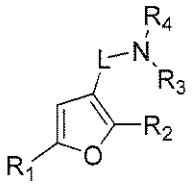
~~WHAT IS CLAIMED:~~

1. A compound of formula (I):



(I),

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

(A) L is $S(O)_2$;

R_1 is phenyl or (6 membered)heteroaryl, each of which is optionally substituted with one or more halogen, cyano, R_2, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$;

each occurrence of R_2 is

(i) $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, or $(C_2–C_8)$ alkynyl, each of which is optionally substituted with one or more halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, $NR_5S(O)_2R_6$, $(C_1–C_8)$heteroalkyl, $(C_3–C_8)$cycloalkyl, (6 to 10 membered) aryl, (5 to 10 membered)heteroaryl, or (3 to 10 membered)heterocyclyl; wherein the heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are each optionally substituted with one or more $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$; or

(ii) $(C_3–C_8)$cycloalkyl optionally substituted with one or more halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, $NR_5S(O)_2R_6$, $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl, $(C_2–C_8)$ alkynyl, $(C_1–C_8)$ heteroalkyl, $(C_3–C_8)$cycloalkyl, (6 to 10 membered) aryl, (5 to 10 membered)heteroaryl, or (3 to 10 membered)heterocyclyl; wherein the alkyl, alkenyl and alkynyl are each optionally substituted with one or more halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$; and the heteroalkyl, cycloalkyl,

aryl, heteroaryl and heterocyclyl are each optionally substituted with one or more $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$;

R_3 is hydrogen or R_2;

R_4 is phenyl or (5 to 6 membered)heteroaryl, each of which is optionally substituted with one or more halogen, cyano, R_2, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, $NR_5S(O)_2R_6$, optionally substituted (6 to 10 membered)aryl, optionally substituted (5 to 10 membered)heteroaryl, or optionally substituted (3 to 10 membered)heterocyclyl; and

R_5 and R_6 are each independently hydrogen, $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_8)$heteroalkyl, $(C_3–C_8)$cycloalkyl, $(C_7–C_{12})$aralkyl, phenyl, (5 to 6 membered)heteroaryl, or (3 to 7 membered)heterocyclyl; or R_5 and R_6 together form a 3 to 10 membered ring; or

(B) L is C(O);

R_1 is phenyl or (5 to 6 membered)heteroaryl, each of which is optionally substituted with one or more halogen, cyano, R_2, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$;

each occurrence of R_2 is

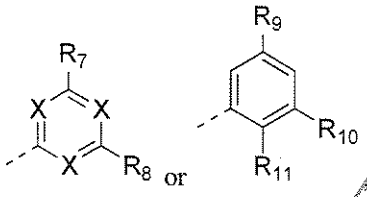
(i) $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, or $(C_2–C_8)$ alkynyl, each of which is optionally substituted with one or more halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, $NR_5S(O)_2R_6$, $(C_1–C_8)$heteroalkyl, $(C_3–C_8)$cycloalkyl, (6 to 10 membered) aryl, (5 to 10 membered)heteroaryl, or (3 to 10 membered)heterocyclyl; wherein the heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are each optionally substituted with one or more $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$; or

(ii) $(C_3–C_8)$cycloalkyl optionally substituted with one or more halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, $NR_5S(O)_2R_6$, $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl, $(C_2–C_8)$ alkynyl, $(C_1–C_8)$ heteroalkyl, $(C_3–C_8)$cycloalkyl, (6 to 10 membered) aryl, (5 to 10 membered)heteroaryl, or (3 to 10 membered)heterocyclyl; wherein the

alkyl, alkenyl and alkynyl are each optionally substituted with one or more halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$; and the heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are each optionally substituted with one or more $(C_1–C_6)$alkyl, $(C_2–C_6)$ alkenyl, $(C_2–C_6)$alkynyl, halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$;

R_3 is hydrogen or R_2;

R_4 is



wherein (i) each X is independently N or CH; and R_7 and R_8 are each independently halogen or CF_3; (ii) R_9 is chloro or CF_3; R_{10} is fluoro, chloro, or CF_3; and R_{11} is hydrogen, fluoro, chloro, CF_3, or $(C_1–C_4)$alkyl;

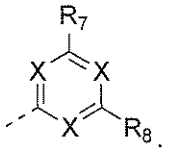
R_5 and R_6 are each independently hydrogen, $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_8)$heteroalkyl, $(C_3–C_8)$cycloalkyl, $(C_7–C_{12})$aralkyl, phenyl, (5 to 6 membered)heteroaryl, or (3 to 7 membered)heterocyclyl; or R_5 and R_6 together form a 3 to 10 membered ring; and

(i) when R_7 and R_8 are both CF_3 and X is CH, R_1 is not 3,4-dichlorophenyl or 3,5-dichlorophenyl; and (ii) when R_9 and R_{10} are both CF_3 and R_{11} is hydrogen, R_1 is not 3,4-dichlorophenyl or 3,5-dichlorophenyl.

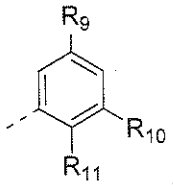
2. The compound of claim 1, wherein L is $S(O)_2$.

3. The compound of claim 1, wherein L is C(O).

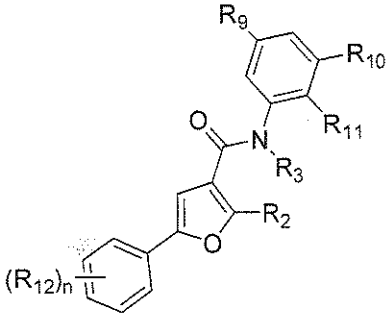
4. The compound of claim 3, wherein R_4 is



5. The compound of claim 3, wherein R_4 is



6. The compound of claim 5, having formula (V):



(V),

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof; wherein:

R_2 is CH_3 or CF_3;

R_3 is hydrogen, $(C_1–C_4)$alkyl, or benzyl;

R_9 is chloro or CF_3;

R_{10} is fluoro, chloro, or CF_3;

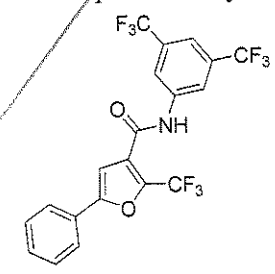
R_{11} is hydrogen, fluoro, chloro, CF_3, or $(C_1–C_4)$alkyl;

R_{12} is fluoro, chloro, bromo, methyl, hydroxyl, or methoxyl,

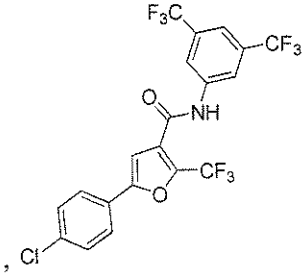
n is 0, 1, or 2; and

when R_9 and R_{10} are both CF_3, R_{11} is hydrogen, and n is 2; then R_{12} is not chloro.

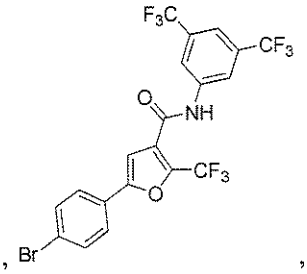
7. The compound of any one of claims 1 and 3–6, wherein the compound is:



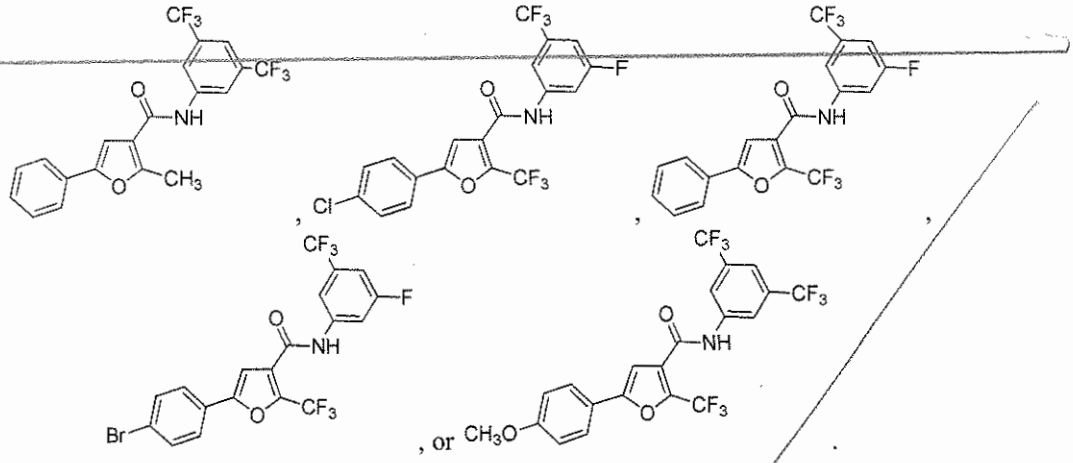
,



,



,



8. A pharmaceutical composition comprising a compound of any one of claims 1–7, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, and at least one pharmaceutically acceptable excipient or carrier.

9. The pharmaceutical composition of claim 8, further comprising one or more additional active agents.

10. Use of a compound of any one of claims 1–7, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, or a pharmaceutical composition of claim 8 or 9 in the manufacture of a medicament for treating, preventing, or ameliorating one or more symptoms of a disorder mediated by cap-dependent protein translation.

11. Use of a compound of any one of claims 1–7, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, or a pharmaceutical composition of claim 8 or 9 in the manufacture of a medicament for treating, preventing, or ameliorating one or more symptoms of a disorder mediated by eIF4E.

12. Use of a compound of any one of claims 1–7, or an enantiomer, a mixture of enantiomers, or a mixture of

two or more diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, or a pharmaceutical composition of claim 8 or 9 in the manufacture of a medicament for treating, preventing, or ameliorating one or more symptoms of a disorder mediated by the Hedgehog pathway.

13. The use of any one of claims 10–12, wherein the disorder is cancer, a proliferative disorder, breast cancer, triple negative breast cancer, ER+ breast cancer, ER- breast cancer, basal cell nevus syndrome (Gorlin syndrome), basal cell carcinoma, skin cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, brain cancer, medulloblastoma, glioblastoma, colorectal cancer, ovarian cancer, liver cancer, pancreatic cancer, pancreatic carcinoma, pancreatic angiosarcoma, pancreatic adenosarcoma, gastric cancer, gastroesophageal junction cancer, prostate cancer, cervical cancer, bladder cancer, head and neck cancer, lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, solid tumors that cannot be removed by surgery, locally advanced solid tumors, metastatic solid tumors, leukemia, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), or recurrent or refractory tumors.

14. Use of a compound of any one of claims 1–7, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable salt, solvate, hydrate, or prodrug thereof, or a pharmaceutical composition of claim 8 or 9 in the manufacture of a medicament for treating, preventing, or ameliorating one or more symptoms of a disorder, wherein the disorder is cancer, a proliferative disorder, breast cancer, triple negative breast cancer, ER+ breast cancer, ER- breast cancer, basal cell nevus syndrome (Gorlin syndrome), basal cell carcinoma, skin cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, brain cancer, medulloblastoma, glioblastoma, colorectal cancer, ovarian cancer, liver cancer, pancreatic cancer, pancreatic carcinoma, pancreatic angiosarcoma, pancreatic adenosarcoma, gastric cancer, gastroesophageal junction cancer, prostate cancer, cervical cancer, bladder cancer, head and neck cancer, lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, solid tumors that cannot be removed by surgery, locally advanced solid tumors, metastatic solid tumors, leukemia, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), or recurrent or refractory tumors.

15. The use of any one of claims 13 or 14, wherein the cancer is resistant to conventional therapy.

16. The use of any one of claims 13 or 14, wherein the cancer is vincristine-resistant.

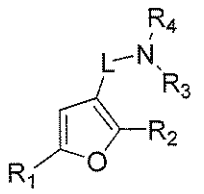
17. The use of any one of claims 13 or 14, wherein the cancer is taxol-resistant.

18. The use of any one of claims 13 or 14, wherein the cancer is cytarabine-resistant.

19. The use of any one of claims 13 or 14, wherein the cancer is doxorubicin-resistant.

WHAT IS CLAIMED:

1. A compound of formula (I):



(I),

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt or hydrate thereof; wherein:

(A) L is $S(O)_2$;

R_1 is phenyl or (6 membered)heteroaryl, each of which is optionally substituted with one or more halogen, cyano, R_2, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$;

each occurrence of R_2 is:

(i) $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, or $(C_2–C_8)$ alkynyl, each of which is optionally substituted with one or more halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, $NR_5S(O)_2R_6$, $(C_1–C_8)$heteroalkyl, $(C_3–C_8)$cycloalkyl, (6 to 10 membered) aryl, (5 to 10 membered)heteroaryl, or (3 to 10 membered)heterocyclyl; wherein the heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are each optionally substituted with one or more $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl, $(C_2–C_6)$alkynyl, halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$; or

(ii) $(C_3–C_8)$cycloalkyl optionally substituted with one or more halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, $NR_5S(O)_2R_6$, $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl, $(C_2–C_8)$ alkynyl, $(C_1–C_8)$ heteroalkyl, $(C_3–C_8)$cycloalkyl, (6 to 10 membered) aryl, (5 to 10 membered)heteroaryl, or (3 to 10 membered)heterocyclyl; wherein the alkyl, alkenyl and alkynyl are each optionally substituted with one or more halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$; and the heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are each optionally substituted with one or more $(C_1–C_6)$alkyl, $(C_2–C_6)$ alkenyl,

$(C_2–C_6)$alkynyl, halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$;

R_3 is hydrogen or R_2;

R_4 is phenyl or (5 to 6 membered)heteroaryl, each of which is optionally substituted with one or more halogen, cyano, R_2, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, $NR_5S(O)_2R_6$, optionally substituted (6 to 10 membered)aryl, optionally substituted (5 to 10 membered)heteroaryl, or optionally substituted (3 to 10 membered)heterocyclyl; and

R_5 and R_6 are each independently hydrogen, $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_8)$heteroalkyl, $(C_3–C_8)$cycloalkyl, $(C_7–C_{12})$aralkyl, phenyl, (5 to 6 membered)heteroaryl, or (3 to 7 membered)heterocyclyl; or R_5 and R_6 together form a 3 to 10 membered ring; or

(B) L is C(O);

R_1 is phenyl or (5 to 6 membered)heteroaryl, each of which is optionally substituted with one or more halogen, cyano, R_2, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$;

each occurrence of R_2 is:

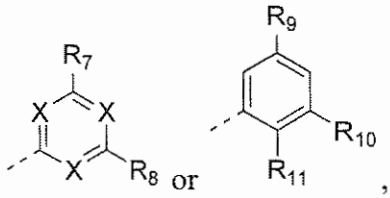
(i) $(C_1–C_8)$alkyl, $(C_2–C_8)$alkenyl, or $(C_2–C_8)$ alkynyl, each of which is optionally substituted with one or more halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, $NR_5S(O)_2R_6$, $(C_1–C_8)$heteroalkyl, $(C_3–C_8)$cycloalkyl, (6 to 10 membered) aryl, (5 to 10 membered)heteroaryl, or (3 to 10 membered)heterocyclyl; wherein the heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are each optionally substituted with one or more $(C_1–C_6)$alkyl, $(C_2–C_6)$alkenyl,
$(C_2–C_6)$alkynyl, halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$; or

(ii) $(C_3–C_8)$cycloalkyl optionally substituted with one or more halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, $NR_5S(O)_2R_6$, $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl, $(C_2–C_8)$ alkynyl, $(C_1–C_8)$ heteroalkyl, $(C_3–C_8)$cycloalkyl, (6 to 10 membered) aryl, (5 to 10 membered)heteroaryl, or (3 to 10 membered)heterocyclyl; wherein the alkyl, alkenyl and alkynyl are each optionally substituted with one or more halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$,

$S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$; and the heteroalkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl are each optionally substituted with one or more $(C_1–C_6)$alkyl, $(C_2–C_6)$ alkenyl, $(C_2–C_6)$alkynyl, halogen, cyano, OR_5, $OC(O)R_5$, $C(O)R_5$, $C(O)OR_5$, $C(O)NR_5R_6$, $NR_5C(O)R_6$, NR_5R_6, $OS(O)R_5$, SR_5, $S(O)R_5$, $S(O)_2R_5$, $S(O)_2NR_5R_6$, or $NR_5S(O)_2R_6$;

R_3 is hydrogen or R_2;

R_4 is



wherein (i) each X is independently N or CH; and R_7 and R_8 are each independently halogen or CF_3; (ii) R_9 is chloro or CF_3; R_{10} is fluoro, chloro, or CF_3; and R_{11} is hydrogen, fluoro, chloro, CF_3, or $(C_1–C_4)$alkyl; and

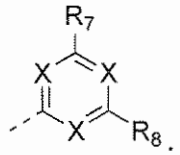
R_5 and R_6 are each independently hydrogen, $(C_1–C_8)$alkyl, $(C_2–C_8)$ alkenyl, $(C_2–C_8)$alkynyl, $(C_1–C_8)$heteroalkyl, $(C_3–C_8)$cycloalkyl, $(C_7–C_{12})$aralkyl, phenyl, (5 to 6 membered)heteroaryl, or (3 to 7 membered)heterocyclyl; or R_5 and R_6 together form a 3 to 10 membered ring;

with the proviso that, (i) when R_7 and R_8 are both CF_3 and X is CH, R_1 is neither 3,4-dichlorophenyl nor 3,5-dichlorophenyl; and (ii) when R_9 and R_{10} are both CF_3 and R_{11} is hydrogen, R_1 is neither 3,4-dichlorophenyl nor 3,5-dichlorophenyl.

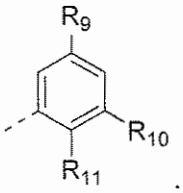
2. The compound of claim 1, wherein L is $S(O)_2$.

3. The compound of claim 1, wherein L is C(O).

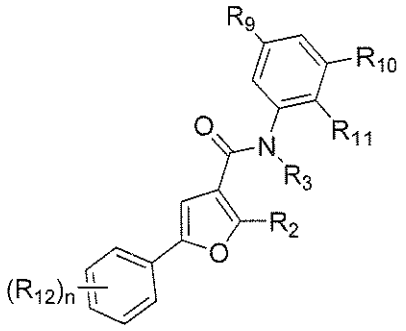
4. The compound of claim 3, wherein R_4 is



5. The compound of claim 3, wherein R_4 is



6. The compound of claim 5, having formula (V):



(V),

or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof; or a pharmaceutically acceptable salt or hydrate thereof; wherein:

R_2 is CH_3 or CF_3;

R_3 is hydrogen, $(C_1–C_4)$alkyl, or benzyl;

R_9 is chloro or CF_3;

R_{10} is fluoro, chloro, or CF_3;

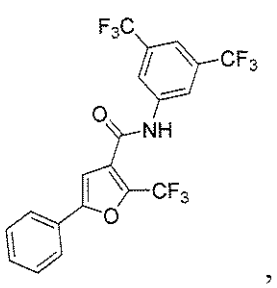
R_{11} is hydrogen, fluoro, chloro, CF_3, or $(C_1–C_4)$alkyl;

R_{12} is fluoro, chloro, bromo, methyl, hydroxyl, or methoxy; and

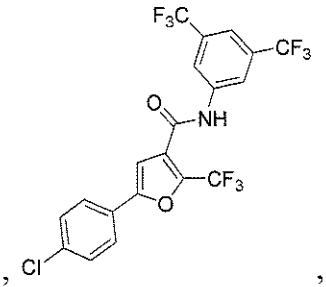
n is 0, 1, or 2;

with the proviso that, when R_9 and R_{10} are both CF_3, R_{11} is hydrogen, and n is 2; then R_{12} is not chloro.

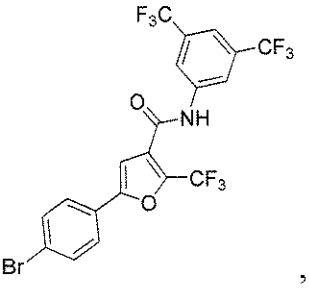
7. The compound of any one of claims 1 and 3–6, wherein the compound is:



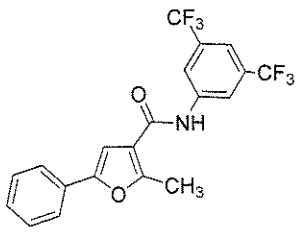
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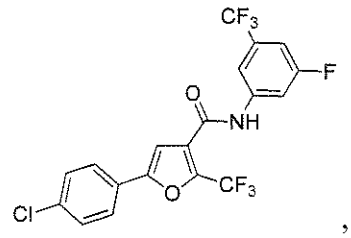
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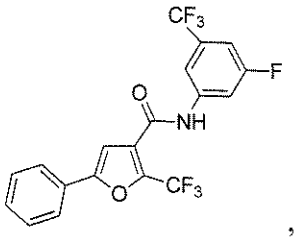
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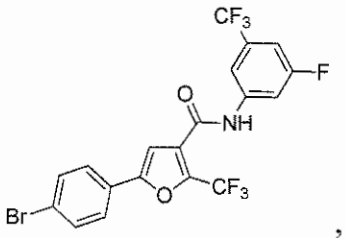
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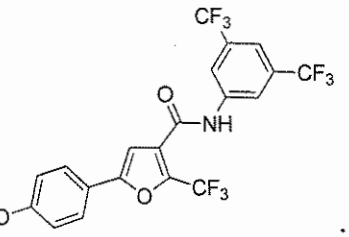


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, or


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8. A pharmaceutical composition comprising a compound of any one of claims 1–7, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable salt or hydrate thereof, and at least one pharmaceutically acceptable excipient or carrier.

9. Use of a compound of any one of claims 1-7, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable salt or hydrate thereof, or a pharmaceutical composition of claim 8 in the manufacture of a medicament for treating, preventing, or ameliorating one or more symptoms of a disorder mediated by cap-dependent protein translation; wherein the disorder is cancer, a proliferative disorder, breast cancer, triple negative breast cancer, ER+ breast cancer, ER- breast cancer, basal cell nevus syndrome (Gorlin syndrome), basal cell carcinoma, skin cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, brain cancer, medulloblastoma, glioblastoma, colorectal cancer, ovarian cancer, liver cancer, pancreatic cancer, pancreatic carcinoma, pancreatic angiosarcoma, pancreatic adenosarcoma, gastric cancer, gastroesophageal junction cancer, prostate cancer, cervical cancer, bladder cancer, kidney cancer, pharynx cancer, head and neck cancer, lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, a solid tumor that cannot be removed by surgery, a locally advanced solid tumor, a metastatic solid tumor, leukemia, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), or a recurrent or refractory tumor.

10. Use of a compound of any one of claims 1-7, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable salt or hydrate thereof, or a pharmaceutical composition of claim 8 in the manufacture of a medicament for treating, preventing, or ameliorating one or more symptoms of a disorder mediated by eIF4E; wherein the disorder is cancer, a proliferative disorder, breast cancer, triple negative breast cancer, ER+ breast cancer, ER- breast cancer, basal cell nevus syndrome (Gorlin syndrome), basal cell carcinoma, skin cancer, lung cancer, small cell

lung cancer, non-small cell lung cancer, brain cancer, medulloblastoma, glioblastoma, colorectal cancer, ovarian cancer, liver cancer, pancreatic cancer, pancreatic carcinoma, pancreatic angiosarcoma, pancreatic adenosarcoma, gastric cancer, gastroesophageal junction cancer, prostate cancer, cervical cancer, bladder cancer, kidney cancer, pharynx cancer, head and neck cancer, lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, a solid tumor that cannot be removed by surgery, a locally advanced solid tumor, a metastatic solid tumor, leukemia, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), or a recurrent or refractory tumor.

11. Use of a compound of any one of claims 1-7, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable salt or hydrate thereof, or a pharmaceutical composition of claim 8 in the manufacture of a medicament for treating, preventing, or ameliorating one or more symptoms of a disorder mediated by the Hedgehog pathway; wherein the disorder is cancer, a proliferative disorder, breast cancer, triple negative breast cancer, ER+ breast cancer, ER- breast cancer, basal cell nevus syndrome (Gorlin syndrome), basal cell carcinoma, skin cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, brain cancer, medulloblastoma, glioblastoma, colorectal cancer, ovarian cancer, liver cancer, pancreatic cancer, pancreatic carcinoma, pancreatic angiosarcoma, pancreatic adenosarcoma, gastric cancer, gastroesophageal junction cancer, prostate cancer, cervical cancer, bladder cancer, kidney cancer, pharynx cancer, head and neck cancer, lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, a solid tumor that cannot be removed by surgery, a locally advanced solid tumor, a metastatic solid tumor, leukemia, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), or a recurrent or refractory tumor.

12. Use of a compound of any one of claims 1-7, or an enantiomer, a mixture of enantiomers, or a mixture of two or more diastereomers thereof, or a pharmaceutically acceptable salt or hydrate thereof, or a pharmaceutical composition of claim 8 in the manufacture of a medicament for treating, preventing, or ameliorating one or more symptoms of a disorder, wherein the disorder is cancer, a proliferative disorder, breast cancer, triple negative breast cancer, ER+ breast cancer, ER- breast cancer, basal cell nevus syndrome (Gorlin syndrome), basal cell carcinoma, skin cancer, lung cancer, small cell lung cancer, non-small cell lung cancer, brain cancer, medulloblastoma, glioblastoma, colorectal cancer,

ovarian cancer, liver cancer, pancreatic cancer, pancreatic carcinoma, pancreatic angiosarcoma, pancreatic adenosarcoma, gastric cancer, gastroesophageal junction cancer, prostate cancer, cervical cancer, bladder cancer, kidney cancer, pharynx cancer, head and neck cancer, lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, a solid tumor that cannot be removed by surgery, a locally advanced solid tumor, a metastatic solid tumor, leukemia, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), or a recurrent or refractory tumor.

13. The use of any one of claims 9-12, wherein the disorder is breast cancer, triple negative breast cancer, ER+ breast cancer, or ER- breast cancer.

14. The use of any one of claims 9-13, wherein the disorder is vincristine-resistant.

15. The use of any one of claims 9-13, wherein the disorder is taxol-resistant.

16. The use of any one of claims 9-13, wherein the disorder is cytarabine-resistant.

17. The use of any one of claims 9-13, wherein the disorder is doxorubicin-resistant.