viability and proliferation, but also restored T cell cytokine secretion. These results showed that ENTs inhibitors either alone or in combination with an adenosine receptor antagonist may be useful for the treatment of cancers.

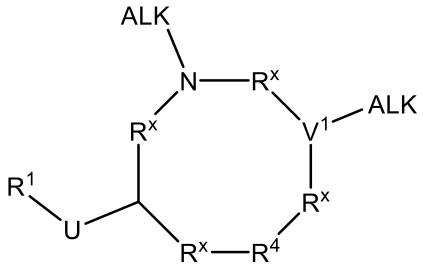
[0006] A variety of drugs such as dilazep, dipyridamole, and draflazine interact with ENTs and alter adenosine levels, and were developed for their cardioprotective or vasodilatory effects.

[0007] Currently, two non-selective ENT1 inhibitors (dilazep and dipyridamole) are on the market (Vlachodimou et al., Bio-Chemical Pharmacology, 2020, 172, 113747). However, their binding kinetics are unknown; moreover, there is still a need for more potent ENTs inhibitors, and especially ENT1 inhibitors to be used for the treatment of cancers, either alone or in combination with an adenosine receptor antagonist.

[0008] Hence, this study focused on finding new and improved ENT1 inhibitors. For that purpose, the Applicant herein provides the macrocyclic diamine derivatives of formula I and II detailed below.

SUMMARY

[0008a] In one aspect of the present disclosure, there is provided a compound of formula I:

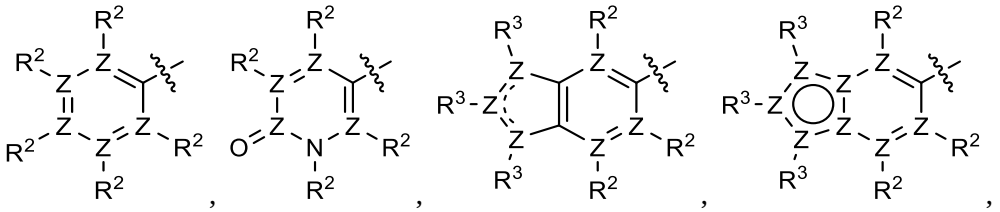


(I)

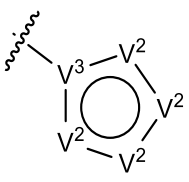
or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is selected from the group consisting of



, and

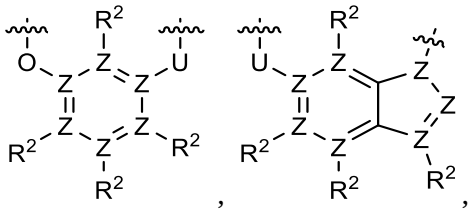


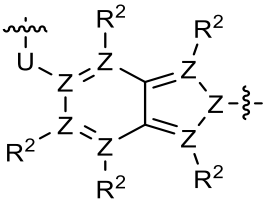
;

each R^2 is independently selected from the group consisting of absent, halogen, -NHR^3, -OR^3, -R^3, -$C(O)R^3$, -CO_2R^3, $C(O)N(R^3)_2$, -$CH_2C(O)N(R^3)_2$, -$S(O)_2R^3$, and -CN;

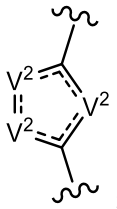
or two instances of R^2 are taken together with the atoms on which they are attached to form a heterocylyl or heteroaryl ring;

each R^3 is independently selected from absent, -H, oxo, ALK, phenyl, heterocylyl, and heteroaryl;

R^4 is selected from the group consisting of  , and

 ;

U is selected from the group consisting of -C(O)-, alkylene , -O-, -$N(R^3)$-, -C(O)O-, -$C(O)N(R^3)$-, and

 ;

each R^x is independently selected from alkylene,

V^1 is selected from -$C(R^3)$-, and -N-;

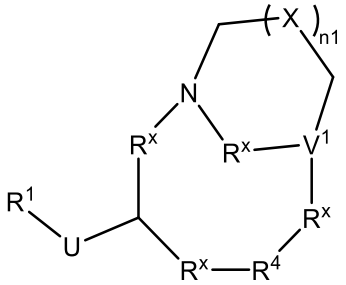
each V^2 is independently selected from -$C(R^3)$=, -$N(R^3)$-, -N=, and -O-;

V^3 is selected from –C=, and -N-; and

Z is C or N,

wherein ALK is unsubstitued alkyl or substituted alkyl, or two instances of ALK may be joined together with their intervening atoms to form a cycloalkyl or heterocyclyl ring.

[0008b]In another aspect of the present disclosure, there is provided a compound of formula II:

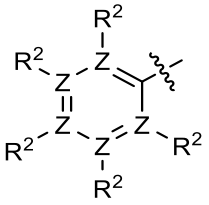
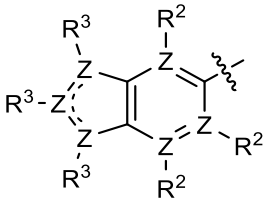
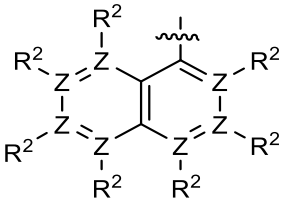
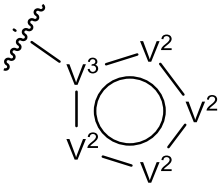


(II)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

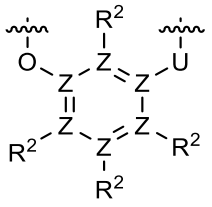
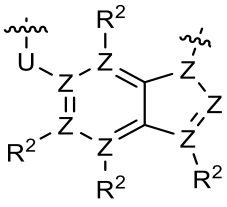
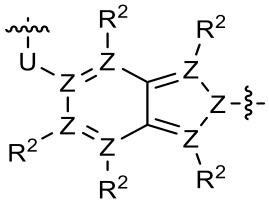
R^1 is selected from the group consisting of ALK, cycloalkyl, heterocylyl,

 ,  ,  , and  ;

each R^2 is independently selected from the group consisting of absent, halogen, $-OR^3$, $-R^3$, $-CO_2R^3$, $C(O)N(R^3)_2$, $-CH_2C(O)N(R^3)_2$, $-S(O)_2R^3$, and -CN;

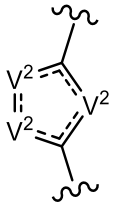
or two instances of R^2 are taken together with the atoms on which they are attached to form a heterocylyl or heteroaryl ring;

each R^3 is independently selected from absent, -H, ALK, phenyl, and heteroaryl;

R^4 is  ,  or  ;

X is selected from the group consisting of $-CH_2-$, -CHF-, $-CF_2-$;

each U is indendently selected from the group consisting of -O-, $-N(R^3)-$, -C(O)O-, $-C(O)N(R^3)-$,

 , -C(O)-, -O-N=C(H)- and alkylene;

each R^x is independently selected from alkylene;

V^1 is selected from $-C(R^3)-$, and -N-;

each V^2 is independently selected from $-C(R^3)=$, $-N(R^3)-$, -N=, and -O-;

V^3 is selected from –C=, and -N-; and

each Z is independently C or N; and

n^1 is a number of 0 or 1,

wherein ALK is unsubstitued alkyl or substituted alkyl, or two instances of ALK may be joined together with their intervening atoms to form a cycloalkyl or heterocyclyl ring.

[0008c] In a further aspect of the present disclosure, there is provided a compound selected from the group consisting of:

(12S)-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

16,16-difluoro-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12S)-16,16-difluoro-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-16,16-difluoro-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

N-(7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl)-3,4,5-trimethoxybenzamide

7^4,7^5-dimethoxy-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12S)-7^4,7^5-dimethoxy-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-7^4,7^5-dimethoxy-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

7^4,7^5-dimethoxy-5-methyl-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12S)-7^4,7^5-dimethoxy-5-methyl-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-7^4,7^5-dimethoxy-5-methyl-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(11R)-7^4,7^5-dimethoxy-6-oxo-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotridecaphane-11-yl 3,4,5-trimethoxybenzoate

(10S)-14-chloro-2-oxo-11H-3-aza-1(6,1)-indazola-7(1,4)-diazepanacyclotridecaphane-10-yl 3,4,5-trimethoxybenzoate

(10R)-14-chloro-2-oxo-11H-3-aza-1(6,1)-indazola-7(1,4)-diazepanacyclotridecaphane-10-yl 3,4,5-trimethoxybenzoate

(12S)-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12S)-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl benzoate

(12R)-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl benzoate

7^4,7^5-dichloro-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12S)-7^4,7^5-dichloro-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-7^4,7^5-dichloro-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

7^5-carbamoyl-7^4-chloro-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(11Z,16E,10S)-14-chloro-2-oxo-12H-3-aza-1(6,2)-indazola-7(1,4)-diazepanacyclotridecaphane-10-yl 3,4,5-trimethoxybenzoate

(11Z,16E,10R)-14-chloro-2-oxo-12H-3-aza-1(6,2)-indazola-7(1,4)-diazepanacyclotridecaphane-10-yl 3,4,5-trimethoxybenzoate

(12S)-7^4-carbamoyl-7^5-chloro-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-7^4-carbamoyl-7^5-chloro-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

7^4-bromo-7^5-chloro-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

7^5-chloro-7^4-cyano-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl benzoate

(12R)-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl benzoate

(12S)-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl benzoate

(Z)-benzaldehyde O-(7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl) oxime

12-hydroxy-7^4,7^5-dimethoxy-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphan-6-one7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-hydroxybenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-fluorobenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-isopropoxybenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(trifluoromethyl)benzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(methylsulfonyl)benzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-phenoxybenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 2-fluorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-bromo-3-cyanobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-methyl-5-(trifluoromethyl)benzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 2-fluoro-4-methoxybenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-methoxy-2-(trifluoromethoxy)benzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl picolinate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl nicotinate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl pyrazine-2-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 6-hydroxynicotinate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl quinoline-5-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl oxazole-4-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 1H-1,2,3-triazole-4-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl acetate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl cyclopropanecarboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-methylbutanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4,4,4-trifluorobutanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl cyclohexanecarboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 1-methylpiperidine-4-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,3-dimethylcyclobutane-1-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 2-(oxetan-3-yl)acetate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl (1R,5S,6r)-3-oxabicyclo[3.1.0]hexane-6-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 5-oxopyrrolidine-3-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 1-benzyl-5-oxopyrrolidine-3-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-methoxycyclohexane-1-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 2,6-difluorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-(trifluoromethoxy)benzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-cyanobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 2-oxo-1,2,3,4-tetrahydroquinoline-6-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(difluoromethoxy)benzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,5-dichlorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4-dichlorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 2,3-dichlorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 2-chloro-6-fluoro-3-methylbenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-fluoro-5-(trifluoromethyl)benzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-fluoro-3-(trifluoromethyl)benzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-cyano-3-fluorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-(trifluoromethyl)benzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,5-difluorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4-difluorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-cyano-4-fluorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-cyanobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-chloro-4-fluorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 1-methyl-1H-benzo[d]imidazole-5-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-(oxazol-5-yl)benzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4,5-dichloro-2-fluorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-triethoxybenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-methoxypropanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(1H-pyrazol-1-yl)propanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-cyanopropanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-cyanobutanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-acetamidobutanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(1H-tetrazol-1-yl)propanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-(dimethylamino)-4-oxobutanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-acetamidopropanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-(methylamino)-4-oxobutanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(1H-1,2,4-triazol-1-yl)propanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-morpholino-4-oxobutanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(4-fluorophenoxy)propanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4,4-difluorocyclohexane-1-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-(trifluoromethyl)cyclohexane-1-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(2,5-dioxopyrrolidin-1-yl)propanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-methoxycyclohexane-1-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl benzoate

(E)-benzaldehyde O-($7^4,7^5$-dimethoxy-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl) oxime

(E)-benzaldehyde O-((12R)-$7^4,7^5$-dimethoxy-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl) oxime

(E)-benzaldehyde O-((12S)-$7^4,7^5$-dimethoxy-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl) oxime12-hydroxy-$7^4,7^5$-dimethoxy-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphan-6-one,

and pharmaceutically acceptable salts or solvates thereof.

[0008d]In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein and at least one pharmaceutically acceptable excipient.

[0008e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for inhibiting ENT1 in a patient need thereof.

[0008f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating cancer in a patient need thereof.

[0008g] In a further aspect of the present disclosure, there is provided a use of a combination of a compound disclosed herein and an adenosine receptor antagonist, in the manufacture of a medicament for treating cancer in a patient need thereof.

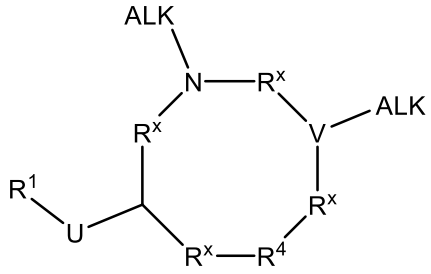
[0008h] In another aspect of the present disclosure, there is provided a kit of parts comprising:

(a) a first part comprising an effective amount of a compound disclosed herein; and

(b) a second part comprising an effective amount of an adenosine receptor antagonist.

[0008i] In a further aspect of the present disclosure, there is provided a compound disclosed herein for use in therapy.

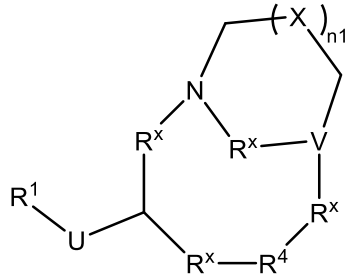
[0009] This present disclosure thus relates to a compound of formula I:



(I)

or a pharmaceutically acceptable salt or solvate thereof, wherein R^x, R^1, R^4, U, V, and ALK are hereafter defined.

[0010] This present disclosure also relates to a compound of formula II:



(II)

or a pharmaceutically acceptable salt or solvate thereof, wherein R^x, R^1, R^4, U, V, X, and n^1 are hereafter defined.

[0011] According to one example, the compound of the present disclosure is of formula IIa or IIa1 as defined hereafter. Preferably, the compound of the present disclosure is selected from the compounds listed in Table 1 hereafter.

[0012] In some examples, the compound according to the present disclosure comprises one chiral center.

[0013] In some examples, the compound according to the present disclosure is racemic mixture containing 'R' isomer and 'S' isomer.

[0014] In some examples, the compound according to the present disclosure is 'R' isomer.

[0015] In some examples, the compound according to the present disclosure is 'S' isomer.

[0016] In some examples, the compound according to the present disclosure comprises more than one chiral center. In some examples, each chiral center comprises the same configuration. In some examples, each chiral center comprises "R" or "S" configurations independently.

[0017] The present disclosure also relates to a pharmaceutical composition comprising a compound of formula I or formula II according to the present disclosure and at least one pharmaceutically acceptable excipient.

[0018] In one example, the pharmaceutical composition according to the present disclosure, further comprises an adenosine receptor antagonist. In one example, the adenosine receptor antagonist is an A2A or A2B receptor antagonist.

[0019] In one example, the adenosine receptor antagonist is selected from:

[0020] 5-bromo-2,6-di-(1H-pyrazol-1-yl)pyrimidin-4-amine;

[0021] (S)-7-(5-methylfuran-2-yl)-3-((6-(([[tetrahydrofuran-3-yl]oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine;

[0022] 6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine;

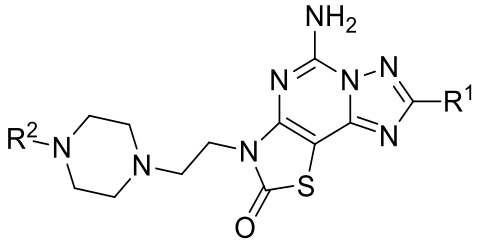
[0023] 3-(2-amino-6-(1-((6-(2-hydroxypropan-2-yl)pyridin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)pyrimidin-4-yl)-2-methylbenzonitrile;

[0024] 2-(2-furanyl)-7-(2-(4-(4-(2-methoxyethoxy)phenyl)-1-piperazinyl)ethyl)-7H-pyrazolo(4,3-e)(1,2,4)triazolo(1,5-c)pyrimidine-5-amine;

[0025] 3-(4-amino-3-methylbenzyl)-7-(2-furyl)-3H-(1,2,3)triazolo(4,5-d)pyrimidine-5-amine; and

[0026] 4-hydroxy-N-(4-methoxy-7-morpholinobenzo[d]thiazol-2-yl)-4-methylpiperidine-1-carboxamide.

[0027] In another example, the adenosine receptor antagonist is the adenosine receptor antagonist is a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 and R^2 are as defined hereafter.

[0028] The present disclosure further relates to a method of inhibiting ENT1 in a patient need thereof, comprising: administering to said patient an effective amount of a compound of formula I or formula II according to the present disclosure.

[0029] The present disclosure also relates to method of treating cancer in a patient need thereof, comprising: administering to said patient an effective amount of a compound of formula I or II according to the

present disclosure.

[0030] The present disclosure is also directed to a method of treating cancer in a patient need thereof, comprising: administering to said patient a combination of a compound of formula I or II according to the present disclosure and an adenosine receptor antagonist. In one example, the compound of formula I or II according to the present disclosure is administered prior to, concomitant with, or subsequent to administration of the adenosine receptor antagonist. In one example, the adenosine receptor antagonist is an A2A or A2B receptor antagonist. In one example, the adenosine receptor antagonist is selected among those listed above.

[0031] The present disclosure further relates to a kit of parts comprising: (a) a first part comprising an effective amount of a compound of formula I or II according to the present disclosure; and (b) a second part comprising an effective amount of an adenosine receptor antagonist.

[0032] In one example, in the kit of parts, the adenosine receptor antagonist is an A2A or A2B receptor antagonist, and is preferably selected among those listed above.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] FIG. 1A depicts a graph of log concentration (M) versus percent proliferation. Purified human T cells were activated with anti-CD3/CD28 dynabeads in the presence of ATP (100 µM) as a source of adenosine for 96h and then proliferation was assessed by CFSE dilution.

[0034] FIG. 1B depicts a graph of log concentration of ENT1 inhibitor (M) versus percent proliferation. Experiment performed as in FIG. A with the addition of HSA and AAG to the culture medium (final concentration 2 and 0.1%, respectively).

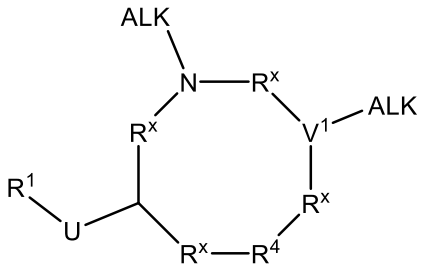
[0035] FIG. 2A depicts a bar graph of percent proliferation normalized to no ATP. Naïve $CD4^+$ T cells were cultured with allogeneic monocyte-derived dendritic cells at a ratio of 10:1 for 96h in the presence of 300 µM ATP as a source of adenosine and the molecules Compound 2 (50 nM), Compound 11 (500 nM) or concentration-matched DMSO. Proliferation of T cells was assessed by CFSE dilution and normalized to the level observed in T cells activated in the absence of ATP.

[0036] FIG. 2B depicts two bar graphs, one showing TNF concentration (pg/mL), and the other showing IFNγ (pg/mL). Experiment performed as described in FIG. 2A and supernatant sampled for analysis of cytokines by alphaLISA. **** = $p < 0{,}0001$; *** = $p < 0{,}001$; ** = $p < 0{,}01$ and * = $p < 0{,}05$; derived from one-way ANOVA with Tukey's multiple comparisons test.

[0037] FIG. 3 depicts a bar graph of percent tetramer. PBMCs from a healthy volunteer donor with previous history of CMV infection and known HLA-A*02 subtype were cultured for 7 days with a peptide (NLVPMVATV) derived from the immunodominant CMV antigen pp65 alongside IL-2, IL-7 and the anti-PD1 antibody nivolumab. ATP was added to the cultures as a source of adenosine, alongside the ENT1 inhibitor molecules as indicated. Expansion of the peptide-specific $CD8^+$ T cell population was monitored via flow cytometry using NLVPMVATV-MHC-I tetramers linked with BV421. ** = $p < 0{,}01$; * = $p < 0{,}05$; derived from one-way ANOVA with Tukey's multiple comparisons test from technical replicates in a single experiment.

WHAT IS CLAIMED IS:

1. A compound of formula I:

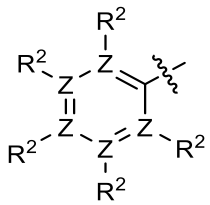
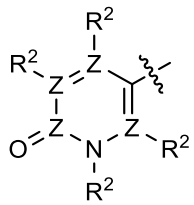
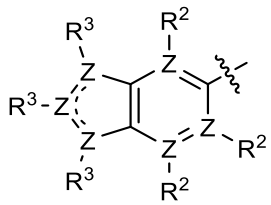
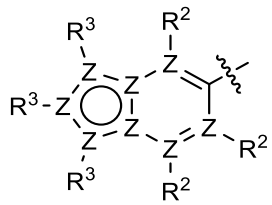


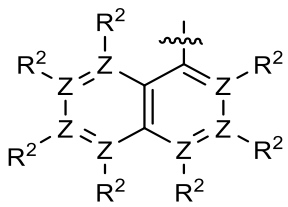
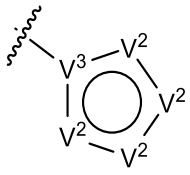
(I)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

R^1 is selected from the group consisting of

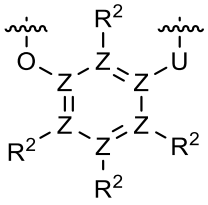
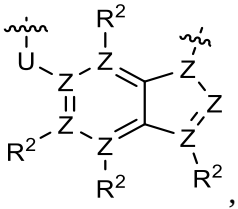
 ,  ,  ,  ,

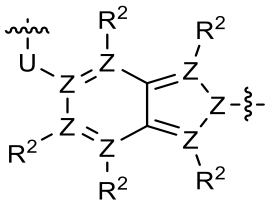
 , and  ;

each R^2 is independently selected from the group consisting of absent, halogen, $-NHR^3$, $-OR^3$, $-R^3$, $-C(O)R^3$, $-CO_2R^3$, $C(O)N(R^3)_2$, $-CH_2C(O)N(R^3)_2$, $-S(O)_2R^3$, and -CN;

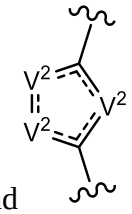
or two instances of R^2 are taken together with the atoms on which they are attached to form a heterocylyl or heteroaryl ring;

each R^3 is independently selected from absent, -H, oxo, ALK, phenyl, heterocylyl, and heteroaryl;

R^4 is selected from the group consisting of  ,  , and

 ;

U is selected from the group consisting of -C(O)-, alkylene , -O-, -N(R^3)-, -C(O)O-, -C(O)N(R^3)-,

 and ;

each R^x is independently selected from alkylene,

V^1 is selected from -C(R^3)-, and -N-;

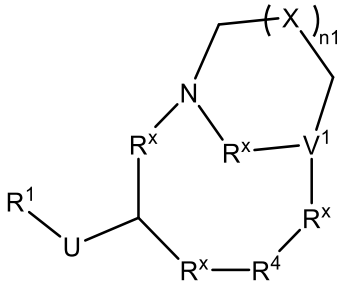
each V^2 is independently selected from -C(R^3)=, -N(R^3)-, -N=, and -O-;

V^3 is selected from –C=, and -N-; and

Z is C or N,

wherein ALK is unsubstitued alkyl or substituted alkyl, or two instances of ALK may be joined together with their intervening atoms to form a cycloalkyl or heterocyclyl ring.

2. A compound of formula II:

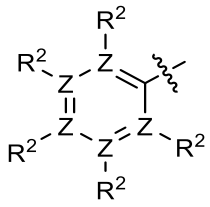
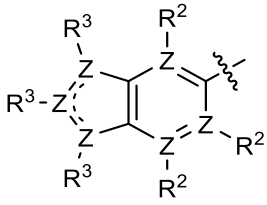
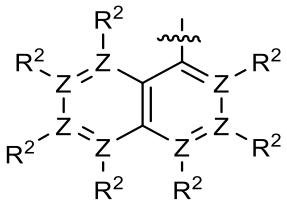
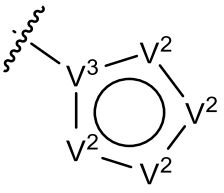


(II)

or a pharmaceutically acceptable salt or solvate thereof,

wherein

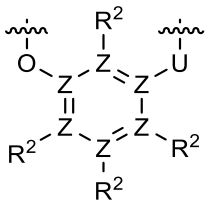
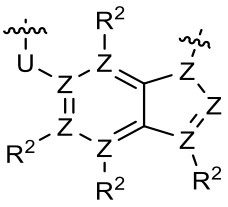
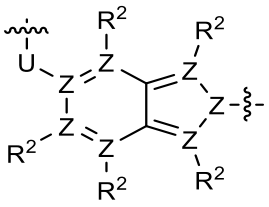
R^1 is selected from the group consisting of ALK, cycloalkyl, heterocylyl,

 ,  ,  , and  ;

each R^2 is independently selected from the group consisting of absent, halogen, $-OR^3$, $-R^3$, $-CO_2R^3$, $C(O)N(R^3)_2$, $-CH_2C(O)N(R^3)_2$, $-S(O)_2R^3$, and -CN;

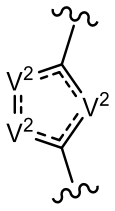
or two instances of R^2 are taken together with the atoms on which they are attached to form a heterocylyl or heteroaryl ring;

each R^3 is independently selected from absent, -H, ALK, phenyl, and heteroaryl;

R^4 is  ,  or  ;

X is selected from the group consisting of $-CH_2-$, -CHF-, $-CF_2-$;

each U is indendently selected from the group consisting of -O-, $-N(R^3)-$, -C(O)O-, $-C(O)N(R^3)-$,

 , -C(O)-, -O-N=C(H)- and alkylene;

each R^x is independently selected from alkylene;

V^1 is selected from $-C(R^3)-$, and -N-;

each V^2 is independently selected from $-C(R^3)=$, $-N(R^3)-$, -N=, and -O-;

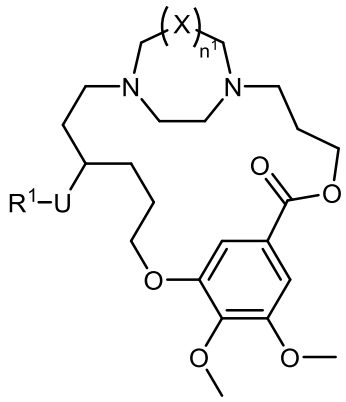
V^3 is selected from –C=, and -N-; and

each Z is independently C or N; and

n^1 is a number of 0 or 1,

wherein ALK is unsubstitued alkyl or substituted alkyl, or two instances of ALK may be joined together with their intervening atoms to form a cycloalkyl or heterocyclyl ring.

3. The compound according to claim 2, of formula IIa:



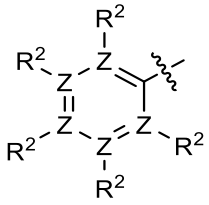
(IIa),

or a pharmaceutically acceptable salt or solvate thereof

wherein

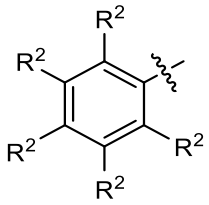
X is CH_2, CHF, or CF_2.

4. The compound of any of claims 1-3, wherein R^1 is



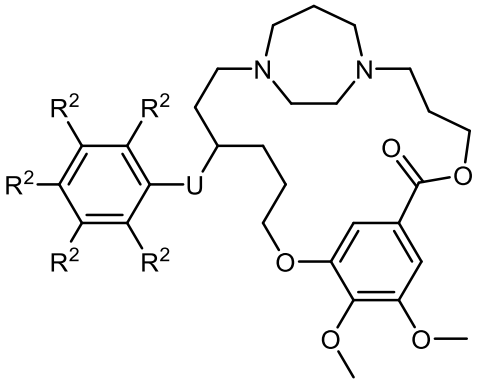
.

5. The compound of claim 4, wherein R^1 is



.

6. The compound of any of claims 1-5, wherein the compound is a compound of formula (IIb):

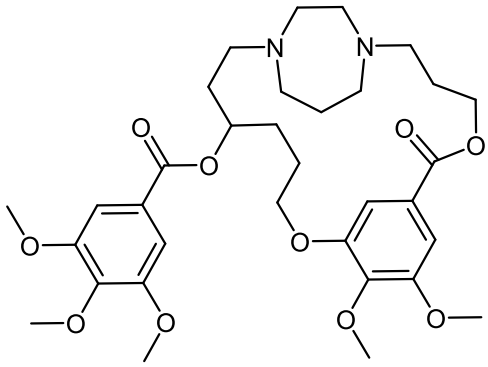


(IIb),

or a pharmaceutically acceptable salt or solvate thereof.

7. The compound of any of claims 1-6, wherein U is -C(O)O-.

8. The compound according to claim 2, of formula IIa1:



(IIa1)

or a pharmaceutically acceptable salt or solvate thereof.

9. A compound selected from the group consisting of:

(12S)-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

16,16-difluoro-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12S)-16,16-difluoro-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-16,16-difluoro-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

N-(7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl)-3,4,5-trimethoxybenzamide

7^4,7^5-dimethoxy-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12S)-7^4,7^5-dimethoxy-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-7^4,7^5-dimethoxy-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

7^4,7^5-dimethoxy-5-methyl-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12S)-7^4,7^5-dimethoxy-5-methyl-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-7^4,7^5-dimethoxy-5-methyl-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(11R)-7^4,7^5-dimethoxy-6-oxo-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotridecaphane-11-yl 3,4,5-trimethoxybenzoate

(10S)-14-chloro-2-oxo-11H-3-aza-1(6,1)-indazola-7(1,4)-diazepanacyclotridecaphane-10-yl 3,4,5-trimethoxybenzoate

(10R)-14-chloro-2-oxo-11H-3-aza-1(6,1)-indazola-7(1,4)-diazepanacyclotridecaphane-10-yl 3,4,5-trimethoxybenzoate

(12S)-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12S)-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl benzoate

(12R)-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl benzoate

7^4,7^5-dichloro-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12S)-7^4,7^5-dichloro-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-7^4,7^5-dichloro-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

7^5-carbamoyl-7^4-chloro-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(11Z,16E,10S)-14-chloro-2-oxo-12H-3-aza-1(6,2)-indazola-7(1,4)-diazepanacyclotridecaphane-10-yl 3,4,5-trimethoxybenzoate

(11Z,16E,10R)-14-chloro-2-oxo-12H-3-aza-1(6,2)-indazola-7(1,4)-diazepanacyclotridecaphane-10-yl 3,4,5-trimethoxybenzoate

(12S)-7^4-carbamoyl-7^5-chloro-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-7^4-carbamoyl-7^5-chloro-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

7^4-bromo-7^5-chloro-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

7^5-chloro-7^4-cyano-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-trimethoxybenzoate

(12R)-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl benzoate

(12R)-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl benzoate

(12S)-7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl benzoate

(Z)-benzaldehyde O-(7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl) oxime

12-hydroxy-7^4,7^5-dimethoxy-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphan-6-one7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-hydroxybenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-fluorobenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-isopropoxybenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(trifluoromethyl)benzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(methylsulfonyl)benzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-phenoxybenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 2-fluorobenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-bromo-3-cyanobenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-methyl-5-(trifluoromethyl)benzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 2-fluoro-4-methoxybenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-methoxy-2-(trifluoromethoxy)benzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl picolinate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl nicotinate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl pyrazine-2-carboxylate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 6-hydroxynicotinate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl quinoline-5-carboxylate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl oxazole-4-carboxylate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 1H-1,2,3-triazole-4-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl acetate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl cyclopropanecarboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-methylbutanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4,4,4-trifluorobutanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl cyclohexanecarboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 1-methylpiperidine-4-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,3-dimethylcyclobutane-1-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 2-(oxetan-3-yl)acetate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl (1R,5S,6r)-3-oxabicyclo[3.1.0]hexane-6-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 5-oxopyrrolidine-3-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 1-benzyl-5-oxopyrrolidine-3-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-methoxycyclohexane-1-carboxylate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 2,6-difluorobenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-(trifluoromethoxy)benzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-cyanobenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 2-oxo-1,2,3,4-tetrahydroquinoline-6-carboxylate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(difluoromethoxy)benzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,5-dichlorobenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4-dichlorobenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 2,3-dichlorobenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 2-chloro-6-fluoro-3-methylbenzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-fluoro-5-(trifluoromethyl)benzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-fluoro-3-(trifluoromethyl)benzoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-cyano-3-fluorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-(trifluoromethyl)benzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,5-difluorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4-difluorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-cyano-4-fluorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-cyanobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-chloro-4-fluorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 1-methyl-1H-benzo[d]imidazole-5-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-(oxazol-5-yl)benzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4,5-dichloro-2-fluorobenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3,4,5-triethoxybenzoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-methoxypropanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(1H-pyrazol-1-yl)propanoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-cyanopropanoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-cyanobutanoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-acetamidobutanoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(1H-tetrazol-1-yl)propanoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-(dimethylamino)-4-oxobutanoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-acetamidopropanoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-(methylamino)-4-oxobutanoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(1H-1,2,4-triazol-1-yl)propanoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-morpholino-4-oxobutanoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(4-fluorophenoxy)propanoate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4,4-difluorocyclohexane-1-carboxylate

7^4,7^5-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 4-(trifluoromethyl)cyclohexane-1-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-(2,5-dioxopyrrolidin-1-yl)propanoate

$7^4,7^5$-dimethoxy-6-oxo-5,8-dioxa-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl 3-methoxycyclohexane-1-carboxylate

$7^4,7^5$-dimethoxy-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl benzoate

(E)-benzaldehyde O-($7^4,7^5$-dimethoxy-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl) oxime

(E)-benzaldehyde O-((12R)-$7^4,7^5$-dimethoxy-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl) oxime

(E)-benzaldehyde O-((12S)-$7^4,7^5$-dimethoxy-6-oxo-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphane-12-yl) oxime12-hydroxy-$7^4,7^5$-dimethoxy-8-oxa-5-aza-1(1,4)-diazepana-7(1,3)-benzenacyclotetradecaphan-6-one,

and pharmaceutically acceptable salts or solvates thereof.

10. The compound according to any one of the claims preceding, wherein the compound comprises only one chiral center.

11. The compound according to claim 10, wherein the compound is racemic mixture containing 'R' isomer and 'S' isomer.

12 The compound according to claim 10, wherein the compound is 'R' isomer.

13. The compound according to claim 10, wherein the compound is 'S' isomer.

14. The compound according to any one of the claims 1-9, wherein the compound comprises more than one chiral center.

15. The compound according to claim 14, wherein the chiral centers comprise 'R' or ‘S' configurations independently.

16. The compound according to claim 14, wherein the chiral centers comprise the same configuration.

17. A pharmaceutical composition comprising a compound according to any one of the claims preceding and at least one pharmaceutically acceptable excipient.

18. The pharmaceutical composition according to claim 17, further comprising an adenosine receptor antagonist.

19. The pharmaceutical composition according to claim 18, wherein the adenosine receptor antagonist is an A2A or A2B receptor antagonist.

20. The pharmaceutical composition according to claim 18, wherein the adenosine receptor antagonist is selected from:

5-bromo-2,6-di-(1H-pyrazol-1-yl)pyrimidin-4-amine;

(S)-7-(5-methylfuran-2-yl)-3-((6-(([tetrahydrofuran-3-yl]oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine;

6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine;

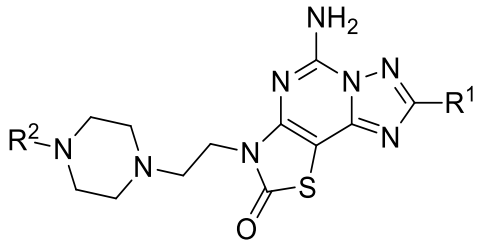
3-(2-amino-6-(1-((6-(2-hydroxypropan-2-yl)pyridin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)pyrimidin-4-yl)-2-methylbenzonitrile;

2-(2-furanyl)-7-(2-(4-(4-(2-methoxyethoxy)phenyl)-1-piperazinyl)ethyl)-7H-pyrazolo(4,3-e)(1,2,4)triazolo(1,5-c)pyrimidine-5-amine;

3-(4-amino-3-methylbenzyl)-7-(2-furyl)-3H-(1,2,3)triazolo(4,5-d)pyrimidine-5-amine; and

4-hydroxy-N-(4-methoxy-7-morpholinobenzo[d]thiazol-2-yl)-4-methylpiperidine-1-carboxamide.

21. The pharmaceutical composition according to claim 18, wherein the adenosine receptor antagonist is a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is a 5- or 6-membered heteroaryl or 5- or 6-membered aryl, wherein heteroaryl or aryl groups are optionally substituted by one or more substituent selected from C_1-C_6 alkyl and halo;

R^2 is a 6-membered aryl or 6-membered heteroaryl,

wherein heteroaryl or aryl groups are optionally substituted by one or more substituent selected from halo, alkyl, heterocyclyl, alkoxy, cycloalkyloxy, heterocyclyloxy, carbonyl, alkylcarbonyl, aminocarbonyl, hydroxycarbonyl, heterocyclylcarbonyl, alkylsulfoxide, alkylsulfonyl, aminosulfonyl, heterocyclylsulfonyl, alkylsulfonimidoyl, carbonylamino, sulfonylamino and alkylsulfonealkyl;

said substituents being optionally substituted by one or more substituent selected from oxo, halo, hydroxy, cyano, alkyl, alkenyl, aldehyde, heterocyclylalkyl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, (heterocyclyl)(alkyl)aminoalkyl, heterocyclyl, heteroaryl, alkylheteroaryl, alkyne, alkoxy, amino, dialkylamino, aminoalkylcarbonylamino, aminocarbonylalkylamino, (aminocarbonylalkyl)(alkyl)amino, alkenylcarbonylamino, hydroxycarbonyl, alkyloxycarbonyl, aminocarbonyl, aminoalkylaminocarbonyl, alkylaminoalkylaminocarbonyl, dialkylaminoalkylaminocarbonyl, heterocyclylalkylaminocarbonyl, (alkylaminoalkyl)(alkyl)aminocarbonyl, alkylaminoalkylcarbonyl, dialkylaminoalkylcarbonyl, heterocyclylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkylsulfoxide, alkylsulfoxidealkyl alkylsulfonyl and alkylsulfonealkyl;

or the heteroaryl or aryl groups are optionally substituted with two substituents that form together with the atoms to which they are attached a 5- or 6-membered aryl ring, a 5- or 6-membered heteroaryl ring, a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocyclyl ring; optionally substituted by one or more substituent selected from oxo, halo, hydroxy, cyano, alkyl, alkenyl, aldehyde, heterocyclylalkyl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, (heterocyclyl)(alkyl)aminoalkyl, heterocyclyl, heteroaryl, alkylheteroaryl, alkyne, alkoxy, amino, dialkylamino, aminoalkylcarbonylamino, aminocarbonylalkylamino, (aminocarbonylalkyl)(alkyl)amino, alkenylcarbonylamino, hydroxycarbonyl, alkyloxycarbonyl, aminocarbonyl, aminoalkylaminocarbonyl, alkylaminoalkylaminocarbonyl, dialkylaminoalkylaminocarbonyl, heterocyclylalkylaminocarbonyl, (alkylaminoalkyl)(alkyl)aminocarbonyl, alkylaminoalkylcarbonyl, dialkylaminoalkylcarbonyl, heterocyclylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkylsulfoxide, alkylsulfoxidealkyl, alkylsulfonyl and alkylsulfonealkyl.

22. Use of compound according to any one of the claims 1 to 16 in the manufacture of a medicament for inhibiting ENT1 in a patient need thereof.

23. Use of compound according to any one of the claims 1 to 16 in the manufacture of a medicament for treating cancer in a patient need thereof.

24. Use of a combination of a compound according to any one of the claims 1 to 16 and an adenosine receptor antagonist, in the manufacture of a medicament for treating cancer in a patient need thereof.

25. The use according to claim 24, wherein the compound according to any one of the claims 1 to 16 is to be administered prior to, concomitant with, or subsequent to administration of the adenosine receptor antagonist.

26. The use according to any one of the claims 24-25, wherein the adenosine receptor antagonist is an A2A or A2B receptor antagonist.

27. The use according to claim 24, wherein the adenosine receptor antagonist is selected from:

5-bromo-2,6-di-(1H-pyrazol-1-yl)pyrimidin-4-amine;

(S)-7-(5-methylfuran-2-yl)-3-((6-(([tetrahydrofuran-3-yl]oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine;

6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine;

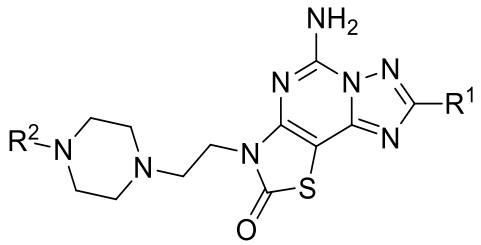
3-(2-amino-6-(1-((6-(2-hydroxypropan-2-yl)pyridin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)pyrimidin-4-yl)-2-methylbenzonitrile;

2-(2-furanyl)-7-(2-(4-(4-(2-methoxyethoxy)phenyl)-1-piperazinyl)ethyl)-7H-pyrazolo(4,3-e)(1,2,4)triazolo(1,5-c)pyrimidine-5-amine;

3-(4-amino-3-methylbenzyl)-7-(2-furyl)-3H-(1,2,3)triazolo(4,5-d)pyrimidine-5-amine; and

4-hydroxy-N-(4-methoxy-7-morpholinobenzo[d]thiazol-2-yl)-4-methylpiperidine-1-carboxamide.

28. The use according to claim 24, wherein the adenosine receptor antagonist is a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is a 5- or 6-membered heteroaryl or 5- or 6-membered aryl, wherein heteroaryl or aryl groups are optionally substituted by one or more substituent selected from C_1-C_6 alkyl and halo;

R^2 is a 6-membered aryl or 6-membered heteroaryl,

wherein heteroaryl or aryl groups are optionally substituted by one or more substituent selected from halo, alkyl, heterocyclyl, alkoxy, cycloalkyloxy, heterocyclyloxy, carbonyl, alkylcarbonyl, aminocarbonyl, hydroxycarbonyl, heterocyclylcarbonyl, alkylsulfoxide, alkylsulfonyl, aminosulfonyl, heterocyclylsulfonyl, alkylsulfonimidoyl, carbonylamino, sulfonylamino and alkylsulfonealkyl;

said substituents being optionally substituted by one or more substituent selected from oxo, halo, hydroxy, cyano, alkyl, alkenyl, aldehyde, heterocyclylalkyl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, (heterocyclyl)(alkyl)aminoalkyl, heterocyclyl, heteroaryl, alkylheteroaryl, alkyne, alkoxy, amino, dialkylamino, aminoalkylcarbonylamino, aminocarbonylalkylamino, (aminocarbonylalkyl)(alkyl)amino, alkenylcarbonylamino, hydroxycarbonyl, alkyloxycarbonyl, aminocarbonyl, aminoalkylaminocarbonyl, alkylaminoalkylaminocarbonyl, dialkylaminoalkylaminocarbonyl, heterocyclylalkylaminocarbonyl, (alkylaminoalkyl)(alkyl)aminocarbonyl, alkylaminoalkylcarbonyl, dialkylaminoalkylcarbonyl, heterocyclylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkylsulfoxide, alkylsulfoxidealkyl alkylsulfonyl and alkylsulfonealkyl;

or the heteroaryl or aryl groups are optionally substituted with two substituents that form together with the atoms to which they are attached a 5- or 6-membered aryl ring, a 5- or 6-membered heteroaryl ring, a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocyclyl ring; optionally substituted by one or more substituent selected from oxo, halo, hydroxy, cyano, alkyl, alkenyl, aldehyde, heterocyclylalkyl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, (heterocyclyl)(alkyl)aminoalkyl, heterocyclyl, heteroaryl, alkylheteroaryl, alkyne, alkoxy, amino, dialkylamino, aminoalkylcarbonylamino, aminocarbonylalkylamino, (aminocarbonylalkyl)(alkyl)amino, alkenylcarbonylamino, hydroxycarbonyl, alkyloxycarbonyl,

aminocarbonyl, aminoalkylaminocarbonyl, alkylaminoalkylaminocarbonyl, dialkylaminoalkylaminocarbonyl, heterocyclylalkylaminocarbonyl, (alkylaminoalkyl)(alkyl)aminocarbonyl, alkylaminoalkylcarbonyl, dialkylaminoalkylcarbonyl, heterocyclylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkylsulfoxide, alkylsulfoxidealkyl, alkylsulfonyl and alkylsulfonealkyl.

29. A kit of parts comprising:

(a) a first part comprising an effective amount of a compound according to any one of the claims 1 to 16; and

(b) a second part comprising an effective amount of an adenosine receptor antagonist.

30. The kit of parts according to claim 29, wherein the adenosine receptor antagonist is an A2A or A2B receptor antagonist.

31. The kit of parts according to claim 29, wherein the adenosine receptor antagonist is selected from:

5-bromo-2,6-di-(1H-pyrazol-1-yl)pyrimidin-4-amine;

(S)-7-(5-methylfuran-2-yl)-3-((6-(([tetrahydrofuran-3-yl]oxy)methyl)pyridin-2-yl)methyl)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-5-amine;

6-(2-chloro-6-methylpyridin-4-yl)-5-(4-fluorophenyl)-1,2,4-triazin-3-amine;

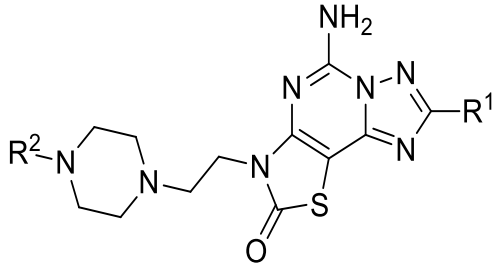
3-(2-amino-6-(1-((6-(2-hydroxypropan-2-yl)pyridin-2-yl)methyl)-1H-1,2,3-triazol-4-yl)pyrimidin-4-yl)-2-methylbenzonitrile;

2-(2-furanyl)-7-(2-(4-(4-(2-methoxyethoxy)phenyl)-1-piperazinyl)ethyl)-7H-pyrazolo(4,3-e)(1,2,4)triazolo(1,5-c)pyrimidine-5-amine;

3-(4-amino-3-methylbenzyl)-7-(2-furyl)-3H-(1,2,3)triazolo(4,5-d)pyrimidine-5-amine; and

4-hydroxy-N-(4-methoxy-7-morpholinobenzo[d]thiazol-2-yl)-4-methylpiperidine-1-carboxamide.

32. The kit of parts according to claim 29, wherein the adenosine receptor antagonist is a compound of Formula (III):



(III)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is a 5- or 6-membered heteroaryl or 5- or 6-membered aryl, wherein heteroaryl or aryl groups are optionally substituted by one or more substituent selected from C_1-C_6 alkyl and halo;

R^2 is a 6-membered aryl or 6-membered heteroaryl,

wherein heteroaryl or aryl groups are optionally substituted by one or more substituent selected from halo, alkyl, heterocyclyl, alkoxy, cycloalkyloxy, heterocyclyloxy, carbonyl, alkylcarbonyl, aminocarbonyl, hydroxycarbonyl, heterocyclylcarbonyl, alkylsulfoxide, alkylsulfonyl, aminosulfonyl, heterocyclylsulfonyl, alkylsulfonimidoyl, carbonylamino, sulfonylamino and alkylsulfonealkyl;

said substituents being optionally substituted by one or more substituent selected from oxo, halo, hydroxy, cyano, alkyl, alkenyl, aldehyde, heterocyclylalkyl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, (heterocyclyl)(alkyl)aminoalkyl, heterocyclyl, heteroaryl, alkylheteroaryl, alkyne, alkoxy, amino, dialkylamino, aminoalkylcarbonylamino, aminocarbonylalkylamino, (aminocarbonylalkyl)(alkyl)amino, alkenylcarbonylamino, hydroxycarbonyl, alkyloxycarbonyl, aminocarbonyl, aminoalkylaminocarbonyl, alkylaminoalkylaminocarbonyl,

dialkylaminoalkylaminocarbonyl, heterocyclylalkylaminocarbonyl, (alkylaminoalkyl)(alkyl)aminocarbonyl, alkylaminoalkylcarbonyl, dialkylaminoalkylcarbonyl, heterocyclylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkylsulfoxide, alkylsulfoxidealkyl alkylsulfonyl and alkylsulfonealkyl;

or the heteroaryl or aryl groups are optionally substituted with two substituents that form together with the atoms to which they are attached a 5- or 6-membered aryl ring, a 5- or 6-membered heteroaryl ring, a 5- or 6-membered cycloalkyl ring or a 5- or 6-membered heterocyclyl ring; optionally substituted by one or more substituent selected from oxo, halo, hydroxy, cyano, alkyl, alkenyl, aldehyde, heterocyclylalkyl, hydroxyalkyl, dihydroxyalkyl, hydroxyalkylaminoalkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, (heterocyclyl)(alkyl)aminoalkyl, heterocyclyl, heteroaryl, alkylheteroaryl, alkyne, alkoxy, amino, dialkylamino, aminoalkylcarbonylamino, aminocarbonylalkylamino, (aminocarbonylalkyl)(alkyl)amino, alkenylcarbonylamino, hydroxycarbonyl, alkyloxycarbonyl, aminocarbonyl, aminoalkylaminocarbonyl, alkylaminoalkylaminocarbonyl, dialkylaminoalkylaminocarbonyl, heterocyclylalkylaminocarbonyl, (alkylaminoalkyl)(alkyl)aminocarbonyl, alkylaminoalkylcarbonyl, dialkylaminoalkylcarbonyl, heterocyclylcarbonyl, alkenylcarbonyl, alkynylcarbonyl, alkylsulfoxide, alkylsulfoxidealkyl, alkylsulfonyl and alkylsulfonealkyl.

33. The compound according to any one of the claims 1 to 16 for use in therapy.