BETA-LACTAM DERIVATIVES FOR THE TREATMENT OF DISEASES

CROSS REFERENCE TO RELATED PASSWORDS

[0001] This application claims the benefit of PCT/CN2021/102061, filed June 24, 2021, PCT/CN2021/107806, filed July 22, 2021, and PCT/CN2021/142624, filed December 29, 2021, each of which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

[0002] The disclosure relates to beta-lactam derivates which function as inhibitors of glutaminyl-peptide cyclotransferase-like protein (QPCTL).

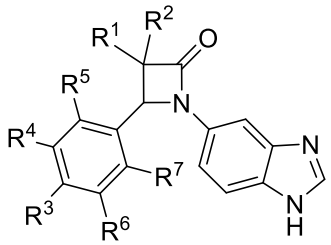
BACKGROUND OF THE INVENTION

[0003] Glutaminyl-peptide cyclotransferase, also known as glutaminyl cyclase (GC), catalyzes the conversion of N-terminal L-glutaminyl residues of peptides to pyroglutamyl groups. This enzyme belongs to the family of transferases, specifically the aminoacyltransferases and is present in the pituitary and adrenal glands, where it is important for the generation of the N-terminal pyroglutamyl groups of peptide hormones such as neurotensin and thyrotropin-releasing hormone. Glutaminyl cyclase also catalyzes the conversion of N-terminal L-glutamyl residues to pyroglutamyl residues. This activity may contribute to the formation of several amyloid-related plaque forming peptides, contributing to Alzheimer's disease pathology. Glutaminyl cyclase is also considered to be a diagnostic marker of thyroid tumors.

SUMMARY

[0004] The present disclosure addresses the above need and provides additional advantages as well.

[0004a] In an aspect of the present disclosure, there is provided a compound of Formula (I), a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof,



Formula (I)

wherein,

R^1 is halogen, -OH, -OR^{10a}, -SR^{10a}, -CN, amino, -$NR^{22}R^{23}$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl, and

R^2 is H, halogen, -OH, -OR^{10b}, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted C_1-C_6 heteroalkyl; or

R^1 and R^2 taken together with the carbon atom to which they are attached form a 3-7 membered cyclic or heterocyclic ring; or

R^1 and R^2 taken together form an oxo or a double bond to $CR^{12a}R^{12b}$, wherein R^{12a} and R^{12b} are each independently hydrogen, halogen, -OH, amino, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each of R^4, R^5, R^6, and R^7 is independently selected from H and halogen;

R^3 is -OR^{11}, halogen, -SR^{11}, -S(=O)R^{21}, -$S(=O)_2R^{21}$, -$NHS(=O)_2R^{21}$, -$S(=O)_2NR^{22}R^{23}$, -C(=O)R^{21}, -OC(=O)R^{21}, -C(=O)OR^{22}, -OC(=O)OR^{22}, -C(=O)$NR^{22}R^{23}$, -OC(=O)$NR^{22}R^{23}$, -$NR^{22}R^{23}$, -NO_2, -$NHS(=O)_2R^{21}$, -$NR^{22}C(=O)NR^{22}R^{23}$, -$NR^{22}C(=O)R^{21}$, -$NR^{22}C(=O)OR^{21}$, substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted C_2-C_8 alkenyl, substituted or unsubstituted C_2-C_8 alkynyl, substituted or unsubstituted C_1-C_8 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted bicyclic or polycyclic heteroaryl;

R^{10a} and R^{10b} are each independently substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, or substituted or unsubstituted C_1-C_6 heteroalkyl; and

R^{11} is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted bicyclic or polycyclic heteroaryl; and

R^{21}, R^{22}, and R^{23} are each independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, or C_2-C_7 heterocycloalkyl, wherein each of the alkyl, heteroalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted.

[0004b] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

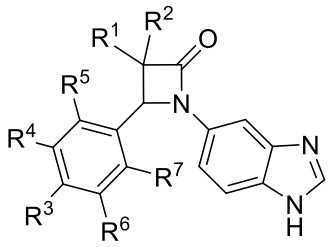
[0004c] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a disease or condition in a subject in need thereof, wherein the disease or condition is associated with an aberrant glutaminyl-peptide cyclotransferase-like protein (QPCTL) activity.

[0004d] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating cancer in a subject in need thereof.

[0004e] In a further aspect of the present disclosure, there is provided a use of a compound disclosed herein, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a disease or condition in a subject in need thereof, wherein the disease or condition is a disease that engages innate immune system.

[0004f] In another aspect of the present disclosure, there is provided a compound disclosed herein, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.

[0005] In some examples, the present disclosure provides a compound represented by Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I);

wherein:

R^1 is halogen, -OH, -OR^{10a}, -SR^{10a}, -CN, amino, -$NR^{22}R^{23}$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl, and

R^2 is H, halogen, -OH, -OR^{10b}, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted C_1-C_6 heteroalkyl; or

R^1 and R^2 taken together with the carbon atom to which they are attached form a 3-7 membered cyclic or heterocyclic ring; or

R^1 and R^2 taken together form an oxo or a double bond to $CR^{12a}R^{12b}$, wherein R^{12a} and R^{12b} are each independently hydrogen, halogen, -OH, amino, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

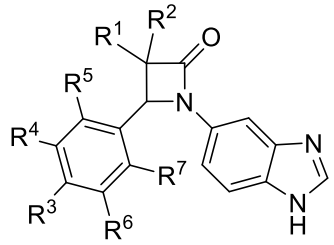
each of R^4, R^5, R^6, and R^7 is independently selected from H and halogen; R^3 is -OR^{11}, halogen, -SR^{11}, -S(=O)R^{21}, -S(=O)$_2R^{21}$, -NHS(=O)$_2R^{21}$, -S(=O)$_2NR^{22}R^{23}$, -C(=O)R^{21}, -OC(=O)R^{21}, -C(=O)OR^{22}, -OC(=O)OR^{22}, -C(=O)$NR^{22}R^{23}$, -OC(=O)$NR^{22}R^{23}$, -$NR^{22}R^{23}$, -NO_2, -NHS(=O)$_2R^{21}$, -NR^{22}C(=O)$NR^{22}R^{23}$, -NR^{22}C(=O)R^{21}, -NR^{22}C(=O)OR^{21}, substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted C_2-C_8 alkenyl, substituted or unsubstituted C_2-C_8 alkynyl, substituted or unsubstituted C_1-C_8 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted bicyclic or polycyclic heteroaryl;

R^{10a} and R^{10b} are each independently substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, or substituted or unsubstituted C_1-C_6 heteroalkyl; and

R^{11} is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted bicyclic or

R^{21}, R^{22}, and R^{23} are each independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, or C_2-C_7 heterocycloalkyl, wherein each of the alkyl, heteroalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted.

[0006] In some examples, the present disclosure provides a compound represented by Formula (I), or a pharmaceutically acceptable salt or solvate thereof:

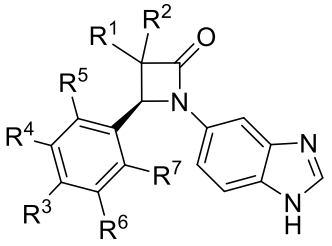


Formula (I),

wherein,

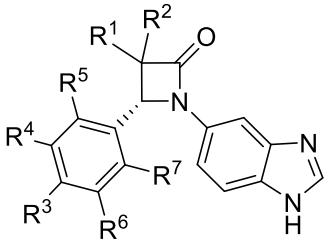
R^{21}, R^{22}, and R^{23} are each independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, or C_2-C_7 heterocycloalkyl, wherein each of the alkyl, heteroalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted.

[0007] In some examples, the disclosure provides a compound represented by Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



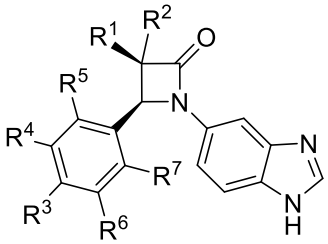
Formula (Ia).

[0008] In some examples, the disclosure provides a compound represented by Formula (Ib), or a pharmaceutically acceptable salt or solvate thereof:



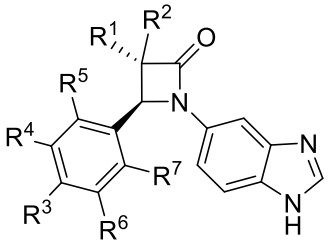
Formula (Ib).

[0009] In some examples, the disclosure provides a compound represented by Formula (Iaa), or a pharmaceutically acceptable salt or solvate thereof:



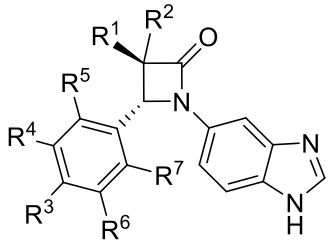
Formula (Iaa).

[0010] In some examples, the disclosure provides a compound represented by Formula (Iab), or a pharmaceutically acceptable salt or solvate thereof:



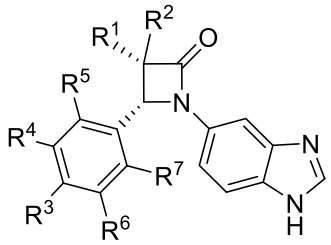
Formula (Iab).

[0011] In some examples, the disclosure provides a compound represented by Formula (Iba), or a pharmaceutically acceptable salt or solvate thereof:



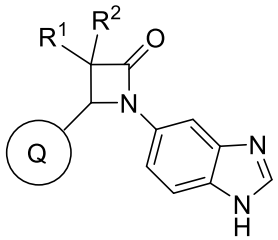
Formula (Iba).

[0012] In some examples, the disclosure provides a compound represented by Formula (Ibb), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ibb).

[0013] In another example, the disclosure provides for a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II)

wherein,

R^1 is H, halogen, -OH, -OR^{10a}, -SR^{10a}, -CN, amino, -$NR^{22}R^{23}$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl, and

R^2 is H, halogen, -OH, -OR^{10b}, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted C_1-C_6 heteroalkyl; or

R^1 and R^2 taken together with the carbon atom to which they are attached form a 3-7 membered cyclic or heterocyclic ring; or

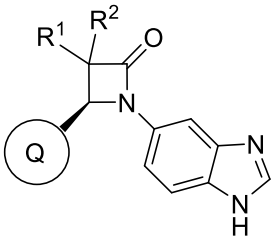
R^1 and R^2 taken together form an oxo or a double bond to $CR^{12a}R^{12b}$, wherein R^{12a} and R^{12b} are each independently hydrogen, halogen, -OH, amino, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

ring Q is a substituted or unsubstituted 5 or 6 membered heteroaryl;

R^{10a} and R^{10b} are each independently substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, or substituted or unsubstituted C_1-C_6 heteroalkyl; and

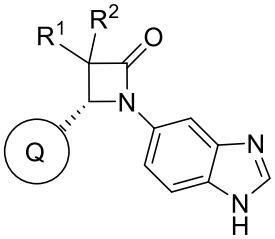
R^{22} and R^{23} are each independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, or C_2-C_7 heterocycloalkyl, wherein each of the alkyl, heteroalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted.

[0014] In some examples, the compound of Formula (II) has a structure of Formula (IIa), pharmaceutically acceptable salt or solvate thereof:



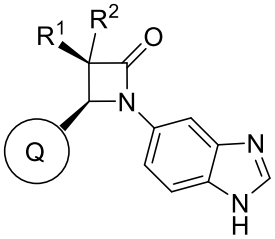
Formula (IIa).

[0015] In some examples, the compound of Formula (II) has a structure of Formula (IIb), pharmaceutically acceptable salt or solvate thereof:



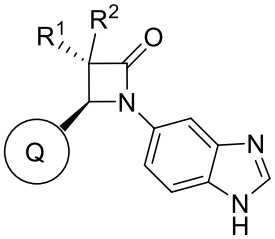
Formula (IIb).

[0016] In some examples, the compound of Formula (II) has a structure of Formula (IIaa), pharmaceutically acceptable salt or solvate thereof:



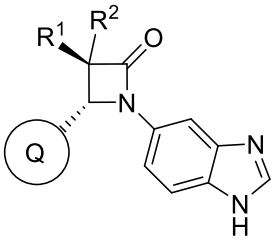
Formula (IIaa).

[0017] In some examples, the compound of Formula (II) has a structure of Formula (IIab), pharmaceutically acceptable salt or solvate thereof:



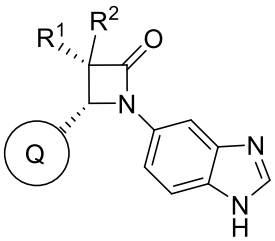
Formula (IIab).

[0018] In some examples, the compound of Formula (II) has a structure of Formula (IIba), pharmaceutically acceptable salt or solvate thereof:

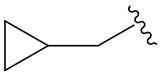


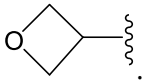
Formula (IIba).

[0019] In some examples, the compound of Formula (II) has a structure of Formula (IIbb), pharmaceutically acceptable salt or solvate thereof:



Formula (IIbb).

[0020] In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^1 is halogen, -OH, $-SR^{10a}$, -CN, amino, $-NR^{22}R^{23}$, $-OR^{10a}$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^1 is -OH, $-OR^{10a}$, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted C_3-C_6 cycloalkyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^1 is -OH. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^1 is $-OR^{10a}$, and R^{10a} is substituted or unsubstituted C_1-C_6 alkyl. In some examples, R^1 is $-OCH_3$. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^1 is substituted or unsubstituted C_1-C_6 alkyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^1 is C_1-C_6 alkyl that is optionally substituted with one to five substituents selected from halogen, -OH, amino, cyano, oxime, oxo, mono-$C_{1\text{-}6}$ alkylamino, di-$C_{1\text{-}6}$ alkylamino, substituted or unsubstituted $C_{1\text{-}6}$ alkoxy, substituted or unsubstituted $C_{3\text{-}7}$ cycloalkyl, substituted or unsubstituted $C_{2\text{-}8}$ heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^1 is $-CH_3$, $-CHF_2$, $-CF_3$, , $-CH_2OH$, $-CH_2CH_3$, $-CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_3$, or benzyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^1 is

substituted or unsubstituted C_2-C_7 heterocycloalkyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^1 is . In some examples, R^1 is H.

[0021] In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^2 is H, halogen, -OH, or substituted or unsubstituted C_1-C_6 alkyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^2 is H. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^2 is $-CH_3$.

[0022] In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^1 and R^2 taken together with the carbon atom to which they are attached form a 3-7 membered cyclic or heterocyclic ring. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb) , R^1 and R^2 taken together with the carbon atom to which they are attached form a cyclopropyl or a cyclobutyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^1 and R^2 taken together form an oxo. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^1 and R^2 taken together form a double bond to $CR^{12a}R^{12b}$, wherein R^{12a} and R^{12b} are each independently hydrogen, halogen, -OH, amino, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^{12a} is hydrogen and R^{12b} is hydrogen, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted phenyl, or substituted or unsubstituted monocyclic heteroaryl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^{12a} is hydrogen and R^{12b} is hydrogen or phenyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^{12a} is hydrogen and R^{12b} is hydrogen.

[0023] In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^5 is H, F, Cl, or Br. In some examples, R^5 is F. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^7 is H, F, Cl, or Br. In some examples, R^7 is F. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^4 is H, F, Cl, or Br. In some examples, R^4 is H. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^6 is H, F, Cl, or Br. In some examples, R^6 is H.

[0024] In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is substituted or unsubstituted monocyclic heteroaryl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is

substituted or unsubstituted 5 or 6 membered monocyclic heteroaryl having 1-4 ring heteroatoms independently selected from N, O and S. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is substituted or unsubstituted 5-membered monocyclic heteroaryl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is substituted or unsubstituted bicyclic heteroaryl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is a fused bicyclic heteroaryl having 8 to 10 ring atoms, 1, 2, 3, 4 or 5 ring heteroatoms independently selected from N, O and S. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is substituted or unsubstituted C_2-C_7 heterocycloalkyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is a monocyclic 5 or 6 membered heterocycloalkyl having 1 to 3 ring heteroatoms independently selected from N, O and S. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is substituted or unsubstituted C_3-C_8 cycloalkyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl, each of which is optionally substituted. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is phenyl or naphthyl, each of which is optionally substituted. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is substituted with one or more R^{31}, and each R^{31} is independently selected from cyano, oxime, oxo, halogen, hydroxy, amino, mono-C_{1-6} alkylamino, di-C_{1-6} alkylamino, substituted or unsubstituted C_{1-6} alkyl, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{2-8} heterocycloalkyl, heteroaryl, substituted or unsubstituted heterocycloalkyl-C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkyl-heterocycloalkyl, substituted or unsubstituted C_{1-6} alkyl-aryl, substituted or unsubstituted C_{1-6} alkyl-heteroaryl, substituted or unsubstituted C_{1-6} alkoxy-aryl, substituted or unsubstituted C_{1-6} alkoxy-heterocycloalkyl, and substituted or unsubstituted C_{1-6} alkoxy-heteroaryl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is $-OR^{11}$, $-SR^{11}$, $-S(=O)R^{21}$, $-S(=O)_2R^{21}$, $-NHS(=O)_2R^{21}$, $-S(=O)_2NR^{22}R^{23}$, $-C(=O)R^{21}$, $-OC(=O)R^{21}$, $-C(=O)OR^{22}$, $-OC(=O)OR^{22}$, $-C(=O)NR^{22}R^{23}$, $-OC(=O)NR^{22}R^{23}$, $-NR^{22}R^{23}$, $-NO_2$, $-NHS(=O)_2R^{21}$, $-NR^{22}C(=O)NR^{22}R^{23}$, $-NR^{22}C(=O)R^{21}$, $-NR^{22}C(=O)OR^{21}$, halogen, substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted C_2-C_8 alkenyl, substituted or unsubstituted C_2-C_8 alkynyl, or substituted or unsubstituted C_1-C_8 heteroalkyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is $-OR^{11}$, $-SR^{11}$, substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted C_2-C_8 alkenyl, substituted or unsubstituted C_2-C_8 alkynyl, or substituted or unsubstituted C_1-C_8 heteroalkyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is $-OR^{11}$.

[0025] In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^{11} is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted bicyclic heteroaryl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^{11} is substituted or unsubstituted C_1-C_6 alkyl or substituted or unsubstituted C_3-C_6 cycloalkyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^{11} is substituted C_1-C_4 alkyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^{11} is substituted with one or more substituents selected from cyano, oxime, oxo, halogen, -CN, $-NH_2$, $-NH(CH_3)$, $-N(CH_3)_2$, -OH, $-CO_2H$, $-CO_2$(C_1-C_4 alkyl), $-C(=O)NH_2$, $-C(=O)NH$(C_1-C_4 alkyl), $-C(=O)N$(C_1-C_4 alkyl)$_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH$(C_1-C_4 alkyl), $-S(=O)_2N$(C_1-C_4 alkyl)$_2$, $-SC_1$-C_4 alkyl, $-S(=O)C_1$-C_4 alkyl, $-S(=O)_2$(C_1-C_4 alkyl), mono-$C_{1\text{-}6}$ alkylamino, di-$C_{1\text{-}6}$ alkylamino, substituted or unsubstituted $C_{1\text{-}6}$ alkyl, substituted or unsubstituted $C_{2\text{-}6}$ alkenyl, substituted or unsubstituted $C_{2\text{-}6}$ alkynyl, substituted or unsubstituted $C_{1\text{-}6}$ alkoxy, substituted or unsubstituted $C_{3\text{-}7}$ cycloalkyl, substituted or unsubstituted $C_{2\text{-}8}$ heterocycloalkyl, heteroaryl, substituted or unsubstituted heterocycloalkyl-$C_{1\text{-}6}$ alkyl, substituted or unsubstituted $C_{1\text{-}6}$ alkyl-heterocycloalkyl, substituted or unsubstituted $C_{1\text{-}6}$ alkyl-aryl, substituted or unsubstituted $C_{1\text{-}6}$ alkyl-heteroaryl, substituted or unsubstituted $C_{1\text{-}6}$ alkoxy-aryl, substituted or unsubstituted $C_{1\text{-}6}$ alkoxy-heterocycloalkyl, and substituted or unsubstituted $C_{1\text{-}6}$ alkoxy-heteroaryl. In some examples, R^{11} is substituted with one or more substituents selected from halogen, -OH, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 fluoroalkyl, C_1-C_4 heteroalkyl, C_1-C_4 alkoxy, or C_1-C_4 fluoroalkoxy. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^{11} is substituted with one or more substituents selected from halogen, -OH, and C_3-C_6 cycloalkyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^{11} is substituted with one or more F.

[0026] In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is $-S(=O)R^{21}$, $-S(=O)_2R^{21}$, $-NHS(=O)_2R^{21}$, $-S(=O)_2NR^{22}R^{23}$, $-C(=O)R^{21}$, $-OC(=O)R^{21}$, $-C(=O)OR^{22}$, $-OC(=O)OR^{22}$, $-C(=O)NR^{22}R^{23}$, $-OC(=O)NR^{22}R^{23}$, $-NR^{22}R^{23}$, $-NO_2$, $-NHS(=O)_2R^{21}$, $-NR^{22}C(=O)NR^{22}R^{23}$, $-NR^{22}C(=O)R^{21}$, or $-NR^{22}C(=O)OR^{21}$. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^{21}, R^{22}, and R^{23} are each independently selected from hydrogen and C_1-C_4 alkyl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is substituted C_1-C_8 alkyl, substituted C_2-C_8 alkenyl, substituted C_2-C_8 alkynyl, substituted C_1-C_8 heteroalkyl, wherein the alkyl, alkenyl, alkynyl or heteroalkyl is substituted with at least one substituent selected from substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic

heteroaryl, and substituted or unsubstituted bicyclic or polycyclic heteroaryl. In some examples of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb), R^3 is $-OR^{11}$ or $-SR^{11}$, wherein R^{11} is substituted C_1-C_6 alkyl, substituted C_2-C_6 alkenyl, substituted C_2-C_6 alkynyl, substituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted bicyclic or polycyclic heteroaryl, wherein the alkyl, alkenyl, alkynyl or heteroalkyl is substituted with at least one substituent selected from substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl, and substituted or unsubstituted bicyclic or polycyclic heteroaryl.

[0027] In some examples, provided herein is a stereoisomer of a compound of Formula (I), (Ia), (Ib), (Iaa), (Iab), (Iba), (Ibb), (II), (IIa), (IIb), (IIaa) (IIab), (IIba), or (IIbb).

[0028] In some examples, the compound is a compound of Table 1, or a pharmaceutically acceptable salt or solvate thereof. In some examples, the compound is a compound of Table 3, or a pharmaceutically acceptable salt or solvate thereof. In some examples, the compound is a compound of Formula (Iaa). In some examples, the compound is a compound of Formula (IIaa).

[0029] In some examples, the compound has a brain/blood AUC of at most about 0.0001, 0.001, 0.01, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1, 2, 5, or 10.

[0030] In another example, the disclosure provides a pharmaceutical composition comprising a compound described herein and at least one pharmaceutically acceptable excipient. In some examples, the pharmaceutical composition is formulated for administration to a mammal by oral administration, intravenous administration, or subcutaneous administration. In some examples, the pharmaceutical composition is in the form of a tablet, a pill, a capsule, a liquid, a suspension, a dispersion, a solution, or an emulsion.

[0031] In another example, the disclosure provides a method a method of modulating glutaminyl-peptide cyclotransferase-like protein (QPCTL) activity in a subject, comprising administering to the subject a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition of described herein. In another example, the disclosure provides a method of inhibiting glutaminyl-peptide cyclotransferase-like protein (QPCTL) activity in a subject, comprising administering to the subject a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition described herein. In another example, the disclosure provides a method of treating a disease or condition in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition of described herein. In some examples, the disease or condition is associated with an aberrant glutaminyl-peptide cyclotransferase-like protein (QPCTL) activity. In some examples, the disease or condition that is associated with an aberrant QPCTL activity is a cancer. In another example, the disclosure provides a method of treating cancer in a subject in need thereof, the method comprising administering to the subject a therapeutically effective

amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, or a pharmaceutical composition described herein.

[0032] In some examples, the cancer is leukemia, acute myeloid leukemia (AML), chronic myeloid leukemia, acute lymphoblastic leukemia (ALL), non-Hodgkin lymphoma (NHL), Hodgkin lymphoma (HL), multiple myeloma (MM) or myelodysplastic syndrome (MDS). In some examples, the cancer is AML. In some examples, the cancer is a solid cancer or a metastatic cancer. In some examples, the cancer is a skin cancer, ocular cancer, gastrointestinal cancer, thyroid cancer, breast cancer, ovarian cancer, central nervous system cancer, laryngeal cancer, cervical cancer, lymphatic system cancer, genitourinary tract cancer, bone cancer, biliary tract cancer, endometrial cancer, liver cancer, lung cancer, prostate cancer, or colon cancer.

[0033] In one example, described herein is a method of treating a disease or condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a herein described compound, or a pharmaceutically acceptable salt or solvate thereof, or a herein described pharmaceutical composition to the subject, wherein the disease or condition is a disease that engages innate immune system. In some examples, the disease is atherosclerosis, a fibrotic disease, ischemia-reperfusion injury, or an infectious disease caused by pathogens. In some examples, the disease is a fibrotic disease selected from liver fibrosis, pulmonary fibrosis, renal fibrosis and scleroderma. In some examples, the diseases are chronic kidney diseases including diabetic nephropathy and Focal Segmental Glomerulosclerosis (FSGS).

[0034] In one example, described herein is a method of treating a disease or condition in a subject in need thereof, the method comprising administering a therapeutically effective amount of a herein described compound, or a pharmaceutically acceptable salt or solvate thereof, or a herein described pharmaceutical composition to the subject, wherein the disease or condition is Kennedy's disease, duodenal cancer with or without Helicobacter pylori infections, Zolliger-Ellison syndrome, gastric cancer with or without Helicobacter pylori infections, pathogenic psychotic conditions, schizophrenia, infertility, neoplasia, inflammatory host responses, cancer, psoriasis, impaired humoral and cell-mediated immune responses, leukocyte adhesion and migration processes in the endothelium, impaired food intake, impaired sleep-wakefulness, impaired homeostatic regulation of energy metabolism, impaired autonomic function, impaired hormonal balance or impaired regulation of body fluids, multiple sclerosis, the Guillain-Barre syndrome, chronic inflammatory demyelinizing polyradiculoneuropathy, mild cognitive impairment, Alzheimer's disease, Familial British Dementia, Familial Danish Dementia, neurodegeneration in Down Syndrome, Huntington's disease, rheumatoid arthritis, pancreatitis and restenosis. In some examples, the method comprises administering a second therapeutic agent. In some examples, the second therapeutic agent is a monoclonal antibody. In some examples, the monoclonal antibody is selected from edrecolomab, rituximab, gemtuzumab ozogamicin, alemtuzumab, ibritumomab tiuxetan, tositumomab, cetuximab, bevacizumab, and trastuzumab. In some examples, the second therapeutic agent is an immune checkpoint inhibitor. In some examples, the immune checkpoint inhibitor is a CTLA-4 inhibitor, a PD-1 inhibitor, or a PD-L1 inhibitor. In some examples, the immune checkpoint

inhibitor is Ipilimumab, Nivolumab, Pembrolizumab, Atezolizumab, Avelumab, Durvalumab or Cemiplimab.

[0035] Additional examples and advantages of the present disclosure will become readily apparent to those skilled in this art from the following detailed description, wherein only illustrative examples of the present disclosure are shown and described. As will be realized, the present disclosure is capable of other and different examples, and its several details are capable of modifications in various obvious respects, all without departing from the disclosure. Accordingly, the drawings and description are to be regarded as illustrative in nature, and not as restrictive.

INCORPORATION BY REFERENCE

[0036] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference. To the extent publications and patents or patent applications incorporated by reference contradict the disclosure contained in the specification, the specification is intended to supersede and/or take precedence over any such contradictory material.

DETAILED DESCRIPTION OF THE INVENTION

[0037] While various embodiments of the invention have been shown and described herein, it will be obvious to those skilled in the art that such embodiments are provided by way of example only. Numerous variations, changes, and substitutions may occur to those skilled in the art without departing from the invention. It should be understood that various alternatives to the embodiments of the invention described herein may be employed.

A. Definitions

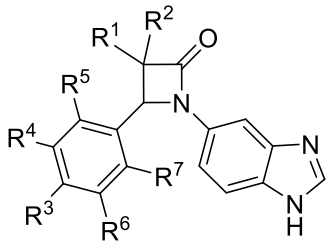
[0038] Unless defined otherwise, all technical and scientific terms used herein have the same meaning as is commonly understood by one of skill in the art to which this invention belongs. All patents and publications referred to herein are incorporated by reference.

[0039] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, and preferably having from one to fifteen carbon atoms (*i.e.*, C_1-C_{15} alkyl). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (*i.e.*, C_1-C_{13} alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*i.e.*, C_1-C_8 alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (*i.e.*, C_1-C_5 alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*i.e.*, C_1-C_4 alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*i.e.*, C_1-C_3 alkyl). In other embodiments, an alkyl comprises one to two carbon atoms (*i.e.*, C_1-C_2 alkyl). In other embodiments, an alkyl comprises one carbon atom (*i.e.*, C_1 alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*i.e.*, C_5-C_{15} alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*i.e.*, C_5-C_8 alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (*i.e.*, C_2-C_5 alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*i.e.*, C_3-C_5 alkyl). In certain embodiments, the alkyl group is selected from

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof,



Formula (I)

wherein,

R^1 is halogen, -OH, -OR^{10a}, -SR^{10a}, -CN, amino, -$NR^{22}R^{23}$, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, or substituted or unsubstituted C_2-C_7 heterocycloalkyl, and

R^2 is H, halogen, -OH, -OR^{10b}, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted C_1-C_6 heteroalkyl; or

R^1 and R^2 taken together with the carbon atom to which they are attached form a 3-7 membered cyclic or heterocyclic ring; or

R^1 and R^2 taken together form an oxo or a double bond to $CR^{12a}R^{12b}$, wherein R^{12a} and R^{12b} are each independently hydrogen, halogen, -OH, amino, substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted aryl, or substituted or unsubstituted heteroaryl;

each of R^4, R^5, R^6, and R^7 is independently selected from H and halogen;

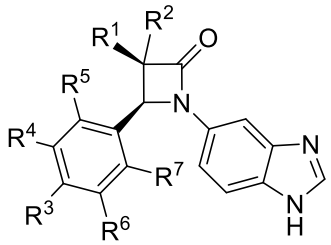
R^3 is -OR^{11}, halogen, -SR^{11}, -$S(=O)R^{21}$, -$S(=O)_2R^{21}$, -$NHS(=O)_2R^{21}$, -$S(=O)_2NR^{22}R^{23}$, -$C(=O)R^{21}$, -$OC(=O)R^{21}$, -$C(=O)OR^{22}$, -$OC(=O)OR^{22}$, -$C(=O)NR^{22}R^{23}$, -$OC(=O)NR^{22}R^{23}$, -$NR^{22}R^{23}$, -NO_2, -$NHS(=O)_2R^{21}$, -$NR^{22}C(=O)NR^{22}R^{23}$, -$NR^{22}C(=O)R^{21}$, -$NR^{22}C(=O)OR^{21}$, substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted C_2-C_8 alkenyl, substituted or unsubstituted C_2-C_8 alkynyl, substituted or unsubstituted C_1-C_8 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted bicyclic or polycyclic heteroaryl;

R^{10a} and R^{10b} are each independently substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, or substituted or unsubstituted C_1-C_6 heteroalkyl; and

R^{11} is substituted or unsubstituted C_1-C_6 alkyl, substituted or unsubstituted C_2-C_6 alkenyl, substituted or unsubstituted C_2-C_6 alkynyl, substituted or unsubstituted C_1-C_6 heteroalkyl, substituted or unsubstituted C_3-C_8 cycloalkyl, substituted or unsubstituted C_2-C_7 heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted naphthyl, substituted or unsubstituted monocyclic heteroaryl, or substituted or unsubstituted bicyclic or polycyclic heteroaryl; and

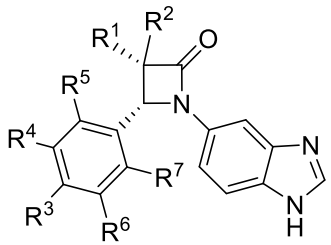
R^{21}, R^{22}, and R^{23} are each independently hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_3-C_8 cycloalkyl, or C_2-C_7 heterocycloalkyl, wherein each of the alkyl, heteroalkyl, cycloalkyl, or heterocycloalkyl is optionally substituted.

2. The compound of claim 1, a stereoisomer or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has a structure of Formula (Iaa),



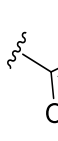
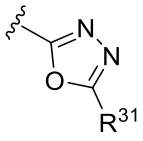
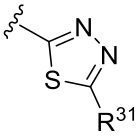
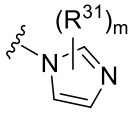
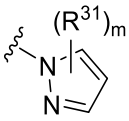
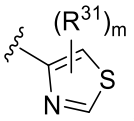
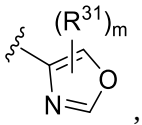
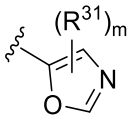
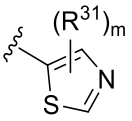
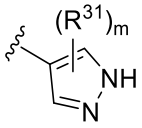
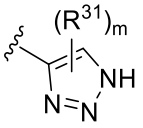
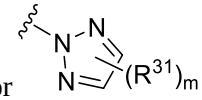
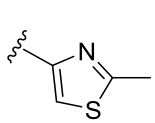
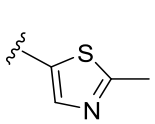
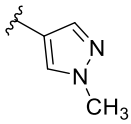
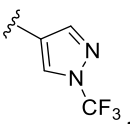
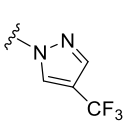
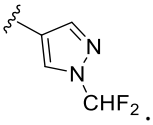
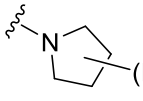
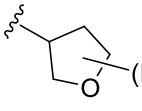
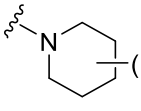
Formula (Iaa).

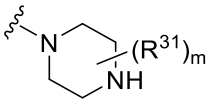
3. The compound of claim 1, a stereoisomer or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has a structure of Formula (Ibb),



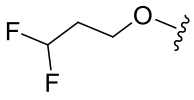
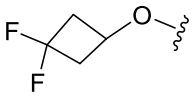
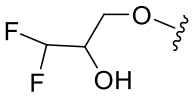
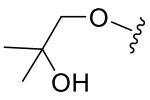
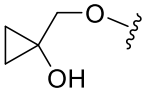
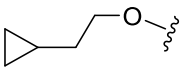
Formula (Ibb).

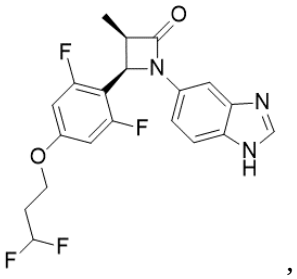
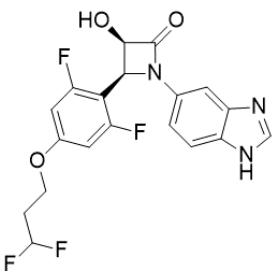
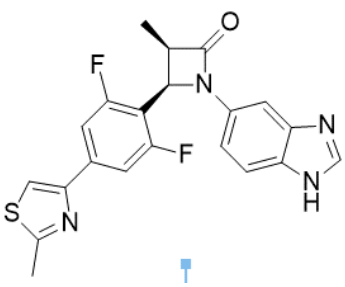
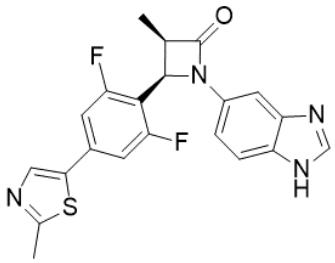
4. The compound of any one of claims 1 to 3, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is -OH, -OR^{10a}, substituted or unsubstituted C_1-C_6 alkyl, or substituted or unsubstituted C_3-C_6 cycloalkyl.
5. The compound of claim 4, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is C_1-C_6 alkyl that is optionally substituted with one to five substituents selected from halogen, -OH, amino, cyano, oxime, oxo, mono-$C_{1\text{-}6}$ alkylamino, di-$C_{1\text{-}6}$ alkylamino, substituted or unsubstituted $C_{1\text{-}6}$ alkoxy, substituted or unsubstituted $C_{3\text{-}7}$ cycloalkyl, substituted or unsubstituted $C_{2\text{-}8}$ heterocycloalkyl, substituted or unsubstituted aryl, and substituted or unsubstituted heteroaryl.
6. The compound of claim 4, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is -CH_3 or cyclopropyl.
7. The compound of any one of claims 1 to 6, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, wherein R^2 is H.

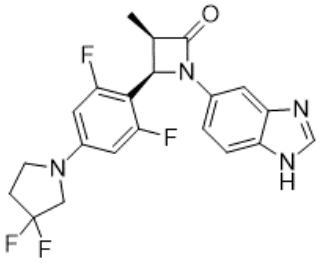
8. The compound of any one of claims 1 to 7, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, wherein R^5 is F and R^7 is F.
9. The compound of any one of claims 1 to 8, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, wherein R^4 is H and R^6 is H.
10. The compound of any one of claims 1 to 9, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is substituted or unsubstituted 5 or 6 membered monocyclic heteroaryl having 1-4 ring heteroatoms independently selected from N, O and S.
11. The compound of claim 10, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is , , , , , , , , , , , or , wherein each R^{31} is independently selected from hydrogen, cyano, halogen, hydroxy, substituted or unsubstituted C_{1-6} alkyl, -OCH_3, -OCD_3, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{2-8} heterocycloalkyl, heteroaryl, substituted or unsubstituted heterocycloalkyl-C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkyl-aryl, substituted or unsubstituted C_{1-6} alkyl-heterocycloalkyl, substituted or unsubstituted C_{1-6} alkyl-heteroaryl, substituted or unsubstituted C_{1-6} alkoxy-aryl, substituted or unsubstituted C_{1-6} alkoxy-heterocycloalkyl, substituted or unsubstituted C_{1-6} alkoxy-heteroaryl, and C_{1-6} alkoxy substituted with hydroxy, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino and di-C_{1-6} alkylamino; and m is 0, 1, 2, or 3.
12. The compound of claim 11, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is , , , , , or .
13. The compound of any one of claims 1 to 9, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is , , , or


, wherein each R^{31} is independently selected from cyano, halogen, hydroxy, substituted or unsubstituted C_{1-6} alkyl, $-OCH_3$, $-OCD_3$, substituted or unsubstituted C_{2-6} alkenyl, substituted or unsubstituted C_{2-6} alkynyl, substituted or unsubstituted C_{1-6} alkoxy, substituted or unsubstituted C_{3-7} cycloalkyl, substituted or unsubstituted C_{2-8} heterocycloalkyl, heteroaryl, substituted or unsubstituted heterocycloalkyl-C_{1-6} alkyl, substituted or unsubstituted C_{1-6} alkyl-aryl, substituted or unsubstituted C_{1-6} alkyl-heterocycloalkyl, substituted or unsubstituted C_{1-6} alkyl-heteroaryl, substituted or unsubstituted C_{1-6} alkoxy-aryl, substituted or unsubstituted C_{1-6} alkoxy-heterocycloalkyl, substituted or unsubstituted C_{1-6} alkoxy-heteroaryl, and C_{1-6} alkoxy substituted with hydroxy, C_{1-6} alkoxy, amino, mono-C_{1-6} alkylamino and di-C_{1-6} alkylamino; and m is 0, 1, 2, 3, 4 or 5.

14. The compound of any one of claims 1 to 9, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is $-OR^{11}$, $-SR^{11}$, substituted or unsubstituted C_1-C_8 alkyl, substituted or unsubstituted C_2-C_8 alkenyl, substituted or unsubstituted C_2-C_8 alkynyl, or substituted or unsubstituted C_1-C_8 heteroalkyl, wherein R^{11} is substituted or unsubstituted C_1-C_6 alkyl or substituted or unsubstituted C_3-C_6 cycloalkyl, and wherein R^{11} is substituted with one or more substituents selected from halogen, -OH, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, C_1-C_4 fluoroalkyl, C_1-C_4 heteroalkyl, C_1-C_4 alkoxy, or C_1-C_4 fluoroalkoxy.

15. The compound of claim 14, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is , , , , , or .

16. The compound of any one of claims 1 to 2 or 9 to 10, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound is , , , ,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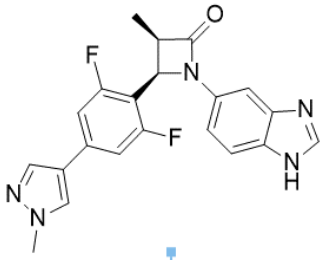
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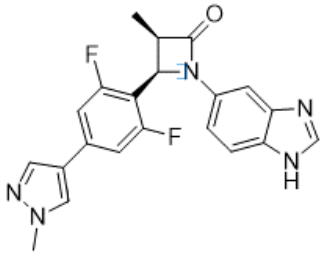
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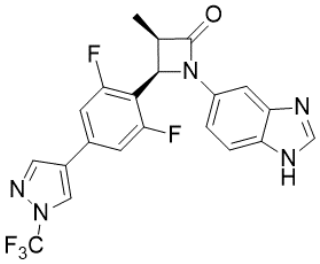
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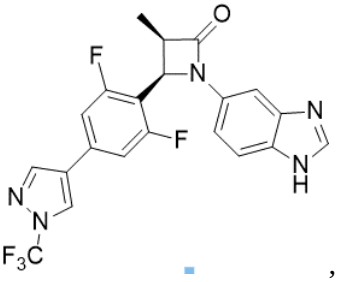
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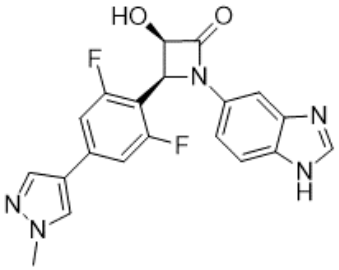
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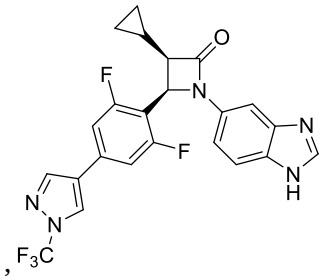
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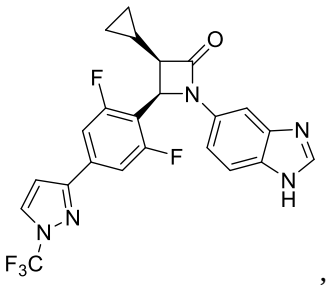
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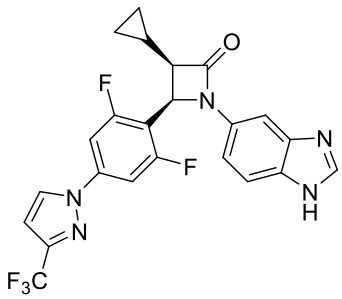
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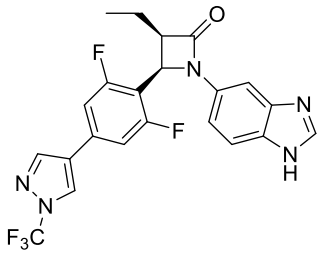
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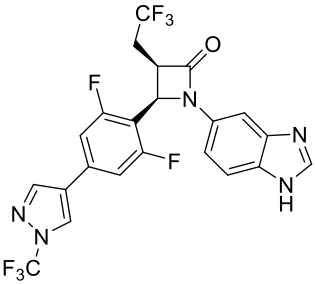
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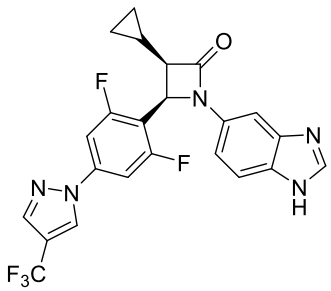
, or a pharmaceutically acceptable salt or stereoisomer thereof.

17. A pharmaceutical composition comprising a compound of any one of claims 1 to 16, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.
18. Use of a compound of any one of claims 1 to 16, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a disease or condition in a subject in need thereof, wherein the disease or condition is associated with an aberrant glutaminyl-peptide cyclotransferase-like protein (QPCTL) activity.

19. Use of a compound of any one of claims 1 to 16, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating cancer in a subject in need thereof.
20. Use of a compound of any one of claims 1 to 16, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for treating a disease or condition in a subject in need thereof, wherein the disease or condition is a disease that engages innate immune system.
21. A compound of any one of claims 1 to 16, a stereoisomer, or a pharmaceutically acceptable salt or solvate thereof, for use in therapy.