, in which each of R_a and R_b, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_a and R_b, together with the nitrogen

atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, and each of R₆, R₇, R₈, R₉, R₁₀, and R₁₁, independently, is H, alkyl, or halo.

2. The compound of claim 1, wherein W is NR₅, in which R₅ is SO₂R_a,


 , or 
 , in which each of R₆ and R₇, independently, is H, alkyl optionally substituted with alkylamino, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, C(O)R_c, C(O)OR_c, C(O)NR_cR_d, or CH₂NR_cR_d, in which each of R_c and R_d, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_c and R_d, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, and R₈ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl.

3. The compound of any preceding claim, wherein B is phenyl and n is 0.

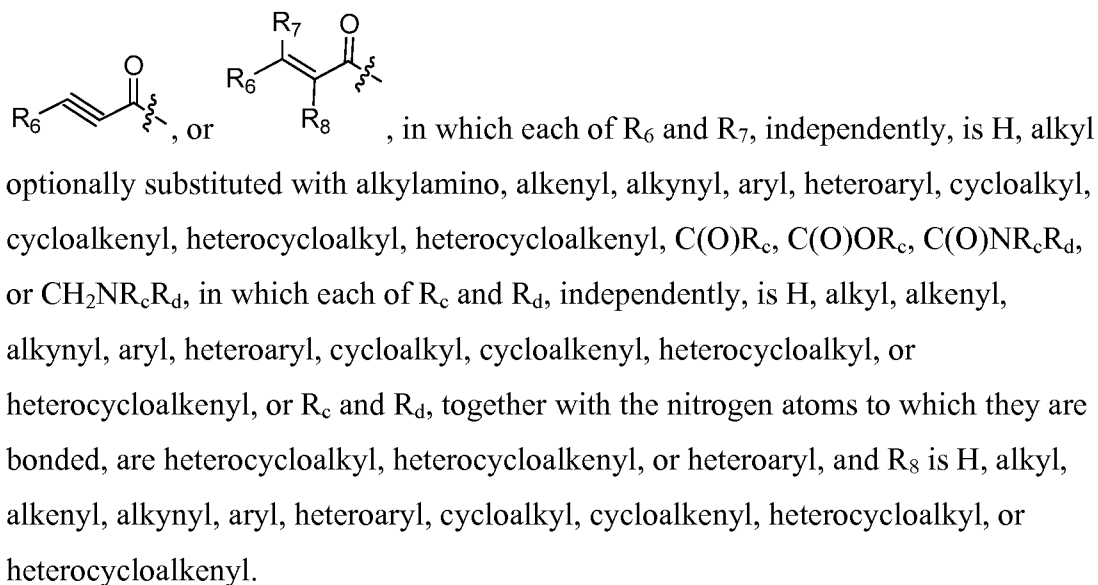
4. The compound of any preceding claim, wherein m is 1 and A is OR₃, R₃ being H, aryl, heteroaryl, or C₁₋₃ alkyl optionally substituted with aryl or heteroaryl.

5. The compound of any preceding claim, wherein X is N, Y is NH, and Z is S.

6. The compound of any preceding claim, wherein A is C(O)OR₃ and m is 0.

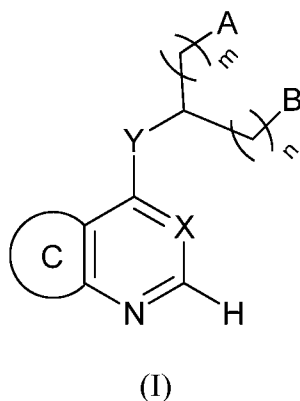
7. The compound of any preceding claim, wherein W is CH₂.

8. The compound of claim 1, wherein W is NR₅, in which R₅ is SO₂R_a,



9. The compound of claim 1, wherein the compound is Compound 12, 62, 210, or 249.

10. A compound of formula (I):



wherein

X is N or CR₁, in which R₁ is CN, CONH₂, halo, or H;

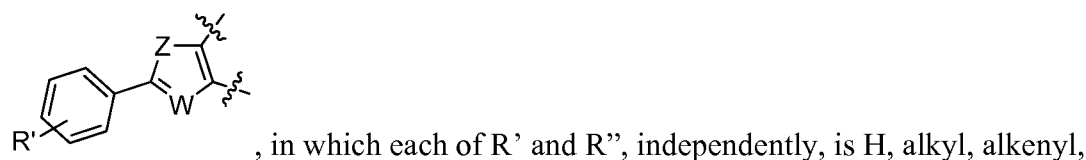
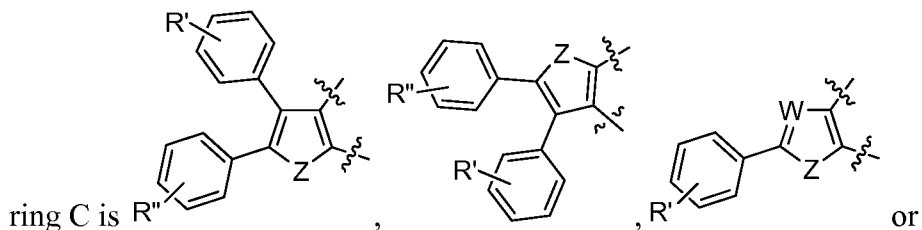
Y is O, S, or NR₂, in which R₂ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

A is alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR₃, OC(O)R₃, C(O)R₃, C(O)OR₃, C(O)NR₃R₄, NR₃R₄, NHC(O)R₃, NHC(O)NR₃R₄, NHC(S)R₃, NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄, in which each of R₃ and R₄, independently, is H, alkyl, alkenyl, alkynyl, silyl, aryl, heteroaryl, cycloalkyl,

cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R₃ and R₄, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl;

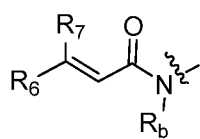
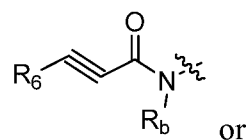
B is aryl or heteroaryl;

each of m and n, independently, is 0, 1, or 2; and



heterocycloalkenyl, halo, nitro, cyano, OR_a, OR_aO, C(O)OR_a, C(O)NR_aR_b, NR_bC(O)R_a, NHC(O)NR_aR_b, NR_bC(S)R_a, NHSO₂R_a, or NR_aR_b, in which each of R_a and R_b, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_a and R_b, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, Z is O or NH, provided that at most one of R' and R'' is H, and W is N or CR₅, in which R₅ is alkenyl, alkynyl, aryl substituted with OR_a, OR_aO, or NR_bC(O)R_a, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, nitro, C(O)OR_a, C(O)NR_aR_b, NR_bC(O)R_a, NHC(O)NR_aR_b, NR_bC(S)R_a, NHSO₂R_a, or NR_aR_b.

11. The compound of claim 10, wherein R' is



, in which R₆ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, C(O)R_c, C(O)OR_c, C(O)NR_cR_d, or CH₂NR_cR_d, in which each of R_c and R_d, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_c and R_d, together with the nitrogen atoms to which they are

bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, and R₇ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl.

12. The compound of claim 10, wherein each of R' and R'', independently, is OR_a.

13. The compound of any of claims 10-12, wherein B is phenyl and n is 0.

14. The compound of any of claims 10-13, wherein m is 1 and A is OR₃, R₃ being H, aryl, heteroaryl, or C₁₋₃ alkyl optionally substituted with aryl or heteroaryl.

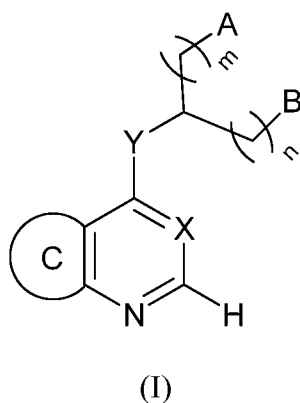
15. The compound of any of claims 10-13, A is C(O)OR₃ and m is 0.

16. The compound of any of claims 10-15, wherein X is N, Y is NH, and Z is O.

17. The compound of any of claims 10-16, wherein W is CR₅, in which R₅ is halo.

18. The compound of claim 10, wherein the compound is Compound 236 or 243.

19. A compound of formula (I):



wherein

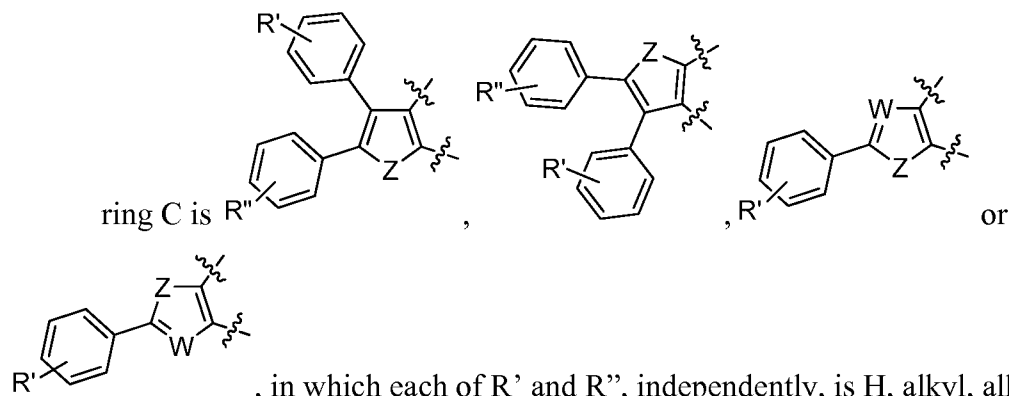
X is N or CR₁, in which R₁ is CN, CONH₂, halo, or H;

Y is O, S, or NR₂, in which R₂ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

A is alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OC(O)R₃, C(O)R₃, C(O)OR₃, C(O)NR₃R₄, NR₃R₄, NHC(O)R₃, NHC(O)NR₃R₄, NHC(S)R₃, NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄, in which each of R₃ and R₄, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R₃ and R₄, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl;

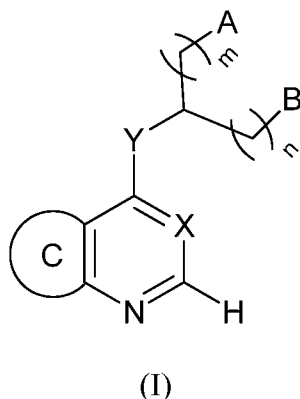
B is aryl or heteroaryl;

each of m and n, independently, is 0, 1, or 2; and



, in which each of R' and R'', independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, nitro, cyano, OR_a, OR_aO, C(O)OR_a, C(O)NR_aR_b, NR_bC(O)R_a, NHC(O)NR_aR_b, NR_bC(S)R_a, NHSO₂R_a, or NR_aR_b, in which each of R_a and R_b, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_a and R_b, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, Z is O or NH, and W is N or CR₅, in which R₅ is alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, nitro, C(O)OR_a, C(O)NR_aR_b, NR_bC(O)R_a, NHC(O)NR_aR_b, NR_bC(S)R_a, NHSO₂R_a, or NR_aR_b.

20. A compound of formula (I):



wherein

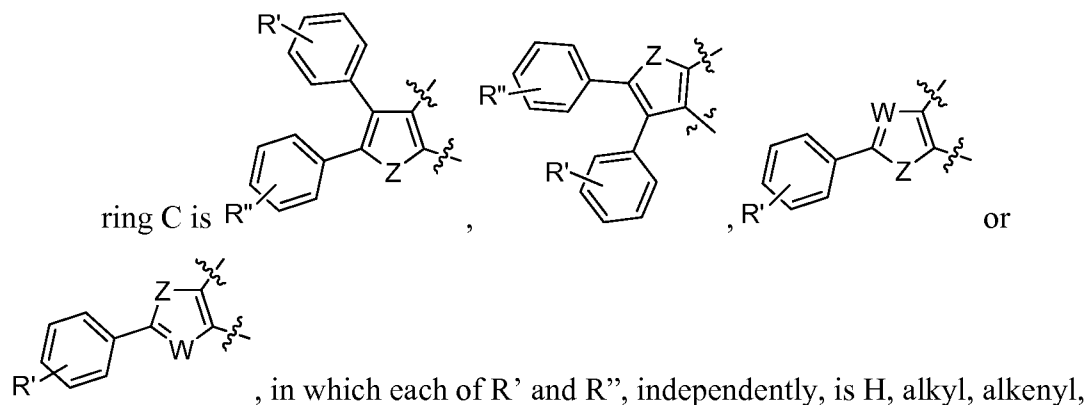
X is N or CR₁, in which R₁ is CN, CONH₂, halo, or H;

Y is O, S, or NR₂, in which R₂ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

A is alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR₃, OC(O)R₃, C(O)R₃, C(O)OR₃, C(O)NR₃R₄, NR₃R₄, NHC(O)R₃, NHC(O)NR₃R₄, NHC(S)R₃, NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄, in which each of R₃ and R₄, independently, is H, alkyl, alkenyl, alkynyl, silyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R₃ and R₄, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl when X is N, and A is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR₃, OC(O)R₃, C(O)R₃, C(O)OR₃, C(O)NR₃R₄, NR₃R₄, NHC(O)R₃, NHC(O)NR₃R₄, NHC(S)R₃, NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄ when X is CR₁;

B is aryl or heteroaryl;

each of m and n, independently, is 0, 1, or 2; and

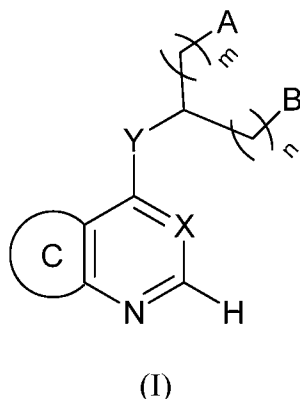


alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, nitro, cyano, OR_a , OR_aO , $C(O)OR_a$, $C(O)NR_aR_b$, $NR_bC(O)R_a$, $NHC(O)NR_aR_b$, $NR_bC(S)R_a$, $NHSO_2R_a$, or NR_aR_b , in which each of R_a and R_b , independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_a and R_b , together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, Z is S, and W is N or CR_5 , in which R_5 is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, nitro, $C(O)OR_a$, $C(O)NR_aR_b$, $NR_bC(O)R_a$, $NHC(O)NR_aR_b$, $NR_bC(S)R_a$, $NHSO_2R_a$, or NR_aR_b .

21. The compound of claim 20, wherein m is 1 and A is OR_3 , R_3 being H, aryl, heteroaryl, or C_{1-3} alkyl optionally substituted with aryl or heteroaryl.

22. The compound of claim 20, wherein the compound is Compound 321.

23. A compound of formula (I):



wherein

X is N or CR_1 , in which R_1 is CN, $CONH_2$, halo, or H;

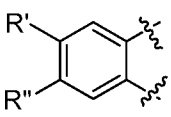
Y is O, S, or NR_2 , in which R_2 is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

A is alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR_3 , $OC(O)R_3$, $C(O)R_3$, $C(O)OR_3$, $C(O)NR_3R_4$, NR_3R_4 , $NHC(O)R_3$, $NHC(O)NR_3R_4$, $NHC(S)R_3$,

NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄, in which each of R₃ and R₄, independently, is H, alkyl, alkenyl, alkynyl, silyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R₃ and R₄, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl;

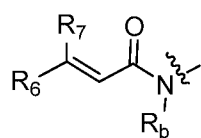
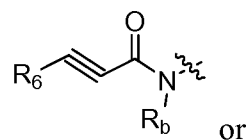
B is aryl or heteroaryl;

each of m and n, independently, is 0, 1, or 2;; and

ring C is , in which each of R' and R'', independently, is H,

alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, nitro, cyano, OR_a, C(O)OR_a, C(O)NR_aR_b, NR_bC(O)R_a, NHC(O)NR_aR_b, NR_bC(S)R_a, NHSO₂R_a, or NR_aR_b, in which each of R_a and R_b, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_a and R_b, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, provided that at least one of R' and R'' is NR_bC(O)R_a, NHC(O)NR_aR_b, NR_bC(S)R_a, or NHSO₂R_a.

24. The compound of claim 23, wherein R' is



, in which R₆ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, C(O)R_c, C(O)OR_c, C(O)NR_cR_d, or CH₂NR_cR_d, in which each of R_c and R_d, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_c and R_d, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, and R₇ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl.

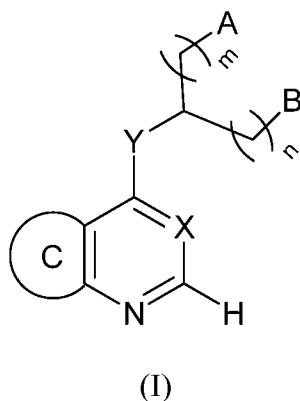
25. The compound of claim 23 or 24, wherein B is phenyl and n is 0.

26. The compound of any of claims 23-25, wherein A is C(O)OR₃ and m is 0.

27. The compound of any of claims 23-25, wherein m is 1 and A is OR₃, R₃ being H, aryl, heteroaryl, or C₁₋₃ alkyl optionally substituted with aryl or heteroaryl.

28. The compound of claim 23, wherein the compound is Compound 133, 147, or 271.

29. A compound of formula (I):



wherein

X is N or CR₁, in which R₁ is CN, CONH₂, halo, or H;

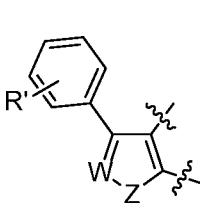
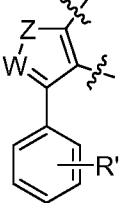
Y is O, S, or NR₂, in which R₂ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl;

A is alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro, OR₃, OC(O)R₃, C(O)R₃, C(O)OR₃, C(O)NR₃R₄, NR₃R₄, NHC(O)R₃, NHC(O)NR₃R₄, NHC(S)R₃, NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄, in which each of R₃ and R₄, independently, is H, alkyl, alkenyl, alkynyl, silyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R₃ and R₄, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl when X is N, and A is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, cyano, nitro,

OR₃, OC(O)R₃, C(O)R₃, C(O)OR₃, C(O)NR₃R₄, NR₃R₄, NHC(O)R₃, NHC(O)NR₃R₄, NHC(S)R₃, NHC(O)OR₃, SO₂R₃, SO₃R₃, or SO₂NR₃R₄ when X is CR₁;

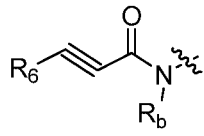
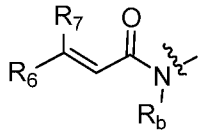
B is aryl or heteroaryl;

each of m and n, independently, is 0, 1, or 2; and

ring C is  or , in which each of R' is H, alkyl,

alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, nitro, cyano, OR_a, OR_aO, C(O)OR_a, C(O)NR_aR_b, NR_bC(O)R_a, NHC(O)NR_aR_b, NR_bC(S)R_a, NHSO₂R_a, or NR_aR_b, in which each of R_a and R_b, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_a and R_b, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, Z is O or S, and W is N or CR₅, in which R₅ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, halo, nitro, C(O)OR_a, C(O)NR_aR_b, NR_bC(O)R_a, NHC(O)NR_aR_b, NR_bC(S)R_a, NHSO₂R_a, or NR_aR_b.

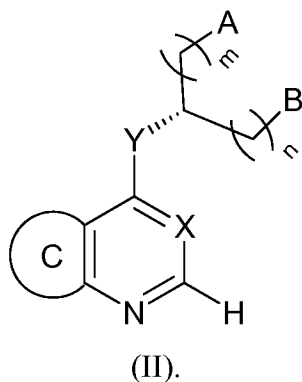
30. The compound of claim 29, wherein m is 1 and A is OR₃, R₃ being H, aryl, heteroaryl, or C₁₋₃ alkyl optionally substituted with aryl or heteroaryl.

31. The compound of claim 29 or 30, wherein R' is  or , in which R₆ is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl, C(O)R_c, C(O)OR_c, C(O)NR_cR_d, or CH₂NR_cR_d, in which each of R_c and R_d, independently, is H, alkyl, alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl, or R_c and R_d, together with the nitrogen atoms to which they are bonded, are heterocycloalkyl, heterocycloalkenyl, or heteroaryl, and R₇ is H, alkyl,

alkenyl, alkynyl, aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl, or heterocycloalkenyl.

32. The compound of claim 29, wherein the compound is Compound 286 or 315.

33. The compound of any preceding claim, wherein the compound is of formula (II):



34. Use of a compound of any of claims 1-33 for treating cancer.

35. Use of a compound of any of claims 1-33 in the manufacture of a medicament for the treatment of cancer.

36. A pharmaceutical composition, comprising a compound of any of claims 1-33 and a pharmaceutically acceptable carrier.

37. A method for inhibiting EGFR or ERBB2 kinase activity, comprising contacting a cell expressing EGFR or ERBB2 kinase with an effective amount of a compound of any of claims 1-33.