Praveen, K., Stang, S., Stone, J.C., Gajewski, T.F., 2006. *T cell anergy is reversed by active Ras and is regulated by diacylglycerol kinase-alpha.* Nat. Immunol. 7 (11), 1166–1173; Olenchock, B.A., Guo, R., Carpenter, J.H., Jordan, M., Topham, M.K., Koretzky, G.A., Zhong, X.P., 2006a. *Disruption of diacylglycerol metabolism impairs the induction of T cell anergy.* Nat. Immunol. 7 (11), 1174–1181.)

Taken together, there is substantial evidence that DGKα and DGKζ are high value targets for cancer immunotherapy. At the same time, there is a lack of compounds with the ability to potently inhibit both DGKα and DGKζ with good selectivity over other diacylglycerol kinases, protein kinases, and/or other lipid kinases.

This invention describes such dual DGK α/ζ inhibitors with excellent selectivity over other protein kinases, across safety / off-target panels and vs. other lipid kinases. These compounds potently activate suboptimally stimulated T-cells and thereby act as intracellular enhancers of co-stimulatory signaling cascades. These DGK α/ζ inhibitors have the potential to increase proliferation, cytotoxicity and the life span of targeted T-cells which may result in improved anticancer activity of CPIs, CD3 engaging T-cell bispecifics and CAR T-cells. Further, by engaging a signaling node central to both TCR and co-stimulatory receptors, it is plausible that these molecules enhance both signals 1 and 2 and thus single agent activity can be achieved, e.g. in inflamed tumors.

There is an ongoing need for new compounds capable of activating and proliferating T-cells, thus enabling the treatment, prevention and/or delay of progression of cancer.

It is, therefore, an object of this invention to provide compounds useful as DGKα/ζ inhibitors for the treatment or prevention or amelioration of such diseases with improved therapeutic properties, in particular improved pharmacokinetic properties.

Summary

In one aspect, the present disclosure provides a compound of formula (I)

iv) phenyl, optionally substituted with one or more halogen, cyano, C_{1-6}-alkoxy, C_{1-6}-haloalkyl, C_{1-6}-alkyl;

v) -O(R^{11a});

vi) -N($R^{11g}R^{11h}$); and

vii) –S(R^{11k});

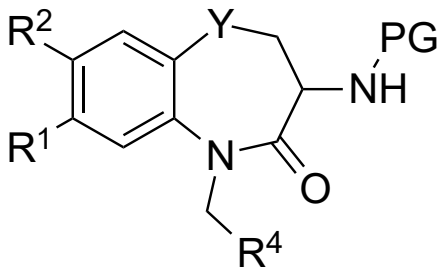
R^{11a} is selected from C_{1-12}-alkyl, halo-C_{1-6}-alkyl, C_{3-7}-cycloalkyl, 3-10 membered -(C_{1-6}-alkyl)heterocyclyl, phenyl, and -C_{1-6}-alkyl-phenyl, wherein said C_{1-12}-alkyl, C_{3-7}-cycloalkyl, phenyl and -C_{1-6}-alkyl-phenyl are optionally substituted with one or more halogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-haloalkoxy;

R^{11g} and R^{11h} are each independently selected from hydrogen, C_{1-6}-alkyl, -(C_{1-6}-alkyl)phenyl;

R^{11k} is selected from hydrogen and halo-C_{1-6}-alkyl;

R^y is selected from hydrogen and C_{1-6}-alkyl.

In another aspect, the present disclosure provides a process for the preparation of a compound as described above, or a pharmaceutically acceptable salt thereof, comprising reacting of a compound of formula (IX)



(IX)

wherein Y, R^1, R^2 and R^4 are as defined above and PG is an amino protecting group, with a suitable deprotection agent to form said compound of formula (I).

In another aspect, the present disclosure provides the compound as described herein, or a pharmaceutically acceptable salt thereof, when manufactured according to the process as described herein.

In another aspect, the present disclosure provides the compound as described herein, or a pharmaceutically acceptable salt thereof, for use as therapeutically active substance.

In another aspect, the present disclosure provides a pharmaceutical composition comprising a compound as described above, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

In another aspect, the present disclosure provides the compound as described herein, or a pharmaceutically acceptable salt thereof, for use in the treatment, prevention and/or delay of progression of cancer.

In another aspect, the present disclosure provides the use of a compound as described herein, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment, prevention and/or delay of progression of cancer.

In another aspect, the present disclosure provides a compound as described herein, or a pharmaceutically acceptable salt thereof, for use in inhibiting activity of at least one of diacylglycerol kinases selected from DGKα and DGKζ.

In another aspect, the present disclosure provides an *in vitro* method of inhibiting activity of at least one of diacylglycerol kinases selected from DGKα and DGKζ comprising administering a therapeutically effective amount of at least one compound as described herein, or a pharmaceutically acceptable salt thereof.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this disclosure belongs. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the disclosure, suitable methods and materials are described below.

All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety.

The nomenclature used in this application is based on IUPAC systematic nomenclature, unless indicated otherwise.

Detailed description of the invention

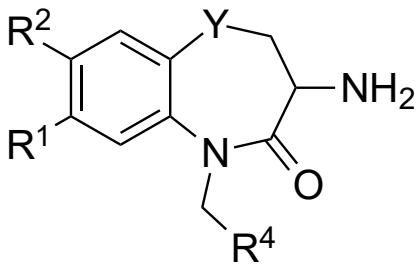
Definitions

"Alkoxy" refers to an alkyl group, as previously defined, attached to the parent molecular moiety via an oxygen atom. Unless otherwise specified, the alkoxy group contains 1 to 12 carbon atoms ("C_{1-12}-alkoxy"), preferably 1 to 10 carbon atoms ("C_{1-10}-alkoxy"), more preferably 1 to 6 carbon atoms ("C_{1-6}-alkoxy"). In some preferred embodiments, the alkoxy group contains 1 to 4 carbon atoms. In still other embodiments, the alkoxy group contains 1 to 3 carbon atoms. Some non-limiting examples of alkoxy groups include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy and tert-butoxy.

"Alkoxyalkyl" refers toan alkyl group, wherein at least one of the hydrogen atoms of the alkyl group has been replaced by an alkoxy group. Preferably, "alkoxyalkyl" refers to an alkyl group wherein 1, 2 or 3 hydrogen atoms, most preferably one hydrogen atom of the alkyl group have been replaced by an alkoxy group. Particularly preferred, yet non-limiting examples of alkoxyalkyl is methoxymethyl and 2-methoxyethyl.

Claims

1. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt thereof, wherein:

Y is S(O), $S(O)_2$ and $S(O)N(R^y)$;

R^1 is 5-membered heteroaryl, wherein R^1 is optionally substituted with one or more R^{10} which can be the same or different;

R^2 is selected from hydrogen and halogen;

R^4 is selected from C_{5-14}-aryl and 5-14 membered heteroaryl, wherein R^4 is optionally substituted with one or more R^{11} which can be the same or different;

R^{10} is $-C(R^{10a}R^{10b})_2-S(O)_2(R^{10c})$;

R^{10a} and R^{10b} are each independently selected from hydrogen and C_{1-6}-alkyl, or R^{10a} and R^{10b}, taken together with the carbon atom to which they are attached, form a C_{3-6}-cycloalkyl;

R^{10c} is selected from hydrogen, C_{1-6}-alkyl, C_{3-6}-cycloalkyl, -N(C_{1-6}-alkyl), halo-C_{1-6}-alkyl, and phenyl, wherein phenyl is optionally substituted with one or more halogen, or C_{1-6}-alkyl;
or R^{10a} and R^{10c}, taken together with the carbon atom and the sulphur atom to which they are attached, form a 3-10 membered heterocyclyl;

R^{11} is selected from:

i) halogen;

ii) 3-10 membered heterocyclyl, optionally substituted with one or more halo-C_{1-6}-alkyl, C_{3-10}-cycloalkyl;

iii) 5-6 membered heteroaryl, optionally substituted with one or more halogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, C_{3-10}-cycloalkyl, C_{1-6}-haloalkoxy;

iv) phenyl, optionally substituted with one or more halogen, cyano, C_{1-6}-alkoxy, C_{1-6}-haloalkyl, C_{1-6}-alkyl;

v) -O(R^{11a});

vi) -N($R^{11g}R^{11h}$); and

vii) –S(R^{11k})

R^{11a} is selected from C_{1-12}-alkyl, halo-C_{1-6}-alkyl, C_{3-7}-cycloalkyl, 3-10 membered -(C_{1-6}-alkyl)heterocyclyl, phenyl and -C_{1-6}-alkyl-phenyl, wherein said C_{1-12}-alkyl, C_{3-7}-cycloalkyl, phenyl and -C_{1-6}-alkyl-phenyl are optionally substituted with one or more halogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-haloalkoxy;

R^{11g} and R^{11h} are each independently selected from hydrogen, C_{1-6}-alkyl, -(C_{1-6}-alkyl)phenyl;

R^{11k} is selected from hydrogen and halo-C_{1-6}-alkyl;

R^{y} is selected from hydrogen and C_{1-6}-alkyl.

2. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein R^1 is oxadiazole or tetrazole, wherein R^1 is optionally substituted with one or more R^{10} which can be the same or different.

3. The compound of claim 1 or 2, or a pharmaceutically acceptable salt thereof, wherein R^1 is oxadiazole, wherein R^1 is optionally substituted with one or more R^{10} which can be the same or different.

4. The compound of any one of claims 1 to 3, or a pharmaceutically acceptable salt thereof, wherein R^2 is selected from hydrogen and fluorine.

5. The compound of any one of claims 1 to 4, or a pharmaceutically acceptable salt thereof, wherein R^4 is phenyl.

6. The compound of any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, wherein R^{10a} and R^{10b} are each independently selected from hydrogen and C_{1-6}-alkyl, or R^{10a} and R^{10b}, taken together with the carbon atom to which they are attached, form a C_{3-6}-cycloalkyl.

7. The compound of any one of claims 1 to 6, or a pharmaceutically acceptable salt thereof, wherein R^{10} is C_{3-6}-cycloalkyl substituted with one $-S(O)_2(C_{1-6}$-alkyl).

8. The compound of any one of claims 1 to 7, or a pharmaceutically acceptable salt thereof, wherein R^{10} is 3-6 membered heterocyclyl, wherein the heteroatom is sulphur, substituted with one or more C_{1-10}-alkyl, oxo, wherein the oxo substitution is on the sulphur atom.

9. The compound of any one of claims 1 to 8, or a pharmaceutically acceptable salt thereof, wherein R^{10} is selected from 1-methyl-methylsulfonyl-ethyl.

10. The compound of any one of claims 1 to 9, or a pharmaceutically acceptable salt thereof, wherein R^{11} is

i) halogen;

ii) 3-10 membered heterocyclyl;

iii) 5-6 membered heteroaryl, optionally substituted with one or more halogen, halo-C_{1-6}-alkyl, C_{3-10}-cycloalkyl, C_{1-6}-haloalkoxy;

iv) phenyl, optionally substituted with one or more cyano, C_{1-6}-alkoxy, C_{1-6}-haloalkyl, C_{1-6}-alkyl;

v) $-O(R^{11a})$; R^{11a} is selected from C_{1-12}-alkyl, halo-C_{1-6}-alkyl, C_{3-7}-cycloalkyl, 5-6 membered -(C_{1-6}-alkyl)heteroaryl, phenyl and -C_{1-6}-alkyl-phenyl, wherein said C_{1-12}-alkyl, phenyl, 5-6 membered -(C_{1-6}-alkyl)heteroaryl and -C_{1-6}-alkyl-phenyl are optionally substituted with one or more halogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-haloalkoxy;

vi) -N($R^{11g}R^{11h}$); R^{11g} and R^{11h} are each independently selected from C_{1-6}-alkyl, -(C_{1-6}-alkyl)phenyl;

vii) –S(halo-C_{1-6}-alkyl);

viii) CH_2-O-phenyl ;

11. The compound of any one of claims 1 to 10, or a pharmaceutically acceptable salt thereof, wherein R^{11} is selected from:

i) -O(R^{11a}), wherein R^{11a} is selected from halo-C_{1-6}-alkyl and phenyl, wherein said phenyl is optionally substituted with one or more halogen; or

ii) phenyl, optionally substituted with one or more C_{1-6}-alkoxy, C_{1-6}-haloalkyl;

iii) halogen

iv) 5-6 membered heteroaryl, optionally substituted with one or more halo-C_{1-6}-alkyl, C_{3-10}-cycloalkyl, C_{1-6}-haloalkoxy.

12. The compound of any one of claims 1 to 11, or a pharmaceutically acceptable salt thereof, wherein R^{11} is selected from (trifluoromethyl)phenyl, (trifluoromethyl)-oxadiazolyl, cyclopropyl-oxadiazolyl, phenoxyl, methoxyphenyl, tetrafluoroethoxyl, dichlorophenoxyl, chloro, trifluoromethoxy-2-pyridyl.

13. The compound of any one of claims 1 to 12, or a pharmaceutically acceptable salt thereof, wherein Y is $S(O)_2$.

14. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Y is S(O), $S(O)_2$ and S(O)N(R^y);

R^1 is 5-membered heteroaryl, wherein R^1 is optionally substituted with one or more R^{10} which can be the same or different;

R^2 is selected from hydrogen and fluorine;

R^4 is selected from C_6-aryl and 6-membered heteroaryl, wherein R^4 is optionally substituted with one or more R^{11} which can be the same or different;

R^{10} is C_{3-6}-cycloalkyl substituted with one $-S(O)_2(C_{1-6}$-alkyl);

R^{11} is

i) halogen;

ii) 3-10 membered heterocyclyl;

iii) 5-6 membered heteroaryl, optionally substituted with one or more halogen, halo-C_{1-6}-alkyl, C_{3-10}-cycloalkyl, C_{1-6}-haloalkoxy;

iv) phenyl, optionally substituted with one or more cyano, C_{1-6}-alkoxy, C_{1-6}-haloalkyl, C_{1-6}-alkyl;

v) $-O(R^{11a})$; R^{11a} is selected from C_{1-12}-alkyl, halo-C_{1-6}-alkyl, C_{3-7}-cycloalkyl, 5-6 membered $-(C_{1-6}$-alkyl)heteroaryl, phenyl and $-C_{1-6}$-alkyl-phenyl, wherein said C_{1-12}-alkyl, phenyl, 5-6 membered $-(C_{1-6}$-alkyl)heteroaryl and $-C_{1-6}$-alkyl-phenyl are optionally substituted with one or more halogen, C_{1-6}-alkyl, halo-C_{1-6}-alkyl, C_{1-6}-alkoxy, C_{1-6}-haloalkoxy;

vi) $-N(R^{11g}R^{11h})$; R^{11g} and R^{11h} are each independently selected from C_{1-6}-alkyl, $-(C_{1-6}$-alkyl)phenyl;

vii) –S(halo-C_{1-6}-alkyl);

viii) CH_2-O-phenyl ;

15. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Y is S(O), $S(O)_2$ and $S(O)N(R^y)$;

R^1 is oxadiazole, wherein R^1 is optionally substituted with one or more R^{10} which can be the same or different;

R^2 is selected from hydrogen and fluorine;

R^4 is phenyl;

R^{10} is selected from methyl-methylsulfonyl-ethyl, cyclopropylsulfonyl-methyl-ethyl, methyl-dioxo-thiolanyl, methylsulfonylmethyl, methylsulfonylcyclobutyl;

R^{11} is selected from:

i) -O(R^{11a}), wherein R^{11a} is selected from halo-C_{1-6}-alkyl, phenyl, wherein said phenyl is optionally substituted with one or more halogen;

ii) phenyl, optionally substituted with one or more C_{1-6}-alkoxy, C_{1-6}-haloalkyl;

iii) halogen; and

iv) 5-6 membered heteroaryl, optionally substituted with one or more halo-C_{1-6}-alkyl, C_{3-10}-cycloalkyl, C_{1-6}-haloalkoxy.

16. The compound of claim 1, or a pharmaceutically acceptable salt thereof, wherein:

Y is S(O), $S(O)_2$ and S(O)N(R^y);

R^1 is oxadiazole, wherein R^1 is optionally substituted with one or more R^{10} which can be the same or different;

R^2 is selected from hydrogen and fluorine;

R^4 is phenyl;

R^{10} is methyl-methylsulfonyl-ethyl;

R^{11} is selected from (trifluoromethyl)phenyl, (trifluoromethyl)-oxadiazolyl, cyclopropyl-oxadiazolyl, phenoxyl, methoxyphenyl, tetrafluoroethoxyl, dichlorophenoxyl, chloro and trifluoromethoxy)-2-pyridyl.

17. The compound of any one of claims 1 to 16, or a pharmaceutically acceptable salt thereof, selected from:

(3R)-3-amino-5-[[4-(1-ethylpropoxy)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;

(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-(2,2,2-trifluoroethoxy)phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;

(3R)-3-amino-5-[[4-(cyclopentoxy)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;

(3R)-3-amino-5-[(4-benzyloxyphenyl)methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-[(4-fluorophenyl)methoxy]phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-[(2-fluorophenyl)methoxy]phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-[(3-fluorophenyl)methoxy]phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-(3,3,3-trifluoropropoxy)phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-(trifluoromethylsulfanyl)phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-(phenoxymethyl)phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[(4-phenoxyphenyl)methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-[3-(difluoromethoxy)phenoxy]phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-5-[[4-(3-methylphenoxy)phenyl]methyl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-(2,3-dichlorophenoxy)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-(3-fluorophenoxy)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-(3-chlorophenoxy)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-(3-chloro-4-fluoro-phenoxy)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-[3-(trifluoromethyl)phenoxy]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-[3-fluoro-5-(trifluoromethyl)phenoxy]phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;

(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-[3-(trifluoromethoxy)phenoxy]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-(3-chloro-5-methoxy-phenoxy)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-(3-chloro-5-methoxy-phenoxy)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
4-[4-[[(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1,4-trioxo-2,3-dihydro-1λ6,5-benzothiazepin-5-yl]methyl]phenyl]benzonitrile;
(3R)-3-amino-5-[[4-(4-methoxyphenyl)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-(3-methoxyphenyl)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-(4-methoxy-2-methyl-phenyl)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-[4-(trifluoromethyl)phenyl]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-(3-bromophenoxy)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-(trifluoromethoxy)phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-1,1-diketo-7-[5-(1-mesyl-1-methyl-ethyl)-1,3,4-oxadiazol-2-yl]-5-[4-[5-(trifluoromethoxy)-2-pyridyl]benzyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-[benzyl(methyl)amino]phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-[isopropyl(methyl)amino]phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-[5-(trifluoromethyl)-2-pyridyl]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;

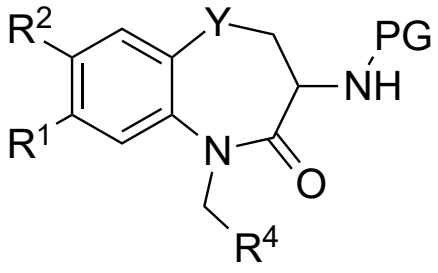
(3R)-3-amino-5-[[4-(5-fluoro-2-pyridyl)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[6-[4-(trifluoromethyl)phenyl]-3-pyridyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-5-[(6-phenoxy-3-pyridyl)methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-5-[[4-(4-methoxyphenyl)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[(4-chlorophenyl)methyl]-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-5-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-(5-cyclopropyl-1,2,4-oxadiazol-3-yl)phenyl]methyl]-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-5-[(4-phenoxyphenyl)methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-5-[[4-(trifluoromethoxy)phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[(4-chlorophenyl)methyl]-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[(4-chlorophenyl)methyl]-8-fluoro-7-[5-(1-methylsulfonylcyclopropyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-5-[(4-tetrahydropyran-4-ylphenyl)methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-5-[[4-(2-methoxy-1,1-dimethyl-ethoxy)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-[4-(trifluoromethyl)phenyl]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-(2,2,2-trifluoroethoxy)phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;

(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-[5-(trifluoromethyl)-2-pyridyl]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[(4-phenoxyphenyl)methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-5-[[4-(4-methoxyphenyl)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-[6-(trifluoromethyl)-3-pyridyl]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-5-[[4-[[3-(trifluoromethyl)-1,2,4-oxadiazol-5-yl]methoxy]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1-oxo-5-[(4-phenoxyphenyl)methyl]-2,3-dihydro-1λ4,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-(4-methoxyphenyl)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methylsulfonylcyclobutyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[(4-phenoxyphenyl)methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methylsulfonylcyclopropyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[(4-phenoxyphenyl)methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-cyclopropylsulfonyl-1-methyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[(4-phenoxyphenyl)methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(2-methyl-1,1-dioxo-thiolan-2-yl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[(4-phenoxyphenyl)methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
2-[5-[(3R)-3-amino-1,1,4-trioxo-5-[[4-[4-(trifluoromethyl)phenyl]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-7-yl]-1,3,4-oxadiazol-2-yl]-N,N-dimethyl-propane-2-sulfonamide;
(3R)-3-amino-7-[5-(1-methyl-1-pyrrolidin-1-ylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-[4-(trifluoromethyl)phenyl]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;

(3R)-3-amino-8-fluoro-7-[2-(methylsulfonylmethyl)tetrazol-5-yl]-1,1-dioxo-5-[(4-phenoxyphenyl)methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one; and
(3R)-3-amino-8-fluoro-7-[1-(methylsulfonylmethyl)tetrazol-5-yl]-1,1-dioxo-5-[(4-phenoxyphenyl)methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one.

18. The compound of any one of claims 1 to 17, or a pharmaceutically acceptable salt thereof, selected from
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-(1,1,2,2-tetrafluoroethoxy)phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-5-[[4-(4-methoxyphenyl)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-5-[(4-phenoxyphenyl)methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-(2,3-dichlorophenoxy)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-(3-chlorophenoxy)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-[4-(trifluoromethyl)phenyl]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[(4-chlorophenyl)methyl]-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-8-fluoro-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-5-[[4-[5-(trifluoromethyl)-1,2,4-oxadiazol-3-yl]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,3,4-oxadiazol-2-yl]-1,1-dioxo-5-[[4-[4-(trifluoromethyl)phenyl]phenyl]methyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one;
(3R)-3-amino-5-[[4-(4-methoxyphenyl)phenyl]methyl]-7-[5-(1-methyl-1-methylsulfonyl-ethyl)-1,2,4-oxadiazol-3-yl]-1,1-dioxo-2,3-dihydro-1λ6,5-benzothiazepin-4-one; and
(3R)-3-amino-1,1-diketo-7-[5-(1-mesyl-1-methyl-ethyl)-1,3,4-oxadiazol-2-yl]-5-[4-[5-(trifluoromethoxy)-2-pyridyl]benzyl]-2,3-dihydro-1λ6,5-benzothiazepin-4-one.

19. A process for the preparation of a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, comprising reacting of compound of formula (IX)



(IX)

wherein Y, R^1, R^2 and R^4 are as defined in any one of claims 1 to 18 and PG is an amino protecting group, with a suitable deprotection agent to form said compound of formula (I).

20. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, when manufactured according to the process of claim 19.

21. The compound of any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, for use as therapeutically active substance.

22. A pharmaceutical composition comprising a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable excipient.

23. The pharmaceutical composition according to claim 22, further comprising an additional therapeutic agent.

24. The compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, for use in the treatment, prevention and/or delay of progression of cancer.

25. The compound for use according to claim 24, wherein the cancer is associated with aberrant diacylglycerol kinase signaling, wherein the diacylglycerol kinase is selected from DGKα and/or DGKζ.

26. The compound for use according to claim 24 or 25, wherein the cancer is selected from the group consisting of B-cell acute lymphoid leukemia, T-cell acute lymphoid leukemia, acute lymphoid leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia B-cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma,

diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom's macroglobulinemia, preleukemia, sarcoma, carcinoma, melanoma, neuroblastoma, renal cell carcinoma, colon cancer, colorectal cancer, breast cancer, epithelial squamous cell cancer, melanoma, stomach cancer, brain cancer, lung cancer (e.g., NSCLC), pancreatic cancer, cervical cancer, ovarian cancer, liver cancer, bladder cancer, prostate cancer, testicular cancer, thyroid cancer, uterine cancer, adrenal cancer and head and neck cancer.

27. The use of a compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, in the preparation of a medicament for the treatment, prevention and/or delay of progression of cancer.

28. The use of claim 27, wherein the cancer is selected from the group consisting of B-cell acute lymphoid leukemia, T-cell acute lymphoid leukemia, acute lymphoid leukemia, chronic myelogenous leukemia, chronic lymphocytic leukemia B-cell prolymphocytic leukemia, blastic plasmacytoid dendritic cell neoplasm, Burkitt's lymphoma, diffuse large B cell lymphoma, follicular lymphoma, hairy cell leukemia, small cell- or a large cell-follicular lymphoma, malignant lymphoproliferative conditions, MALT lymphoma, mantle cell lymphoma, Marginal zone lymphoma, multiple myeloma, myelodysplasia and myelodysplastic syndrome, non-Hodgkin's lymphoma, plasmablastic lymphoma, plasmacytoid dendritic cell neoplasm, Waldenstrom's macroglobulinemia, preleukemia, sarcoma, carcinoma, melanoma, neuroblastoma, renal cell carcinoma, colon cancer, colorectal cancer, breast cancer, epithelial squamous cell cancer, melanoma, stomach cancer, brain cancer, lung cancer (e.g., NSCLC), pancreatic cancer, cervical cancer, ovarian cancer, liver cancer, bladder cancer, prostate cancer, testicular cancer, thyroid cancer, uterine cancer, adrenal cancer and head and neck cancer.

29. A compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof, for use in inhibiting activity of at least one of diacylglycerol kinases selected from DGKα and DGKζ.

30. An *in vitro* method of inhibiting activity of at least one of diacylglycerol kinases selected from DGKα and DGKζ comprising administering a therapeutically effective amount of at least one compound according to any one of claims 1 to 18, or a pharmaceutically acceptable salt thereof.

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