EIF4E INHIBITORS AND USES THEREOF

TECHNICAL FIELD OF THE INVENTION

[0001] The present invention relates to compounds and methods useful for inhibition of Eukaryotic initiation factor 4E (eIF4E). The invention also provides pharmaceutically acceptable compositions comprising compounds of the present invention and methods of using said compositions in the treatment of various disorders.

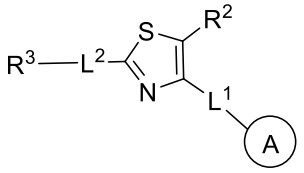
BACKGROUND OF THE INVENTION

[0002] Eukaryotic initiation factor 4E (eIF4E) is a 24 kDa protein that plays a key role in the initiation of translation of select mRNAs. At the initiation of mRNA translation, eIF4E binds to the 7-methylguanosine cap at the 5' end of mRNAs, and forms a complex (called eIF4F) with proteins including the scaffolding protein eIF4G and the helicase eIF4A. The formation of the 4F complex is required for the initiation of cap-dependent translation, and therefore the binding of eIF4E to its cognate partners is a critical event in eIF4E mediated translation.

[0003] A number of studies have suggested that dysregulated eIF4E is important in some cancer phenotypes, and therefore eIF4E is a potential target in the field of oncology.

SUMMARY ~~OF THE INVENTION~~

[0003a] In an aspect of the present disclosure, there is provided a compound of formula **I**:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted ring selected from phenyl, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic aromatic carbocyclic ring, or an 8-10 membered bicyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^1 is a bond, or an optionally substituted C_{1-8} bivalent straight or branched hydrocarbon chain, wherein 1, 2, 3, or 4 methylene units of the hydrocarbon chain are optionally and independently replaced with –O-, -S-, –N(R)-, -C(O)-, or $-S(O)_2-$;

R^2 is halogen, R, -OR, -SR, -C(O)R, -C(O)OR, $-C(O)N(R)_2$, $-S(O)_2R$, $-S(O)_2OR$, or $-S(O)_2N(R)_2$;

L^2 is a bond, or an optionally substituted C_{1-8} bivalent straight or branched hydrocarbon chain, wherein 1, 2, 3, or 4 methylene units of the hydrocarbon chain are optionally and independently replaced with –O-, -S-, –N(R)-, -C(O)-, $-S(O)_2-$, or –Cy-;

R^3 is –CN, -C(O)R, -C(O)OR, $-C(O)N(R)_2$, -N(R)-C(O)-R, -N(R)-C(O)-OR, $-S(O)_2-N(R)_2$, $-S(O)_2-N(R)-C(O)R$, $-C(O)-N(R)-S(O)_2R$, $-C(=NR)-N(R)_2$, $-N(R)-C(=NR)-N(R)_2$, or a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

-Cy- is an optionally substituted bivalent ring selected from phenylene, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 3-6 membered monocyclic, saturated or partially unsaturated, carbocyclic ring, a 3-6 membered monocyclic, saturated or partially unsaturated, heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic aromatic carbocyclic ring, or an 8-10 membered bicyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

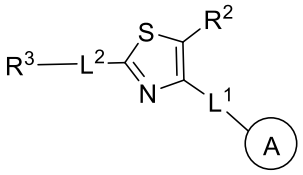
R is hydrogen, optionally substituted $–C_{1-6}$ aliphatic, or an optionally substituted ring selected from phenyl, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 3-6 membered monocyclic, saturated or partially unsaturated, carbocyclic ring, or a 3-6 membered monocyclic, saturated or partially unsaturated, heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

[0003b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound disclosed herein, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

[0003c] In a further aspect of the present disclosure, there is provided a compound disclosed herein, or a pharmaceutically acceptable salt thereof, for use in therapy.

[0003d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for treating a cancer in a patient.

[0004] It has now been found that compounds of the present ~~invention~~disclosure, and pharmaceutically acceptable compositions thereof, are effective as eIF4E inhibitors. In one ~~aspect~~example, the present ~~invention~~ disclosure provides a compound of Formula (**I**):



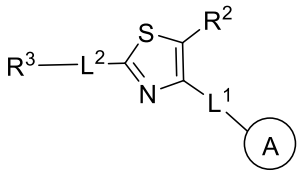
(I)

or a pharmaceutically acceptable salt thereof, wherein each variable is as defined and described herein.

[0005] Compounds of the present ~~invention~~disclosure, and pharmaceutically acceptable compositions thereof, are useful for treating a variety of diseases, disorders or conditions, associated with eIF4E.

CLAIMS

1. A compound of formula **I**:



(I),

or a pharmaceutically acceptable salt thereof, wherein:

Ring A is an optionally substituted ring selected from phenyl, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered bicyclic aromatic carbocyclic ring, or an 8-10 membered bicyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

L^1 is a bond, or an optionally substituted C_{1-8} bivalent straight or branched hydrocarbon chain, wherein 1, 2, 3, or 4 methylene units of the hydrocarbon chain are optionally and independently replaced with –O-, -S-, –N(R)-, -C(O)-, or $-S(O)_2-$;

R^2 is halogen, R, -OR, -SR, -C(O)R, -C(O)OR, $-C(O)N(R)_2$, $-S(O)_2R$, $-S(O)_2OR$, or $-S(O)_2N(R)_2$;

L^2 is a bond, or an optionally substituted C_{1-8} bivalent straight or branched hydrocarbon chain, wherein 1, 2, 3, or 4 methylene units of the hydrocarbon chain are optionally and independently replaced with –O-, -S-, –N(R)-, -C(O)-, $-S(O)_2-$, or –Cy-;

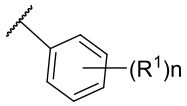
R^3 is –CN, -C(O)R, -C(O)OR, $-C(O)N(R)_2$, -N(R)-C(O)-R, -N(R)-C(O)-OR, $-S(O)_2-N(R)_2$, $-S(O)_2-N(R)-C(O)R$, $-C(O)-N(R)-S(O)_2R$, $-C(=NR)-N(R)_2$, $-N(R)-C(=NR)-N(R)_2$, or a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur;

-Cy- is an optionally substituted bivalent ring selected from phenylene, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 3-6 membered monocyclic, saturated or partially unsaturated, carbocyclic ring, a 3-6 membered monocyclic, saturated or partially unsaturated, heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, an 8-10 membered

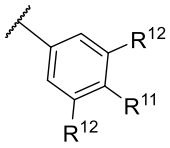
bicyclic aromatic carbocyclic ring, or an 8-10 membered bicyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur; and

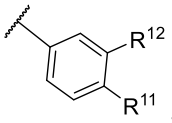
R is hydrogen, optionally substituted –C_{1-6} aliphatic, or an optionally substituted ring selected from phenyl, a 5-6 membered monocyclic heteroaromatic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur, a 3-6 membered monocyclic, saturated or partially unsaturated, carbocyclic ring, or a 3-6 membered monocyclic, saturated or partially unsaturated, heterocyclic ring having 1-4 heteroatoms independently selected from nitrogen, oxygen, and sulfur.

2. The compound of claim 1, wherein Ring A is optionally substituted phenyl.

3. The compound of claim 2, wherein Ring A is 

, wherein each R^1 is independently halogen, R, -$N(R)_2$, -OR, -SR, -C(O)OR, or -$S(O)_2$R, and n is 0, 1, 2, 3, 4, or 5.

4. The compound of claim 2, wherein Ring A is 

or 

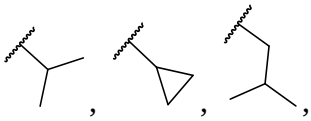
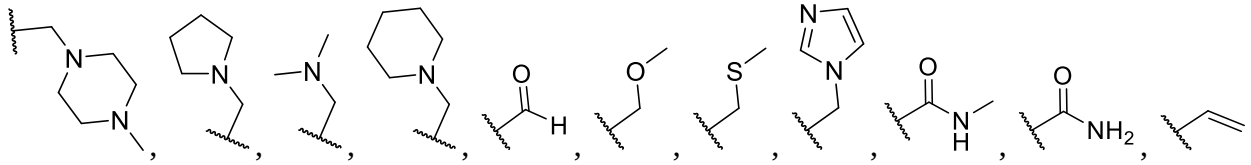
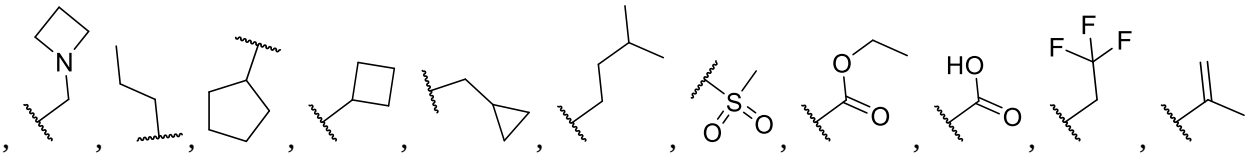
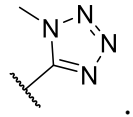
, wherein each of R^{11} and R^{12} is independently halogen, R, -$N(R)_2$, -OR, -SR, -C(O)OR, or -$S(O)_2$R.

5. The compound of claim 4, wherein at least one of R^{12} is not hydrogen.

6. The compound of any one of the preceding claims, wherein L^1 is a bond.

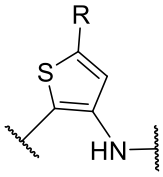
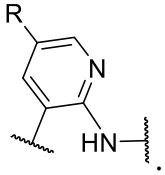
7. The compound of any one of the preceding claims, wherein R^2 is not hydrogen.

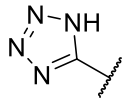
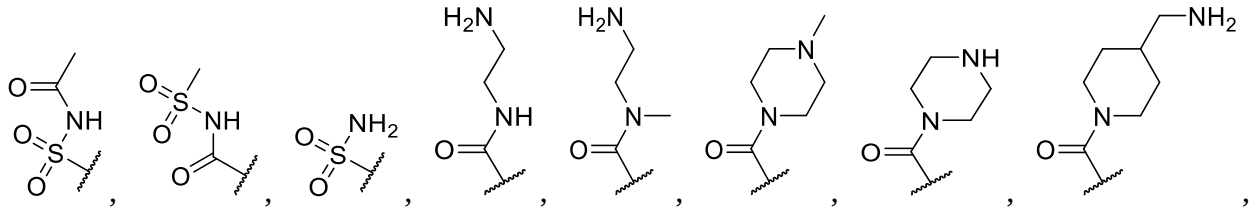
8. The compound of claim 7, wherein R^2 is optionally substituted –C_{1-6} aliphatic.

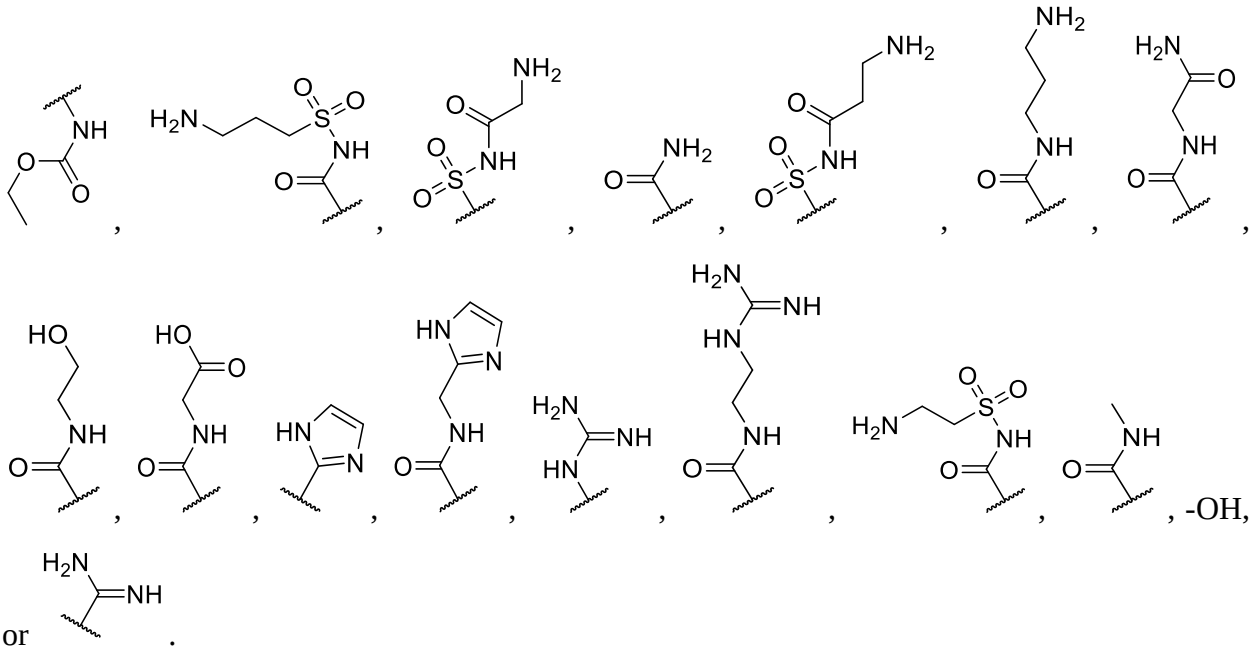
9. The compound of any one of the preceding claims, wherein R^2 is H, , , , -SCH_3, or .

10. The compound of any one of the preceding claims, wherein L^2 does not attach to the thiazole moiety through a carboxamide, or sulfonamide, or diazole moiety.

11. The compound of claim 10, wherein L^2 is

 or .

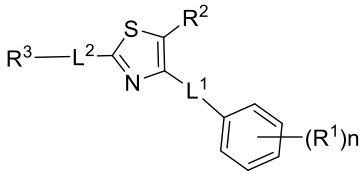
12. The compound of any one of the preceding claims, wherein R^3 is –COOH, –CN, , .



or .

13. The compound of any one of the preceding claims, wherein R is hydrogen or optionally substituted $–C_{1-6}$ aliphatic.

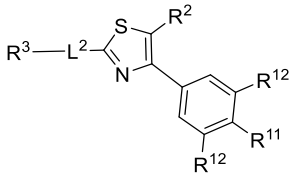
14. The compound of claim 1, wherein the compound is of Formula **II**:



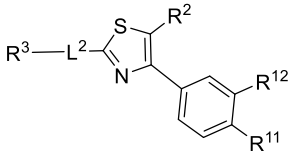
(II)

or a pharmaceutically acceptable salt thereof, wherein R^1 is independently halogen, R, $-N(R)_2$, -OR, -SR, -C(O)OR, or $-S(O)_2R$, and n is 0, 1, 2, 3, 4, or 5.

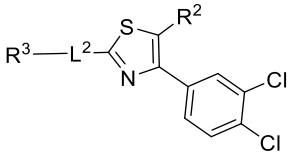
15. The compound of claim 1, wherein the compound is of Formulae **II-a to II-d**:



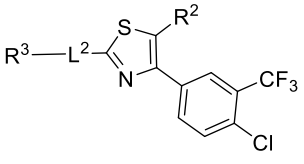
(II-a)



(II-b)



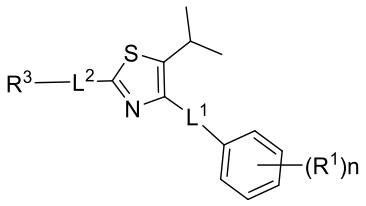
(II-c)



(II-d)

or a pharmaceutically acceptable salt thereof, wherein each of R^{11} and R^{12} is independently halogen, R, -N(R)$_2$, -OR, -SR, -C(O)OR, or -S(O)$_2$R.

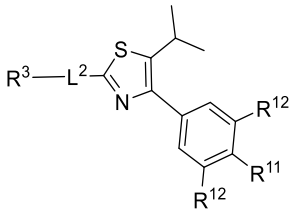
16. The compound of claim 1, wherein the compound is of Formula **III**:



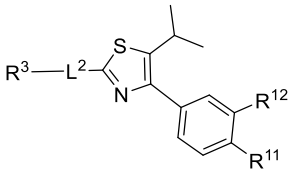
(III)

or a pharmaceutically acceptable salt thereof, wherein R^1 is independently halogen, R, -N(R)$_2$, -OR, -SR, -C(O)OR, or -S(O)$_2$R, and n is 0, 1, 2, 3, 4, or 5.

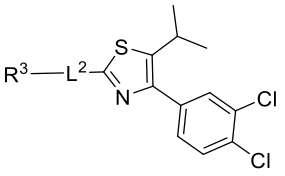
17. The compound of claim 1, wherein the compound is of Formulae **III-a to III-d**:



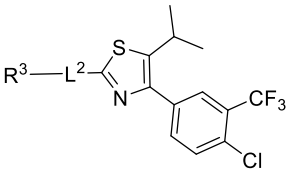
(III-a)



(III-b)



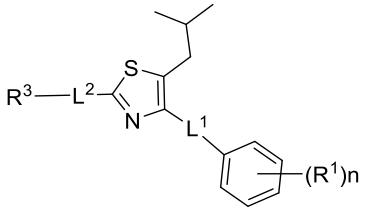
(III-c)



(III-d)

or a pharmaceutically acceptable salt thereof, wherein each of R^{11} and R^{12} is independently halogen, R, -N(R)$_2$, -OR, -SR, -C(O)OR, or -S(O)$_2$R.

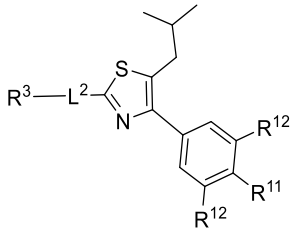
18. The compound of claim 1, wherein the compound is of Formula **IV**:



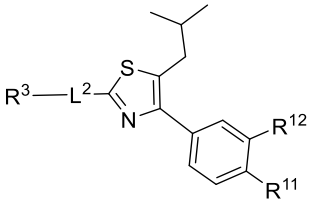
(IV)

or a pharmaceutically acceptable salt thereof, wherein R^1 is independently halogen, R, -N(R)$_2$, -OR, -SR, -C(O)OR, or -S(O)$_2$R, and n is 0, 1, 2, 3, 4, or 5.

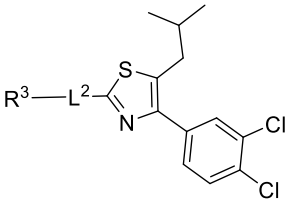
19. The compound of claim 1, wherein the compound is of Formulae **IV-a to IV-d**:



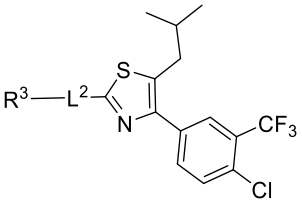
(IV-a)



(IV-b)



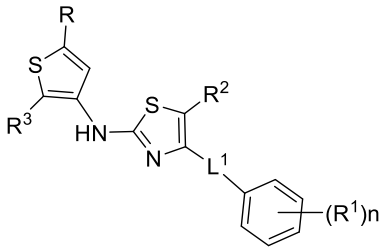
(IV-c)



(IV-d)

or a pharmaceutically acceptable salt thereof, wherein each of R^{11} and R^{12} is independently halogen, R, -$N(R)_2$, -OR, -SR, -C(O)OR, or -$S(O)_2$R.

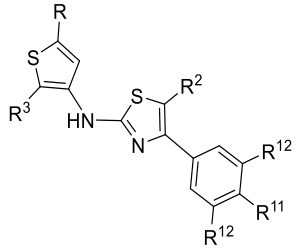
20. The compound of claim 1, wherein the compound is of Formula **V**:



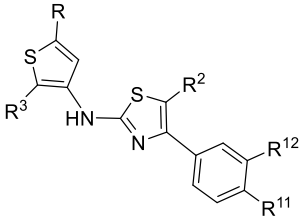
(V)

or a pharmaceutically acceptable salt thereof, wherein R^1 is independently halogen, R, -$N(R)_2$, -OR, -SR, -C(O)OR, or -$S(O)_2$R, and n is 0, 1, 2, 3, 4, or 5.

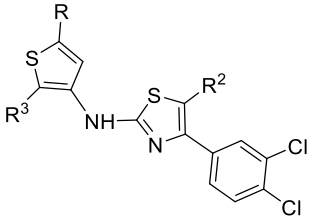
21. The compound of claim 1, wherein the compound is of Formulae **V-a to V-d**:



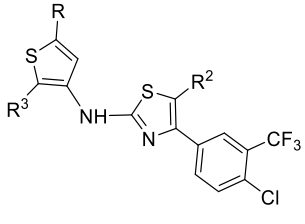
(V-a)



(V-b)



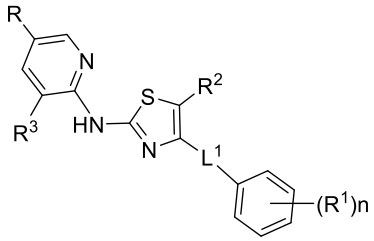
(V-c)



(V-d)

or a pharmaceutically acceptable salt thereof, wherein each of R^{11} and R^{12} is independently halogen, R, -$N(R)_2$, -OR, -SR, -C(O)OR, or -$S(O)_2$R.

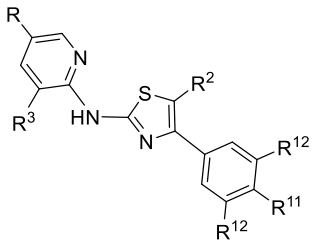
22. The compound of claim 1, wherein the compound is of Formula **VI**:



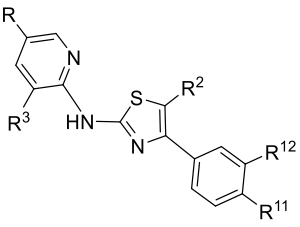
(VI)

or a pharmaceutically acceptable salt thereof, wherein R^1 is independently halogen, R, -$N(R)_2$, -OR, -SR, -C(O)OR, or -$S(O)_2R$, and n is 0, 1, 2, 3, 4, or 5.

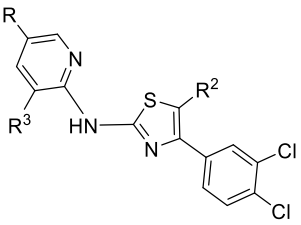
23. The compound of claim 1, wherein the compound is of Formulae **VI-a to VI-d**:



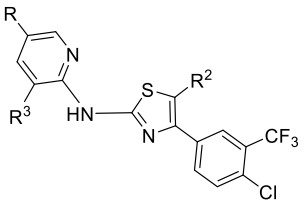
(VI-a)



(VI-b)



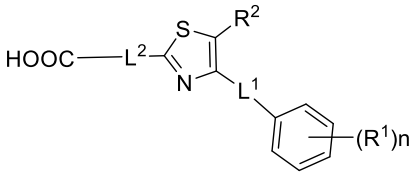
(VI-c)



(VI-d)

or a pharmaceutically acceptable salt thereof, wherein each of R^{11} and R^{12} is independently halogen, R, -$N(R)_2$, -OR, -SR, -C(O)OR, or -$S(O)_2R$.

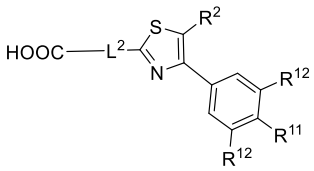
24. The compound of claim 1, wherein the compound is of Formula **VII**:



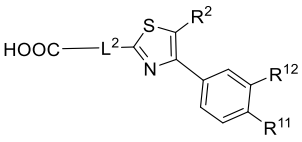
(VII)

or a pharmaceutically acceptable salt thereof, wherein R^1 is independently halogen, R, -$N(R)_2$, -OR, -SR, -C(O)OR, or -$S(O)_2R$, and n is 0, 1, 2, 3, 4, or 5.

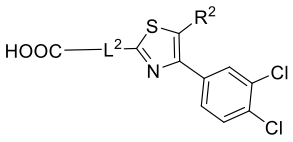
25. The compound of claim 1, wherein the compound is of Formulae **VII-a to VII-d**:



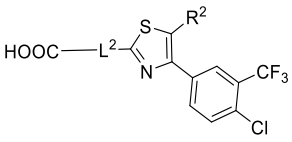
(VII-a)



(VII-b)



(VII-c)



(VII-d)

or a pharmaceutically acceptable salt thereof, wherein each of R^{11} and R^{12} is independently halogen, R, -$N(R)_2$, -OR, -SR, -C(O)OR, or -$S(O)_2$R.

26. The compound of claim 1, or a pharmaceutically acceptable salt thereof, selected from Table 1.

27. A pharmaceutical composition comprising the compound of any one of claims 1-26, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier, adjuvant, or vehicle.

28. A compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, for use in therapy.

~~28~~29. Use of a compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament ~~A method~~ for treating a cancer in a patient ~~comprising administering to the patient the compound of any one of claims 1-27, or a pharmaceutically acceptable salt thereof~~.