ADENOSINE RECEPTOR ANTAGONISTS AND USES THEREOF

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application No. 62/638,737, filed March 5, 2018 and U.S. Provisional Application No. 62/688,088 filed June 21, 2018, each of which is incorporated herein by reference.

FIELD OF THE INVENTION

[0002] Described herein are compounds, methods of making such compounds, pharmaceutical compositions and medicaments comprising such compounds, and methods of using such compounds in the treatment of conditions, diseases, or disorders that would benefit from modulation of A_{2B} adenosine receptor activity.

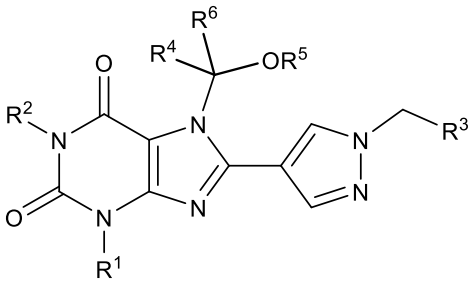
BACKGROUND OF THE INVENTION

[0003] Adenosine, an endogenous nucleoside, ubiquitously exists inside and outside of living cells. It plays multiple physiological roles to maintain the homeostasis of cells, tissues, and organs. Adenosine can exert its biological effects by interacting with a family of adenosine receptors known as A_1, A_{2A}, A_{2B}, and A_3 adenosine receptors. A_1 adenosine receptors mediate mechanisms of tissue protection, especially for cardioprotection. A_{2A} adenosine receptors modulate coronary vasodilation and cancer immunity. A_{2B} adenosine receptors play a role in signaling pathways.

[0004] Some A_{2B} adenosine receptor antagonists are relatively insoluble in aqueous media and/or difficult to formulate using conventional pharmaceutical excipients, and thus can be difficult to formulate in a manner that provides reproducible plasma levels of the compound in mammals, in particular humans. A need exists for improving the bioavailability A_{2B} adenosine receptor antagonists.

SUMMARY ~~OF THE INVENTION~~

[0005] In one example~~aspect~~, described herein is a compound represented by Formula (A):



Formula (A)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

each R^{10} is independently selected from hydrogen and alkyl;

R^{11} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, -C(=O)R^{12}, -C(=O)-OR^{12}, -C(=O)N(R^{12})(R^8), -C(=O)-SR^{12}, or -P(=O)(OR^9)$_2$;

R^{12} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, -alkyl-(substituted or unsubstituted phenyl), or -alkyl-(substituted or unsubstituted heteroaryl);

m is 1, 2, 3, 4, 5, or 6;

n is 1, 2, 3, 4, 5, or 6;

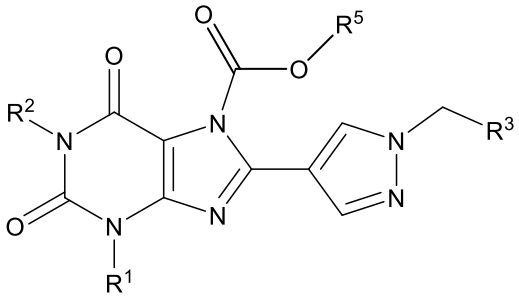
p is 1, 2, 3, 4, 5, or 6;

wherein substituted means that the referenced group is substituted with one or more additional groups individually and independently selected from halogen, -CN, -NH_2, -NH(alkyl), -N(alkyl)$_2$, -OH, -CO_2H, -CO_2alkyl, -C(=O)NH_2, -C(=O)NH(alkyl), -C(=O)N(alkyl)$_2$, -S(=O)$_2$$NH_2$, -S(=O)$_2$NH(alkyl), -S(=O)$_2$N(alkyl)$_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone.

[0006] In some examples~~embodiments~~, R^4 is C_1-C_6alkyl; R^6 is selected from hydrogen, and C_1-C_6alkyl; or R^4 and R^6 are taken together with the carbon atom to which they are attached to form a carbonyl (C=O).

[0007] In some examples~~embodiments~~, R^4 is methyl, ethyl, or n-propyl; R^6 is selected from hydrogen, methyl, ethyl, and n-propyl; or R^4 and R^6 are taken together with the carbon atom to which they are attached to form a carbonyl (C=O).

[0008] In some examples~~embodiments~~, the compound has the following structure of Formula (III):



Formula (III)

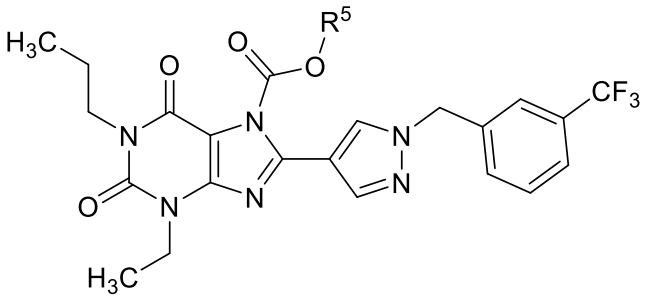
or a pharmaceutically acceptable salt or solvate thereof.

[0009] In some examples~~embodiments~~, R^1 and R^2 are each independently selected from substituted or unsubstituted C_1-C_6alkyl; R^3 is selected from substituted or unsubstituted phenyl.

[0010] In some examples~~embodiments~~, R^1 and R^2 are each independently selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, tert-pentyl, neopentyl, isopentyl, sec-pentyl, 3-pentyl, n-hexyl, isohexyl, 3-methylpentyl, 2,3-dimethylbutyl, and neohexyl.

[0011] In some examples~~embodiments~~, R^1 is ethyl; R^2 is n-propyl; and R^3 is 3-(trifluoromethyl)phenyl.

[0012] In some examples~~embodiments~~, the compound has the following structure:

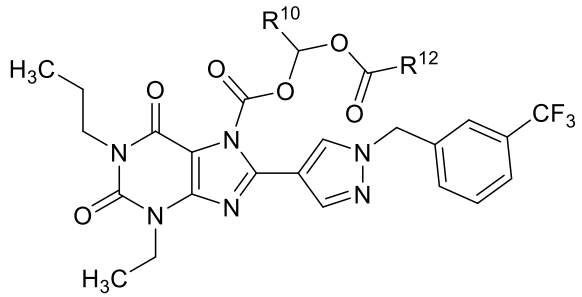


or a pharmaceutically acceptable salt or solvate thereof.

[0013] In some examples~~embodiments~~, R^5 is R^7; R^7 is C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic C_3-C_8cycloalkyl, substituted or unsubstituted bicyclic C_5-C_{10}cycloalkyl, substituted or unsubstituted monocyclic C_2-C_8heterocycloalkyl, substituted or unsubstituted bicyclic C_5-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -CH_2-(substituted or unsubstituted phenyl), -CH_2-(substituted or unsubstituted heteroaryl), -CH_2-(substituted or unsubstituted C_2-C_8heterocycloalkyl), -$CH(R^{10})O$-R^{11}, -$(CH_2CH_2O)_n$-R^{11}, or -$(C(R^{10})_2)_p$-OR^{11}; each R^{10} is independently selected from hydrogen and methyl; R^{11} is hydrogen, C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, -$C(=O)R^{12}$, -$C(=O)$-OR^{12}, -$C(=O)N(R^{12})(R^8)$, -$C(=O)$-SR^{12}, or -$P(=O)(OR^9)_2$.

[0014] In some examples~~embodiments~~, R^7 is C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, -CH_2-(substituted or unsubstituted phenyl), -CH_2-(substituted or unsubstituted heteroaryl), -CH_2-(substituted or unsubstituted C_2-C_8heterocycloalkyl), -$CH(R^{10})O$-R^{11}, or -$(CH_2CH_2O)_n$-R^{11}; R^{10} is hydrogen and methyl; R^{11} is hydrogen, C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, -$C(=O)R^{12}$, -$C(=O)$-OR^{12}, -$C(=O)N(R^{12})(R^8)$, -$C(=O)$-SR^{12}, or -$P(=O)(OH)_2$.

[0015] In some examples~~embodiments~~, the compound has one of the following structures:



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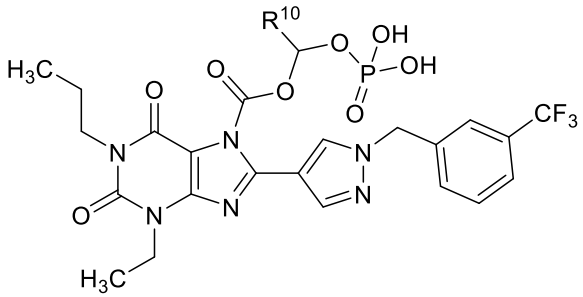
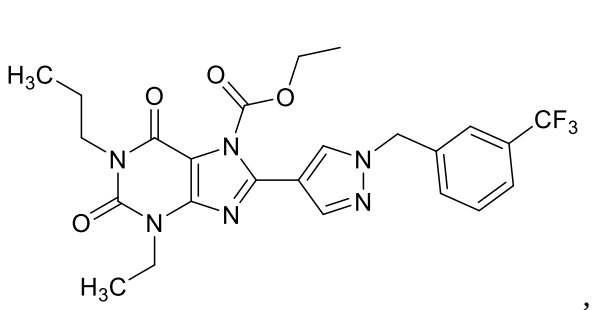


or a pharmaceutically acceptable salt or solvate thereof.

[0016] In some examples~~embodiments~~, the compound has one of the following structures:



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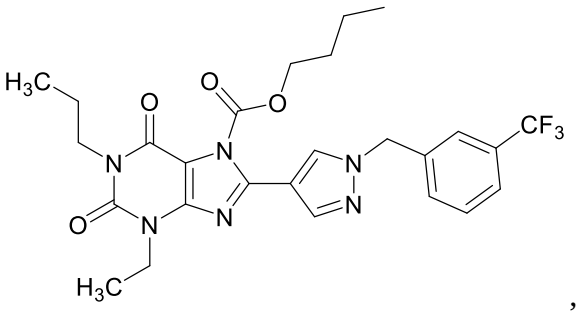

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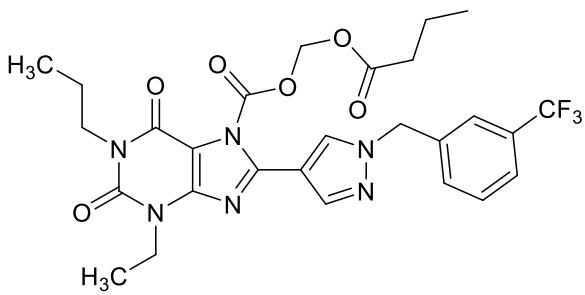

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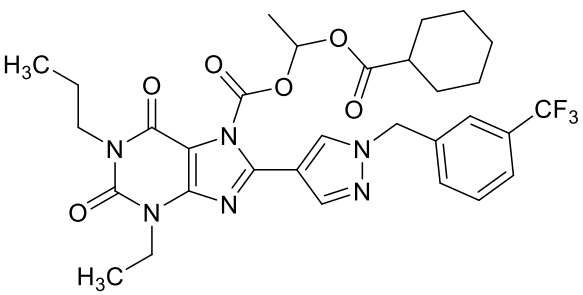

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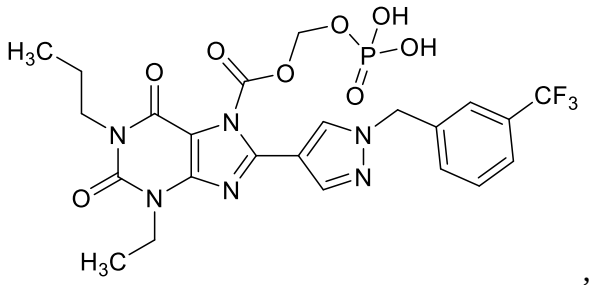

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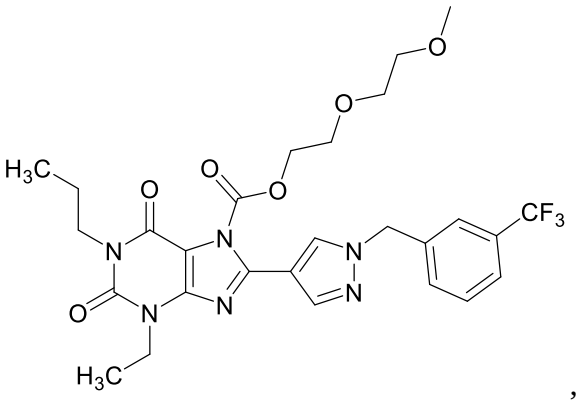

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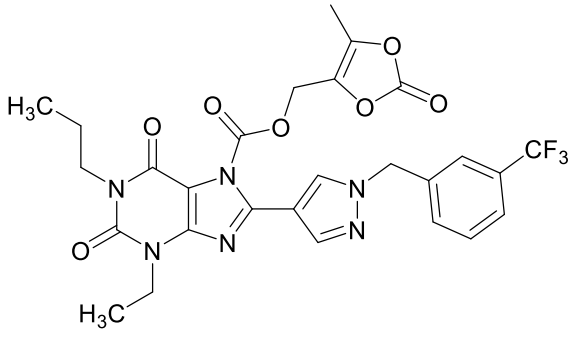
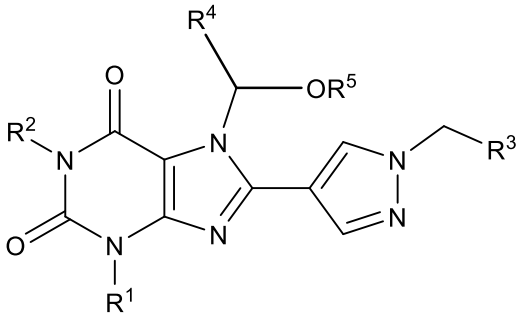


;

or a pharmaceutically acceptable salt or solvate thereof.

[0017] In some examples~~embodiments~~, the compound has the following structure of Formula (I):



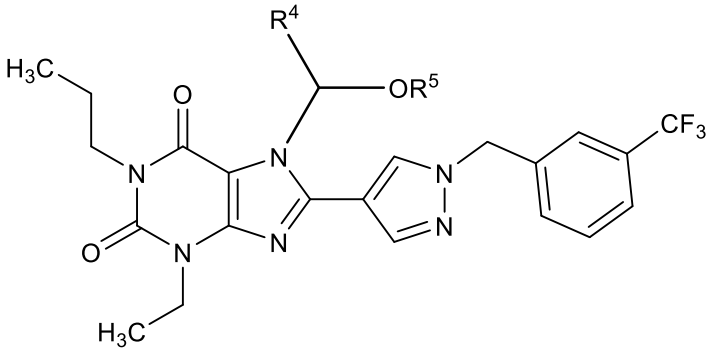
Formula (I)

or a pharmaceutically acceptable salt or solvate thereof.

[0018] In some examples~~embodiments~~, R^1 and R^2 are each independently selected from substituted or unsubstituted C_1-C_6alkyl; R^3 is selected from substituted or unsubstituted phenyl.

[0019] In some examples~~embodiments~~, R^1 is ethyl; R^2 is n-propyl; and R^3 is 3-(trifluoromethyl)phenyl.

[0020] In some examples~~embodiments~~, the compound has the following structure:



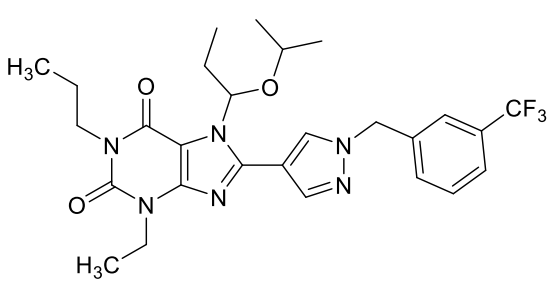
or a pharmaceutically acceptable salt or solvate thereof.

[0021] In some examples~~embodiments~~, R^4 is methyl or ethyl; R^5 is hydrogen, R^7, -C(=O)R^7, -C(=O)-OR^7, -C(=O)N(R^7)(R^8), -C(=O)-SR^7, or -P(=O)(OR^9)$_2$; R^7 is C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic C_3-C_8cycloalkyl, substituted or unsubstituted bicyclic C_5-C_{10}cycloalkyl, substituted or unsubstituted monocyclic C_2-C_8heterocycloalkyl, substituted or unsubstituted bicyclic C_5-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -CH_2-(substituted or unsubstituted phenyl), -CH_2-(substituted or unsubstituted heteroaryl), -CH_2-(substituted or unsubstituted C_2-C_8heterocycloalkyl), -CH(R^{10})O-R^{11}, -(CH_2CH_2O)$_n$-R^{11}, or -(C(R^{10})$_2$)$_p$-OR^{11}; each R^{10} is independently selected from hydrogen and methyl; R^{11} is hydrogen, C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, -C(=O)R^{12}, -C(=O)-OR^{12}, -C(=O)N(R^{12})(R^8), -C(=O)-SR^{12}, or -P(=O)(OR^9)$_2$.

[0022] In some examples~~embodiments~~, R^5 is R^7, -C(=O)R^7, -C(=O)-OR^7, -C(=O)N(R^7)(R^8), -C(=O)-SR^7, or -P(=O)(OH)$_2$; R^7 is C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or

unsubstituted cyclohexyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted bicyclo[1.1.1]pentanyl, substituted or unsubstituted bicyclo[2.2.1]heptanyl, substituted or unsubstituted bicyclo[2.2.2]octanyl, substituted or unsubstituted bicyclo[3.2.1]octanyl, substituted or unsubstituted bicyclo[3.3.0]octanyl, substituted or unsubstituted bicyclo[4.3.0]nonanyl, or substituted or unsubstituted decalinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, $-CH_2-$(substituted or unsubstituted phenyl), $-CH_2-$(substituted or unsubstituted heteroaryl), $-CH_2-$(substituted or unsubstituted C_2-C_8heterocycloalkyl), $-CH(R^{10})O-R^{11}$, $-(CH_2CH_2O)_n-R^{11}$, or $-(C(R^{10})_2)_p-OR^{11}$; each R^{10} is independently selected from hydrogen and methyl; R^{11} is hydrogen, C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, $-C(=O)R^{12}$, $-C(=O)-OR^{12}$, $-C(=O)N(R^{12})(R^8)$, $-C(=O)-SR^{12}$, or $-P(=O)(OR^9)_2$.

[0023] In some examples~~embodiments~~, the compound has one of the following structures: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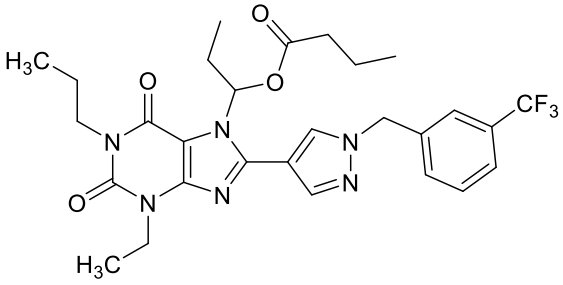
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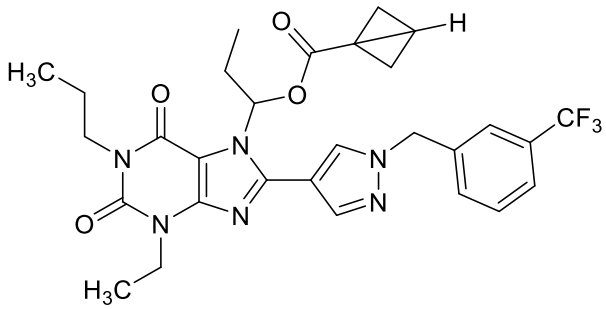
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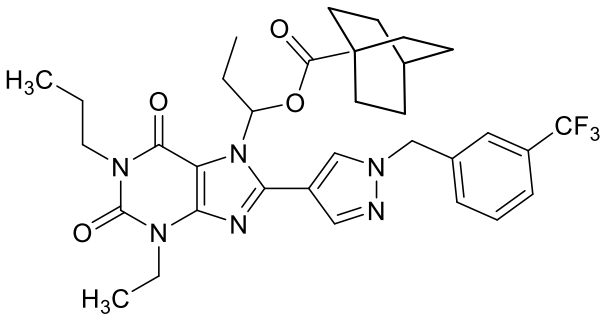
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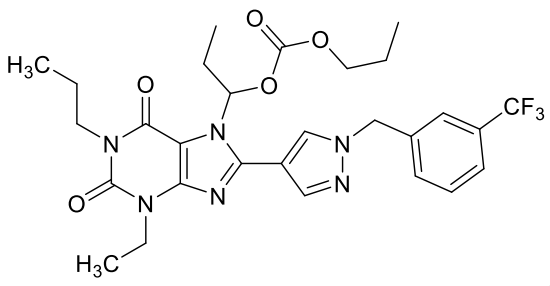
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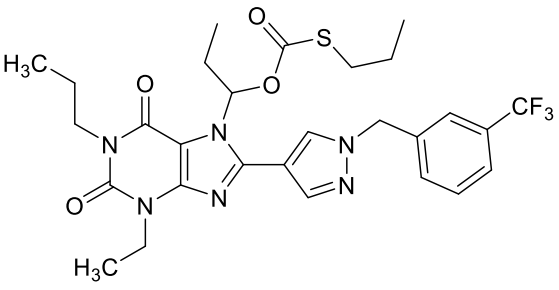
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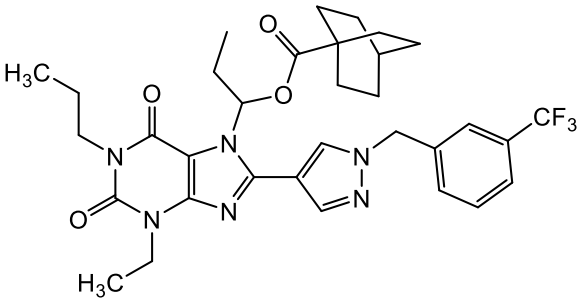
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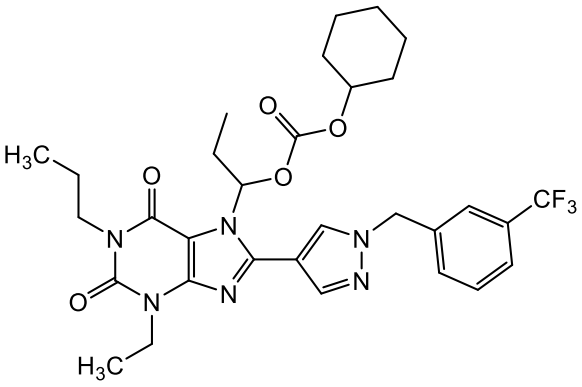
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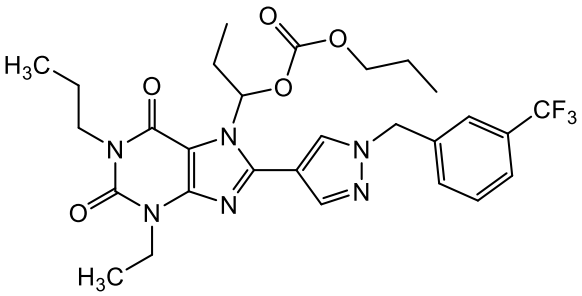
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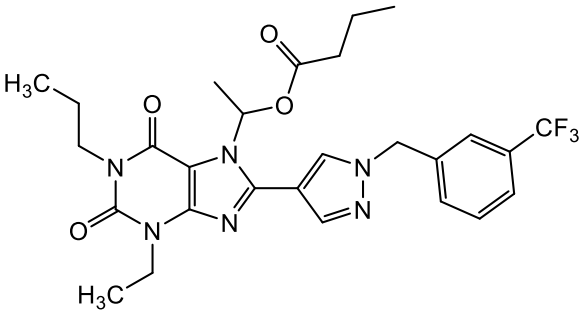
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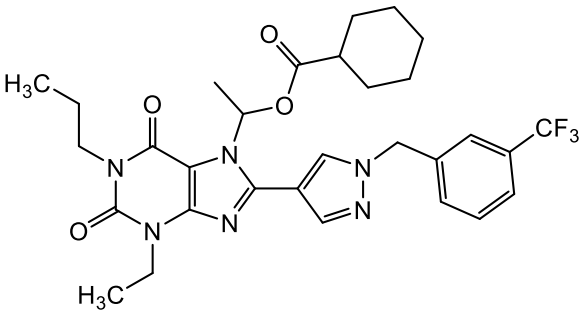
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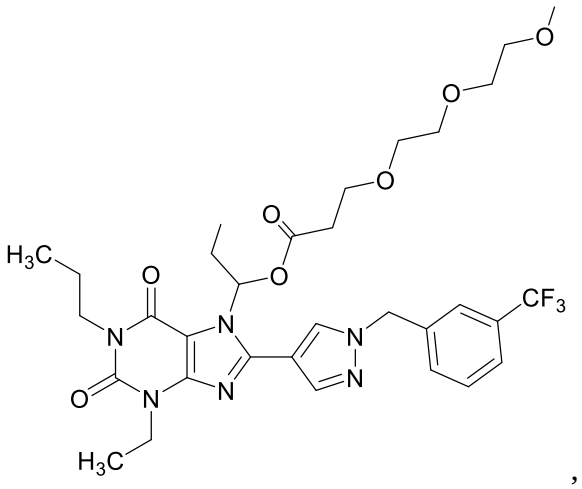
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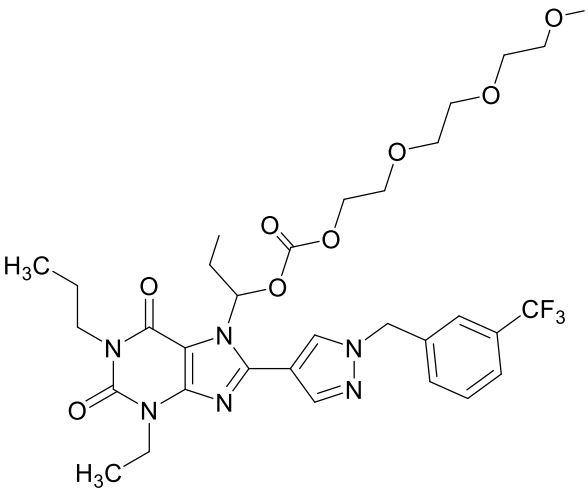
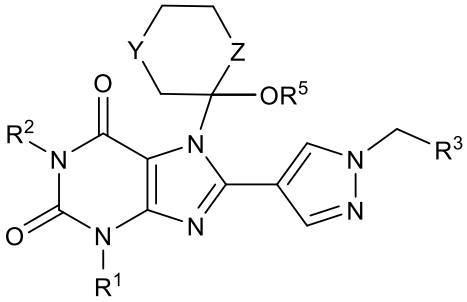

or ;

or a pharmaceutically acceptable salt or solvate thereof.

[0024] In some examples~~embodiments~~, the compound has the following structure of Formula (II):



Formula (II)

wherein:

Y is selected from -CH_2-, O, S, -NR^{15}-, and -$S(O)_2$-;

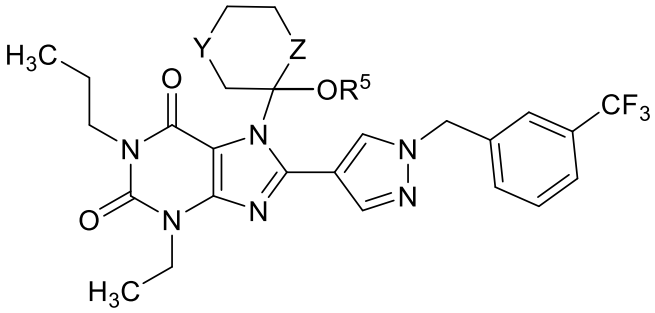
Z is O or S;

or a pharmaceutically acceptable salt or solvate thereof.

[0025] In some examples~~embodiments~~, R^1 and R^2 are each independently selected from substituted or unsubstituted C_1-C_6alkyl; R^3 is selected from substituted or unsubstituted phenyl.

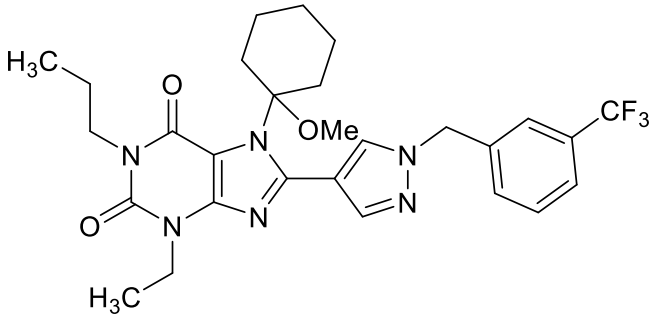
[0026] In some examples~~embodiments~~, R^1 is ethyl; R^2 is n-propyl; and R^3 is 3-(trifluoromethyl)phenyl.

[0027] In some examples~~embodiments~~, the compound has the following structure:



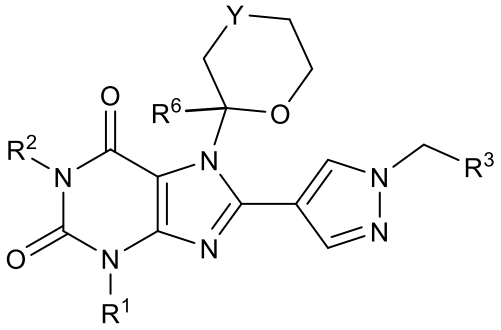
or a pharmaceutically acceptable salt or solvate thereof.

[0028] In some examples~~embodiments~~, the compound has the following structure:



or a pharmaceutically acceptable salt or solvate thereof.

[0029] In some examples~~embodiments~~, the compound has the following structure of Formula (IIa):



Formula (IIa)

wherein:

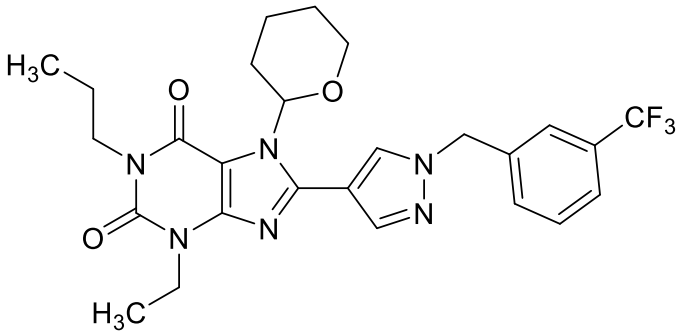
Y is selected from -CH_2-, O, S, -NR^{15}-, and -$S(O)_2$-;

or a pharmaceutically acceptable salt or solvate thereof.

[0030] In some examples~~embodiments~~, R^1 and R^2 are each independently selected from substituted or unsubstituted C_1-C_6alkyl; R^3 is selected from substituted or unsubstituted phenyl.

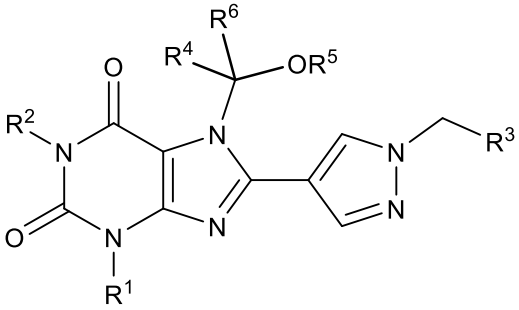
[0031] In some examples~~embodiments~~, R^1 is ethyl; R^2 is n-propyl; and R^3 is 3-(trifluoromethyl)phenyl.

[0032] In some examples~~embodiments~~, the compound has the following structure:



or a pharmaceutically acceptable salt or solvate thereof.

[0033] In another example~~aspect~~, described herein is a compound represented by Formula (B):



Formula (B)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 and R^2 are each independently selected from hydrogen, and substituted or unsubstituted alkyl;

R^7 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, -alkyl-(substituted or unsubstituted phenyl), -alkyl-(substituted or unsubstituted heteroaryl), -alkyl-(substituted or unsubstituted cycloalkyl),-alkyl-(substituted or unsubstituted heterocycloalkyl), $-(C(R^{10})_2O)_m-R^{11}$, $-(CH_2CH_2O)_n-R^{11}$, or $-(C(R^{10})_2)_p-OR^{11}$;

each R^9 is independently selected from hydrogen and alkyl;

each R^{10} is independently selected from hydrogen and alkyl;

R^{11} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, $-C(=O)R^{12}$, $-C(=O)-OR^{12}$, $-C(=O)N(R^{12})(R^8)$, $-C(=O)-SR^{12}$, or $-P(=O)(OR^9)_2$;

R^{12} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, -alkyl-(substituted or unsubstituted phenyl), or -alkyl-(substituted or unsubstituted heteroaryl);

m is 1, 2, 3, 4, 5, or 6;

n is 1, 2, 3, 4, 5, or 6.

p is 1, 2, 3, 4, 5, or 6;

wherein substituted means that the referenced group is substituted with one or more additional groups individually and independently selected from halogen, -CN, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -OH, $-CO_2H$, $-CO_2$alkyl, $-C(=O)NH_2$, -C(=O)NH(alkyl), $-C(=O)N(alkyl)_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH(alkyl)$, $-S(=O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone.

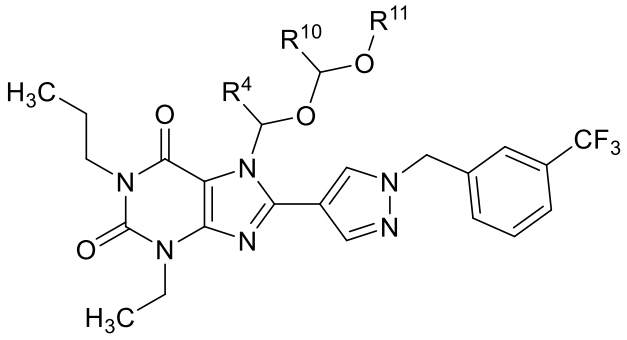
[0034] In some examples~~embodiments~~, R^4 is hydrogen; R^6 is hydrogen; R^5 is substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, -alkyl-(substituted or unsubstituted phenyl), -alkyl-(substituted or unsubstituted heteroaryl), -alkyl-(substituted or unsubstituted cycloalkyl),-alkyl-(substituted or unsubstituted heterocycloalkyl), $-(C(R^{10})_2O)_m-R^{11}$, $-C(=O)-(C(R^{10})_2O)_m-R^{11}$, $-C(=O)-(CH_2CH_2O)_n-R^{11}$, $-C(=O)-R^a$ or $-C(=O)-OR^7$.

[0035] In some examples~~embodiments~~, R^1 and R^2 are each independently selected from substituted or unsubstituted C_1-C_6alkyl; R^3 is selected from substituted or unsubstituted phenyl.

[0036] In some examples~~embodiments~~, R^1 and R^2 are each independently selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, tert-pentyl, neopentyl, isopentyl, sec-pentyl, 3-pentyl, n-hexyl, isohexyl, 3-methylpentyl, 2,3-dimethylbutyl, and neohexyl.

[0037] In some examples~~embodiments~~, R^1 is ethyl; R^2 is n-propyl; and R^3 is 3-(trifluoromethyl)phenyl.

[0038] In some examples~~embodiments~~, the compound has the following structure:

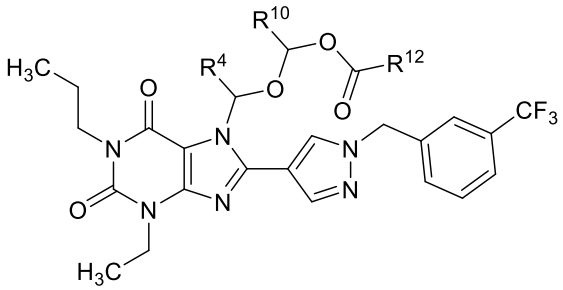


;

or a pharmaceutically acceptable salt or solvate thereof.

[0039] In some examples~~embodiments~~, R^{11} is hydrogen, substituted or unsubstituted alkyl, -C(=O)R^{12}, -C(=O)-OR^{12}, -C(=O)N(R^{12})(R^8), or -P(=O)(OR^9)$_2$.

[0040] In some examples~~embodiments~~, the compound has one of the following structures:



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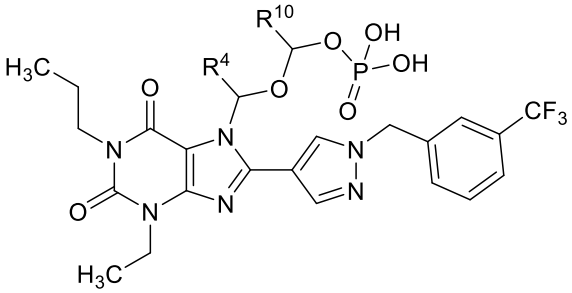
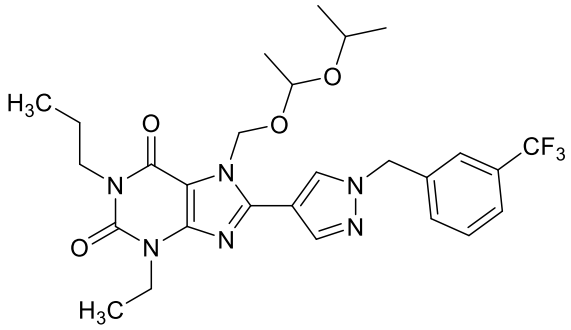


;

or a pharmaceutically acceptable salt or solvate thereof.

[0041] In some examples~~embodiments~~, the compound has one of the following structures:



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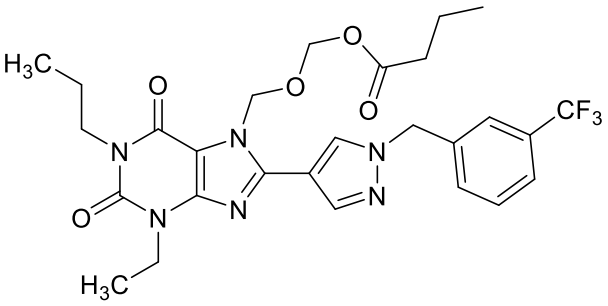

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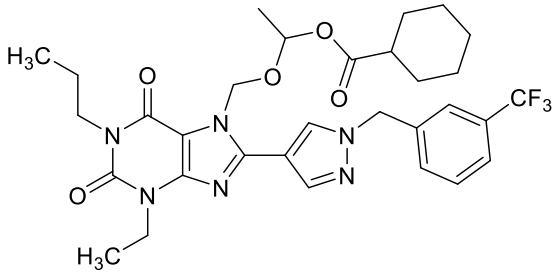

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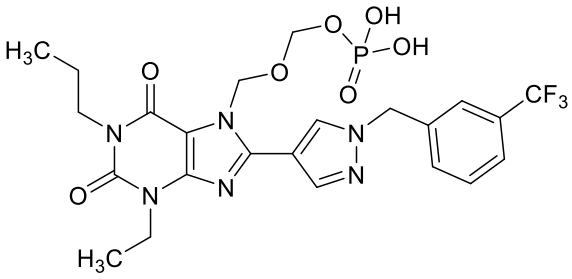
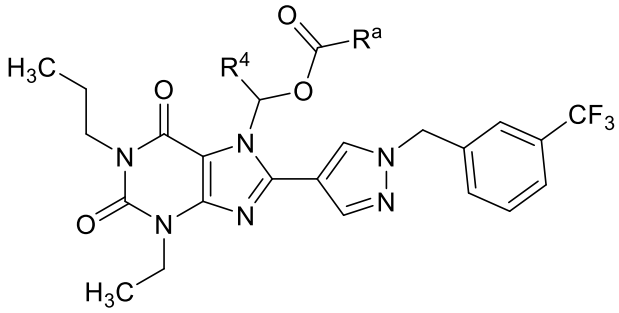


;

or a pharmaceutically acceptable salt or solvate thereof.

[0042] In some examples~~embodiments~~, R^5 is -C(=O)-$(C(R^{10})_2O)_m$-R^{11}, -C(=O)-$(CH_2CH_2O)_n$-R^{11}, -C(=O)-R^a or -C(=O)-OR^7.

[0043] In some examples~~embodiments~~, the compound has the following structure:

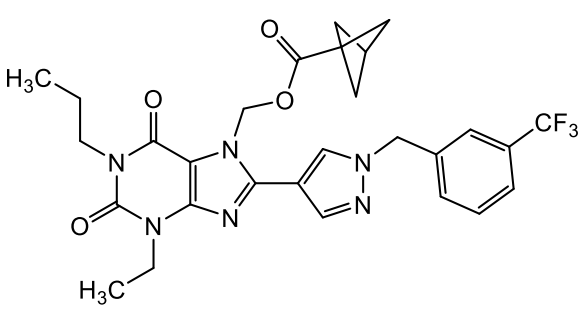


or a pharmaceutically acceptable salt or solvate thereof.

[0044] In some examples~~embodiments~~, R^a is substituted or unsubstituted bicyclic cycloalkyl that is a fused bicyclic cycloalkyl, bridged bicyclic cycloalkyl, or spiro bicyclic cycloalkyl; or R^a is substituted or unsubstituted bicyclic heterocycloalkyl that is a fused bicyclic heterocycloalkyl, bridged bicyclic heterocycloalkyl, or spiro bicyclic heterocycloalkyl; or R^a is substituted or unsubstituted bicyclic heteroaryl.

[0045] In some examples~~embodiments~~, R^a is substituted or unsubstituted bicyclo[1.1.1]pentanyl, substituted or unsubstituted bicyclo[2.2.1]heptanyl, substituted or unsubstituted bicyclo[2.2.2]octanyl, substituted or unsubstituted bicyclo[3.2.1]octanyl, substituted or unsubstituted bicyclo[3.3.0]octanyl, substituted or unsubstituted bicyclo[4.3.0]nonanyl, or substituted or unsubstituted decalinyl.

[0046] In some examples~~embodiments~~, the compound has one of the following structures:



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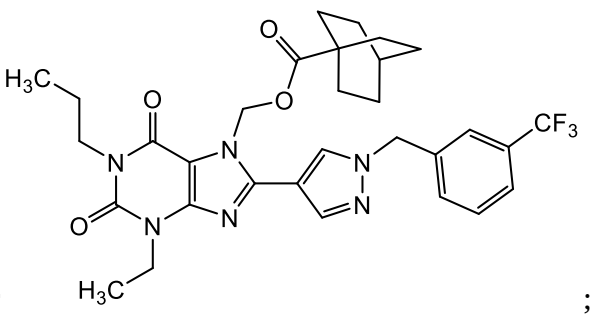


;

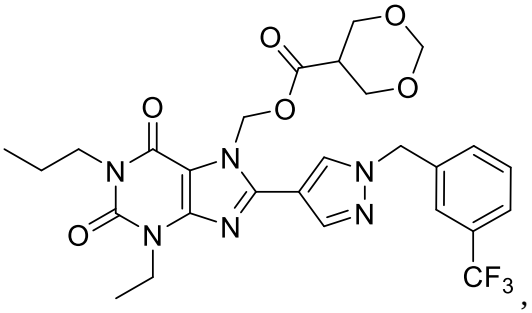
or a pharmaceutically acceptable salt or solvate thereof.

[0047] In some examples~~embodiments~~, R^a is substituted or unsubstituted heterocycloalkyl containing at least one O atom in the ring, substituted or unsubstituted azetidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted azapenyl, substituted or unsubstituted 5-membered heteroaryl, substituted or unsubstituted pyridin-2-yl, substituted or unsubstituted pyridin-4-yl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl.

[0048] In some examples~~embodiments~~, R^a is a substituted or unsubstituted heterocycloalkyl containing at least one O atom in the ring that is substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted dihydrofuranyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted dihydropyranyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted oxepanyl, substituted or unsubstituted oxazepinyl, or substituted or unsubstituted dioxanyl.

[0049] In some examples~~embodiments~~, R^a is a substituted or unsubstituted 5-membered heteroaryl that is substituted or unsubstituted furanyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted oxadiazolyl, or substituted or unsubstituted thiadiazolyl,

[0050] In some examples~~embodiments~~, the compound has one of the following structures: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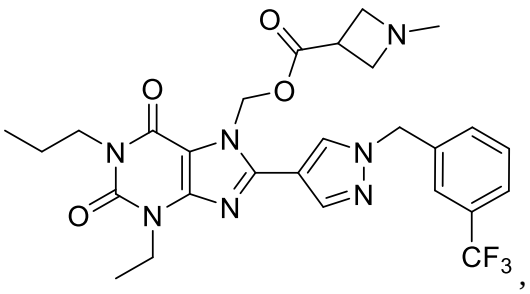
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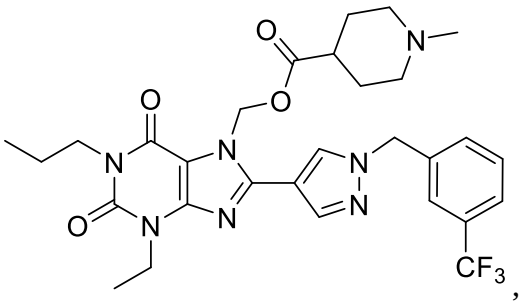
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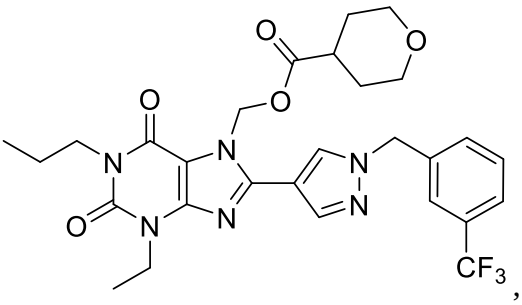
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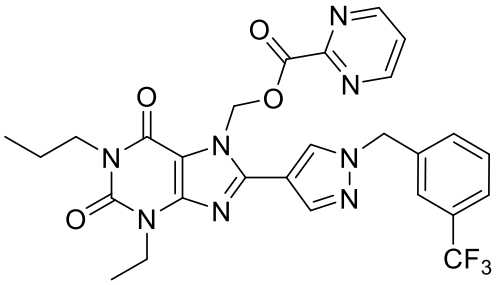
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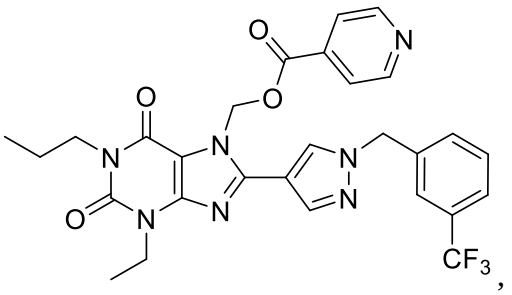
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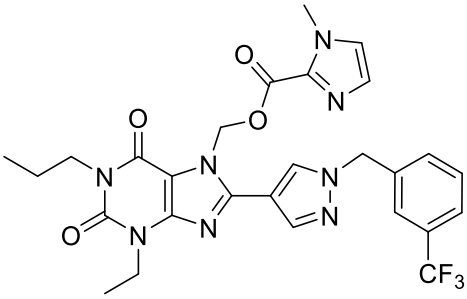
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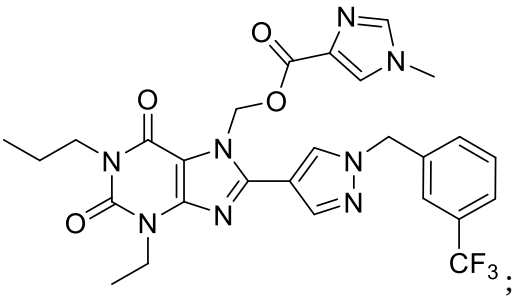
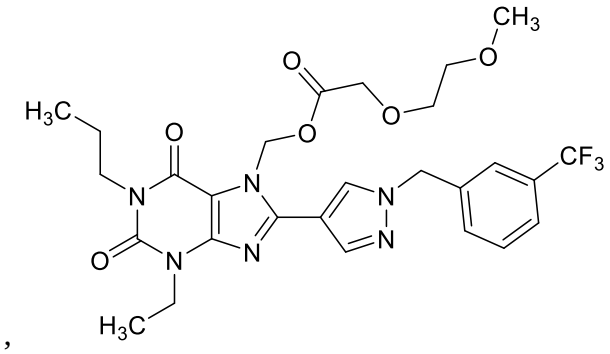

;

or a pharmaceutically acceptable salt or solvate thereof.

[0051] In some examples~~embodiments~~, R^1 is ethyl; R^2 is n-propyl; R^3 is 3-(trifluoromethyl)phenyl; R^5 is -C(=O)-$(C(R^{10})_2O)_m$-R^{11}, -C(=O)-$(CH_2CH_2O)_n$-R^{11}, or -C(=O)-OR^7.

[0052] In some examples~~embodiments~~, the compound has one of the following structures: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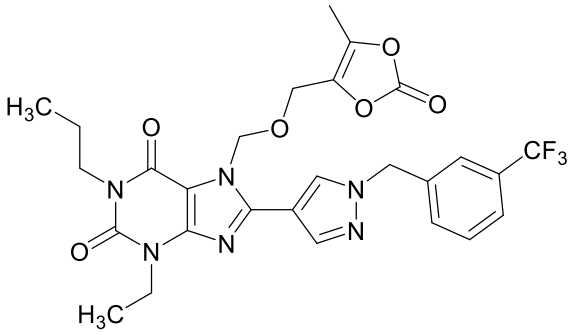
or a pharmaceutically acceptable salt or solvate thereof.

[0053] In some examples~~embodiments~~, R^1 is ethyl; R^2 is n-propyl; R^3 is 3-(trifluoromethyl)phenyl; R^5 is substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, -alkyl-(substituted or unsubstituted phenyl), -alkyl-(substituted or unsubstituted heteroaryl), -alkyl-(substituted or unsubstituted cycloalkyl),-alkyl-(substituted or unsubstituted heterocycloalkyl).

[0054] In some examples~~embodiments~~, the compound has the following structure:



;

or a pharmaceutically acceptable salt or solvate thereof.

[0055] Also described herein is a pharmaceutical formulation, comprising a compound of any one of the compounds disclosed herein, or a pharmaceutically acceptable salt or solvate thereof; and at least one pharmaceutically acceptable excipient.

[0056] In some examples~~embodiments~~, the pharmaceutical composition is formulated for administration to a mammal by oral administration, intravenous administration, or subcutaneous administration.

[0057] In some examples~~embodiments~~, 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.

[0058] In one example~~aspect~~, described herein is a method of modulating the A_{2B} adenosine receptor in a mammal comprising administering to the mammal a compound described herein, or any pharmaceutically acceptable salt or solvate thereof.

[0059] In another example~~aspect~~, described herein is a method of treating a disease or disorder in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound described herein, or a pharmaceutically acceptable salt or solvate thereof, wherein the condition is selected from the group consisting of cardiovascular diseases, fibrosis, neurological disorders, type I hypersensitivity disorders, chronic and acute liver diseases, lung diseases, renal diseases, diabetes, obesity, and cancer. In some examples~~embodiments~~, the disease or disorder is cancer.

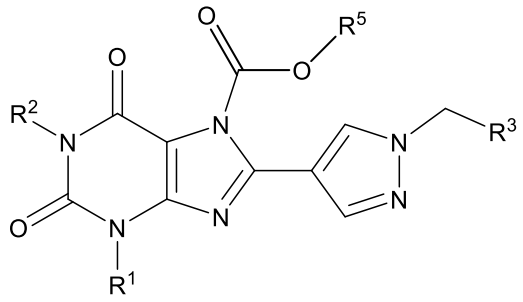
[0060] In some examples~~embodiments~~, the subject is human.

[0061] In any of the aforementioned examples~~aspects~~ are further examples~~embodiments~~ in which an effective amount of the compound described herein, or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal.

[0062] In any of the aforementioned examples~~aspects~~ are further examples~~embodiments~~ comprising single administrations of an effective amount of the compound, including further examples~~embodiments~~ in which the compound is administered once a day to the mammal or the compound is administered to the mammal multiple times over the span of one day. In some examples~~embodiments~~, the compound is

administered on a continuous dosing schedule. In some examples~~embodiments~~, the compound is administered on a continuous daily dosing schedule.

[0062a] In one aspect, the present disclosure refers to a compound represented by Formula (III):



Formula (III)

or a pharmaceutically acceptable salt or solvate thereof;

wherein

R^1 and R^2 are each independently selected from hydrogen and substituted or unsubstituted C_1-C_6alkyl;

R^3 is selected from substituted and unsubstituted phenyl, wherein if R^3 is substituted then R^3 is substituted with one or more groups selected from halogen, -CN, and C_1-C_4fluoroalkyl;

R^5 is hydrogen or R^7;

R^7 is substituted or unsubstituted C_1-C_6alkyl, alkyl-(substituted or unsubstituted heterocycloalkyl), $-(CH_2CH_2O)_n-R^{11}$, or $-(C(R^{10})_2)_p-OR^{11}$;

each R^9 is independently selected from hydrogen and C_1-C_6alkyl;

each R^{10} is independently selected from hydrogen and C_1-C_6alkyl;

R^{11} is hydrogen, substituted or unsubstituted alkyl, $-C(=O)R^{12}$, or $-P(=O)(OR^9)_2$;

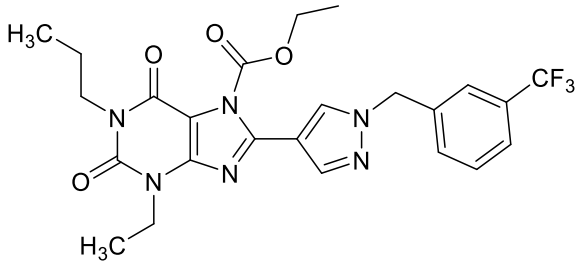
R^{12} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_3-C_{10}cycloalkyl;

n is 1, 2, 3, 4, 5, or 6; and

p is 1, 2, 3, 4, 5, or 6;

wherein substituted means that the referenced group is substituted with one or more additional groups individually and independently selected from C_1-C_6alkyl.

[0062b] In another aspect, the present disclosure refers to a compound of structure: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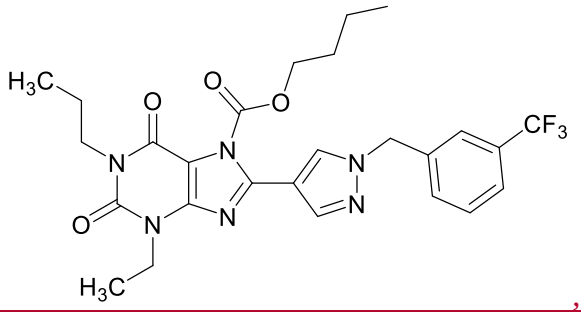
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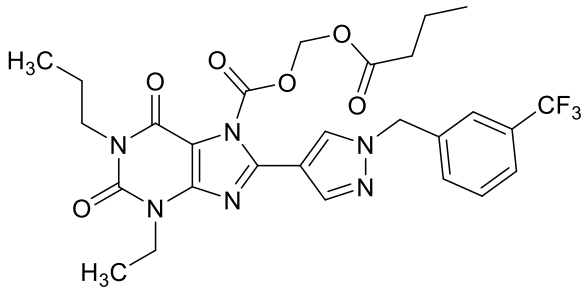
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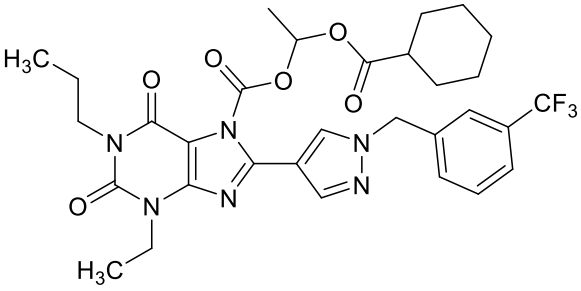
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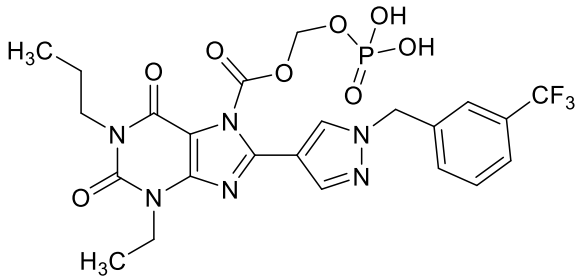
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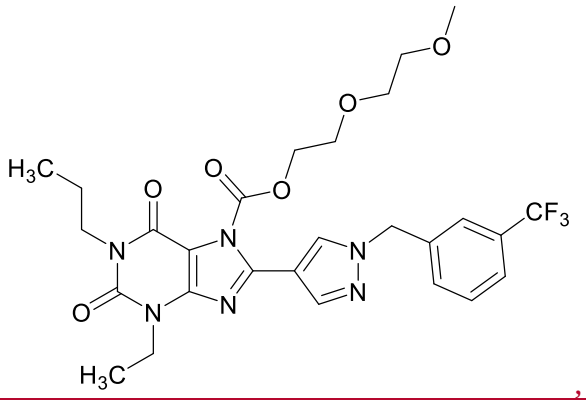
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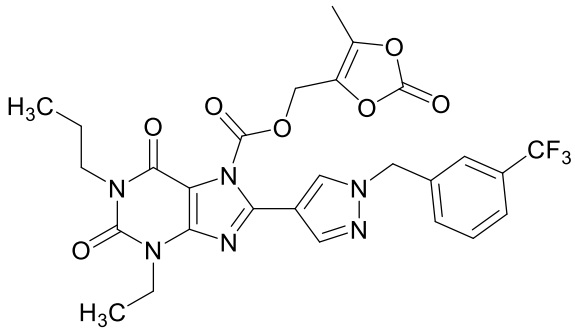
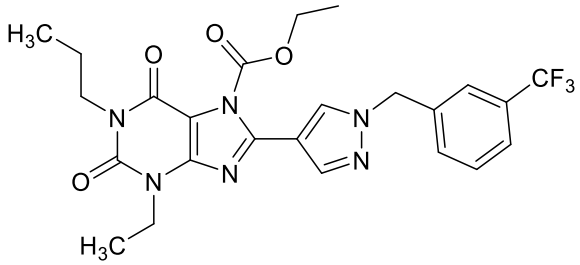

;

or a pharmaceutically acceptable salt or solvate thereof.

[0062c] In another aspect, the present disclosure refers to a pharmaceutical composition, comprising a compound as described herein, or any pharmaceutically acceptable salt or solvate thereof; and at least one pharmaceutically acceptable excipient.

[0062d] In another aspect, the present disclosure refers to a compound of structure: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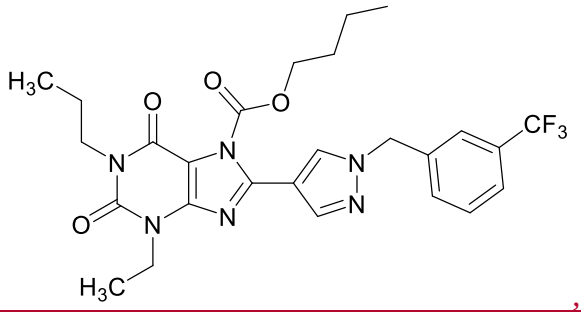
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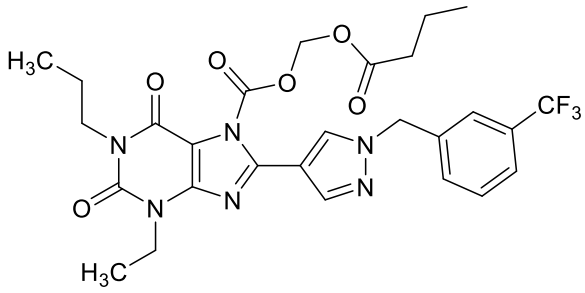
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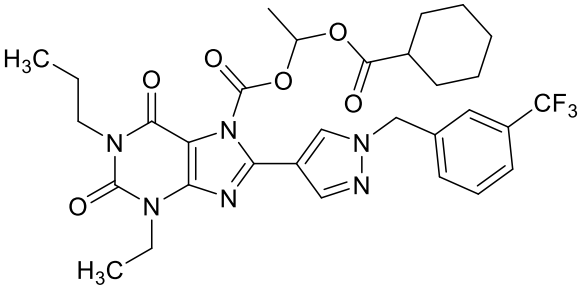
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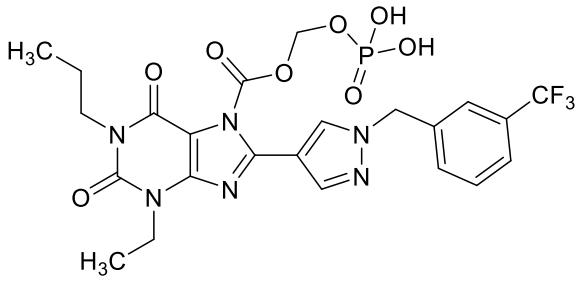
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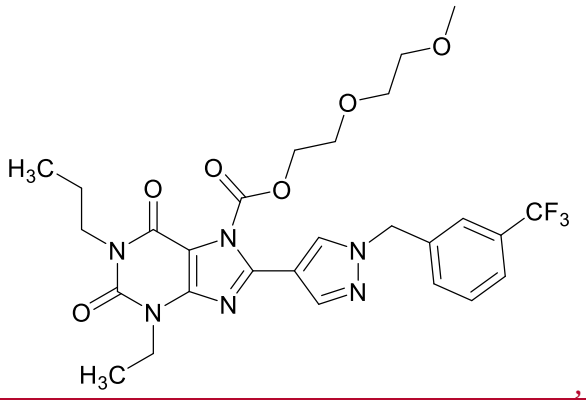
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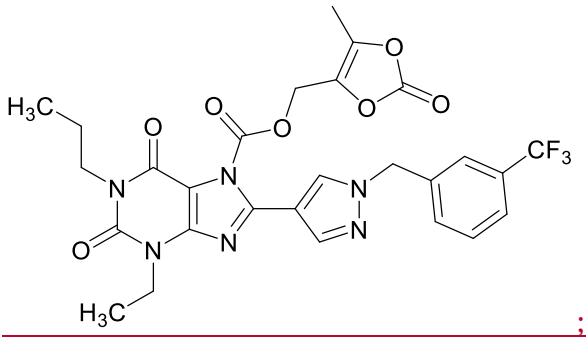
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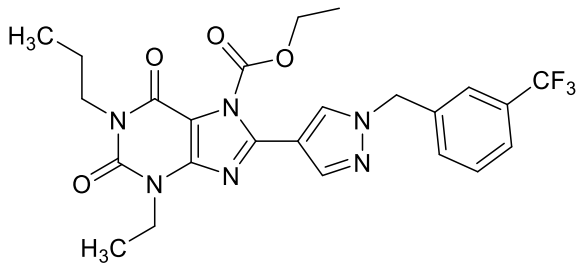
or a pharmaceutically acceptable salt thereof.

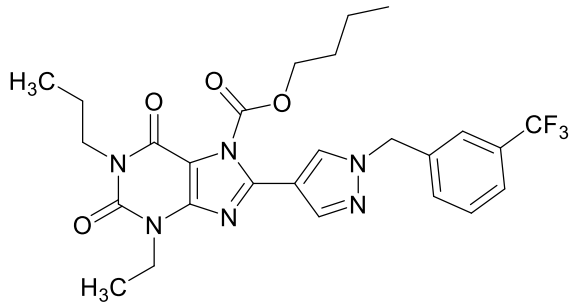
[0062e] In yet another aspect, the present disclosure refers to a pharmaceutical composition, comprising a compound as described herein, or any pharmaceutically acceptable salt thereof; and at least one pharmaceutically acceptable excipient.

[0062f] In yet another aspect, the present disclosure refers to a compound of structure:



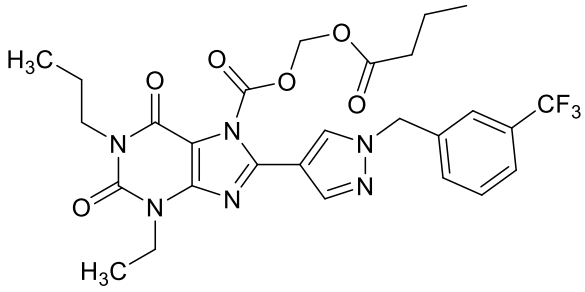
or a pharmaceutically acceptable salt thereof.

[0062g] In yet another aspect, the present disclosure refers to a compound of structure:



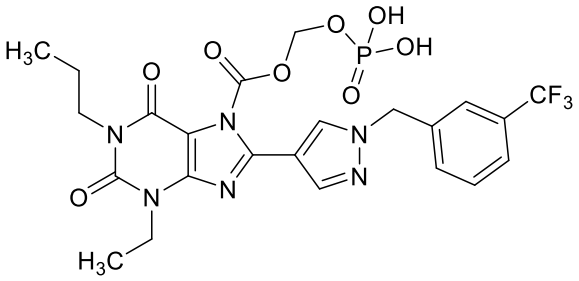
or a pharmaceutically acceptable salt thereof.

[0062h] In yet another aspect, the present disclosure refers to a compound of structure:



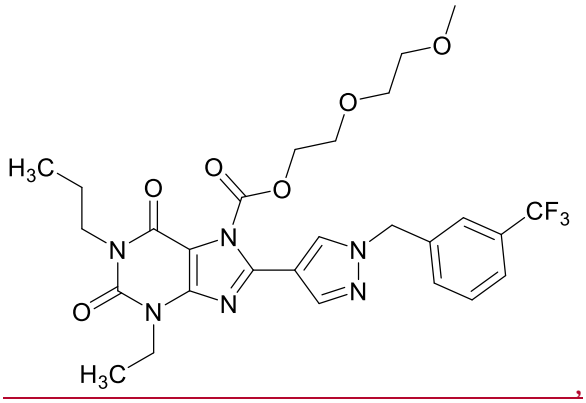
or a pharmaceutically acceptable salt thereof.

[0062i] In yet another aspect, the present disclosure refers to a compound of structure:



or a pharmaceutically acceptable salt thereof.

[0062j] In yet another aspect, the present disclosure refers to a compound of structure:



or a pharmaceutically acceptable salt thereof.

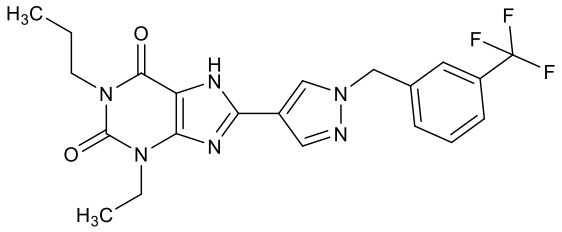
[0063] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[0064] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific ~~embodiments~~examples, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[0065] Disclosed herein are compounds, compositions, formulations, and methods related to A_{2B} adenosine receptor antagonists. For example, the compounds, compositions, and/or formulations disclosed herein can be used in a method of treating a condition in a subject in need thereof. The condition can be cardiovascular diseases, chronic and acute liver disease, lung disease, renal disease, diabetes, obesity, and/or cancer.

[0066] 8-(1-(3-(Trifluoromethyl)benzyl)-1H-pyrazol-4-yl)-3-ethyl-1-propyl-1H-purine-2,6(3H,7H)-dione (Compound 1) is an A_{2B} adenosine receptor antagonist, which is a xanthine unsubstituted at 7-position. It can be relatively insoluble in aqueous media and difficult to formulate using conventional pharmaceutical excipients, and thus can be difficult to formulate in a manner that provides reproducible plasma levels of the compound undergoing evaluation in mammals, in particular humans. Accordingly, new prodrugs of the A_{2B} adenosine receptor antagonist can be developed to improve the formulation, pharmacokinetic profile, and/or bioavailability the A_{2B} adenosine receptor antagonist.



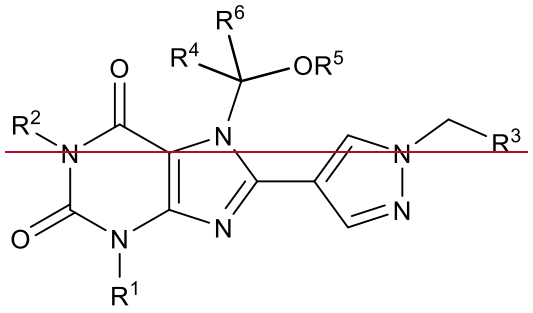
Compound 1

[0067] In some cases, prodrugs can be hydrolyzed by esterase (e.g., in gastrointestinal tract and/or in blood) and converted into Compound 1 in an aqueous solution. In some cases, acid labile prodrugs can be converted into Compound 1 in an acidic environment (e.g., in the stomach). In

CLAIMS

WHAT IS CLAIMED IS:

1. A compound represented by Formula (A):



Formula (A)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 and R^2 are each independently selected from hydrogen, and substituted or unsubstituted alkyl;

R^3 is selected from substituted or unsubstituted phenyl, and substituted or unsubstituted heteroaryl, wherein if R^3 is substituted then R^3 is substituted with one or more groups selected from halogen, -CN, -OH, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-C_4alkoxy, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, and substituted or unsubstituted C_1-C_4heteroalkyl;

R^4 is substituted or unsubstituted alkyl;

R^6 is hydrogen or substituted or unsubstituted alkyl;

or R^4 and R^6 are taken together with the carbon atom to which they are attached to form a carbonyl (C=O);

or R^4 and R^6 are taken together with the carbon atom to which they are attached to form a ring that is a substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted C_2-C_{10}heterocycloalkyl, wherein if the ring is substituted then it is substituted with one or more R^{15};

R^{15} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, -alkyl-(substituted or unsubstituted phenyl), -alkyl-(substituted or unsubstituted heteroaryl), $-C(=O)R^{16}$, $-C(=O)-OR^{16}$, $-C(=O)N(R^{16})_2$;

each R^{16} is independently selected from hydrogen and substituted or unsubstituted alkyl;

R^5 is hydrogen, R^7, $-C(=O)R^7$, $-C(=O)-OR^7$, $-C(=O)N(R^7)(R^8)$, $-C(=O)-SR^7$, or $-P(=O)(OR^9)_2$;

or R^4 and R^5 are taken together with the atoms to which they are attached to form a substituted or unsubstituted C_2-C_{10}heterocycloalkyl;

R^7 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, -alkyl-(substituted or unsubstituted phenyl), -alkyl-(substituted or unsubstituted heteroaryl), -alkyl-(substituted or unsubstituted cycloalkyl), alkyl-(substituted or unsubstituted heterocycloalkyl), $-(C(R^{10})_2O)_m-R^{11}$, $-(CH_2CH_2O)_n-R^{11}$, or $-(C(R^{10})_2)_p-OR^{11}$;

R^8 is hydrogen or alkyl;

or R^7 and R^8 are taken together with the nitrogen atom to which they are attached to form a substituted or unsubstituted C_2-C_{10}heterocycloalkyl;

each R^9 is independently selected from hydrogen and alkyl;

each R^{10} is independently selected from hydrogen and alkyl;

R^{11} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, $-C(=O)R^{12}$, $-C(=O)-OR^{12}$, $-C(=O)N(R^{12})(R^8)$, $-C(=O)-SR^{12}$, or $-P(=O)(OR^9)_2$;

R^{12} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, -alkyl-(substituted or unsubstituted phenyl), or -alkyl-(substituted or unsubstituted heteroaryl);

m is 1, 2, 3, 4, 5, or 6;

n is 1, 2, 3, 4, 5, or 6;

p is 1, 2, 3, 4, 5, or 6;

wherein substituted means that the referenced group is substituted with one or more additional groups individually and independently selected from halogen, -CN, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -OH, $-CO_2H$, $-CO_2$alkyl, $-C(=O)NH_2$, -C(=O)NH(alkyl), $-C(=O)N(alkyl)_2$, $-S(=O)_2NH_2$, $-S(=O)_2$NH(alkyl), $-S(=O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone.

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

R^4 is C_1-C_6alkyl;

~~R^6 is selected from hydrogen, and C_1-C_6alkyl;~~

~~or R^4 and R^6 are taken together with the carbon atom to which they are attached to form a carbonyl (C=O).~~

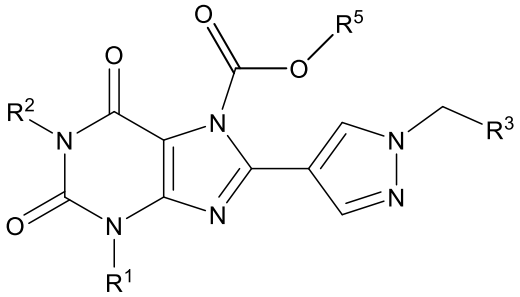
~~3. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein:~~

~~R^4 is methyl, ethyl, or n-propyl;~~

~~R^6 is selected from hydrogen, methyl, ethyl, and n-propyl;~~

~~or R^4 and R^6 are taken together with the carbon atom to which they are attached to form a carbonyl (C=O).~~

~~4.~~1. A~~The~~ compound represented by ~~of claim 3, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following structure of~~ Formula (III):



Formula (III)

or a pharmaceutically acceptable salt or solvate thereof; wherein

R^1 and R^2 are each independently selected from hydrogen and substituted or unsubstituted C_1-C_6 alkyl;

R^3 is selected from substituted and unsubstituted phenyl, wherein if R^3 is substituted then R^3 is substituted with one or more groups selected from halogen, -CN, and C_1-C_4fluoroalkyl;

R^5 is hydrogen or R^7;

R^7 is substituted or unsubstituted C_1-C_6alkyl, alkyl-(substituted or unsubstituted heterocycloalkyl), $-(CH_2CH_2O)_n-R^{11}$, or $-(C(R^{10})_2)_p-OR^{11}$;

each R^9 is independently selected from hydrogen and C_1-C_6alkyl;

each R^{10} is independently selected from hydrogen and C_1-C_6alkyl;

R^{11} is hydrogen, substituted or unsubstituted alkyl, $-C(=O)R^{12}$, or $-P(=O)(OR^9)_2$;

R^{12} is hydrogen, substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_3-C_{10}cycloalkyl;

n is 1, 2, 3, 4, 5, or 6; and

p is 1, 2, 3, 4, 5, or 6;

wherein substituted means that the referenced group is substituted with one or more additional groups individually and independently selected from C_1-C_6alkyl.

~~5.~~2. The compound of ~~any one of~~ claim~~s~~ 1~~-4~~, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 and R^2 are each independently selected from substituted or unsubstituted C_1-C_6alkyl;

R^3 is selected from substituted or unsubstituted phenyl.

~~6.~~3. The compound of ~~any one of~~ claim~~s~~ 1~~-4~~, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 and R^2 are each independently selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, tert-pentyl, neopentyl, isopentyl, sec-pentyl, 3-pentyl, n-hexyl, isohexyl, 3-methylpentyl, 2,3-dimethylbutyl, and neohexyl.

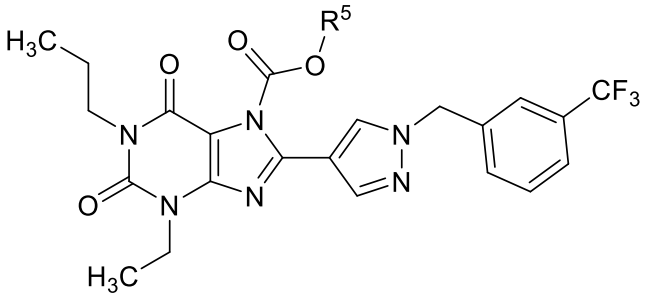
~~7. The compound of claim 6, or a pharmaceutically acceptable salt or solvate thereof, wherein:~~

~~R^1 is ethyl;~~

~~R^2 is n-propyl; and~~

~~R^3 is 3-(trifluoromethyl)phenyl.~~

~~8.~~4. The compound of claim ~~3~~4, wherein the compound has the following structure:



or a pharmaceutically acceptable salt or solvate thereof.

~~9.~~5. The compound of claim ~~4~~8, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^5 is R^7;

R^7 is C_1-C_6alkyl, ~~substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic C_3-C_8cycloalkyl, substituted or unsubstituted bicyclic C_5-C_{10}cycloalkyl, substituted or unsubstituted monocyclic C_2-C_8heterocycloalkyl, substituted or unsubstituted bicyclic C_5-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, -CH_2-(substituted or unsubstituted phenyl), -CH_2-(substituted or unsubstituted heteroaryl), -CH_2-(substituted or unsubstituted C_2-C_8heterocycloalkyl), -$CH(R^{10})O$-R^{11},~~ -$(CH_2CH_2O)_n$-R^{11}, or -$(C(R^{10})_2)_p$-OR^{11};

each R^{10} is independently selected from hydrogen and methyl;

R^{11} is hydrogen, C_1-C_6alkyl, ~~substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl,~~ -C(=O)R^{12}, ~~-C(=O)-OR^{12}, -C(=O)N(R^{12})(R^8), -C(=O)-SR^{12},~~ or -P(=O)(OR^9)$_2$;

R^{12} is substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_3-C_{10}cycloalkyl;

n is 1, 2, 3, 4, 5, or 6; and

p is 1, 2, 3, 4, 5, or 6;

wherein substituted means that the referenced group is substituted with one or more additional groups individually and independently selected from C_1-C_6alkyl.

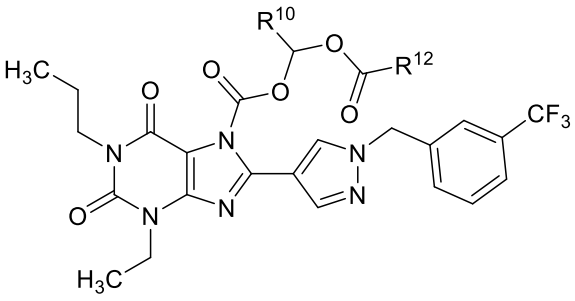
~~10.~~6. The compound of claim ~~5~~9, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^7 is C_1-C_6alkyl~~, substituted or unsubstituted C_1-C_6heteroalkyl, -CH_2-(substituted or unsubstituted phenyl), -CH_2-(substituted or unsubstituted heteroaryl), -CH_2-(substituted or unsubstituted C_2-C_8heterocycloalkyl), -CH(R^{10})O-R^{11}, or -(CH_2CH_2O)$_n$-R^{11};~~

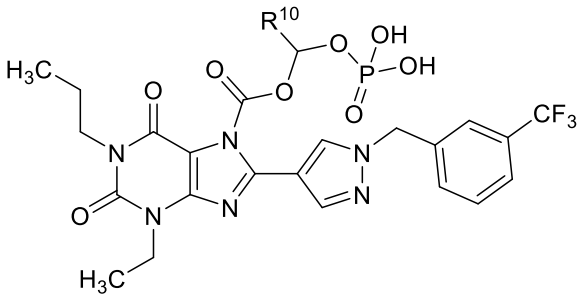
~~R^{10} is hydrogen and methyl;~~

~~R^{11} is hydrogen, C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, -C(=O)R^{12}, -C(=O)-OR^{12}, -C(=O)N(R^{12})(R^8), -C(=O)-SR^{12}, or -P(=O)(OH)$_2$~~.

~~11.~~7. The compound of claim 1~~0~~, wherein the compound has one of the following structures:

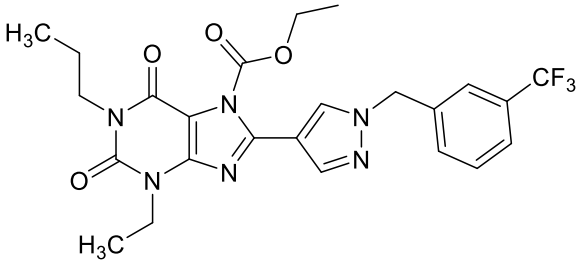


or



or a pharmaceutically acceptable salt or solvate thereof.

~~12.~~8. A compound of structure~~The compound of claim 8, wherein the compound has one of the following structures~~: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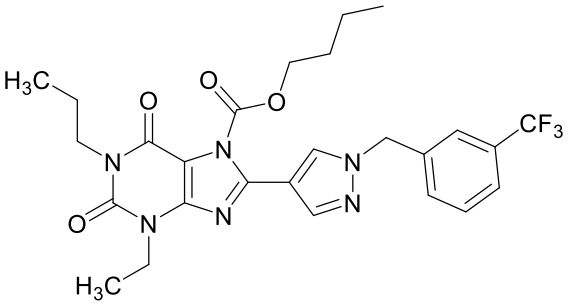
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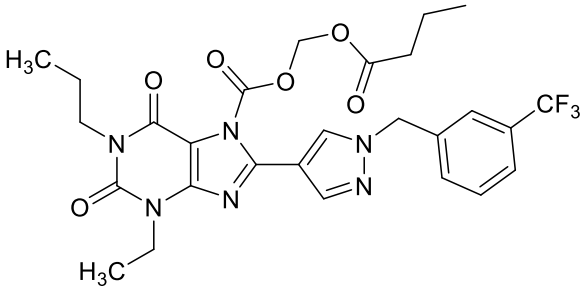
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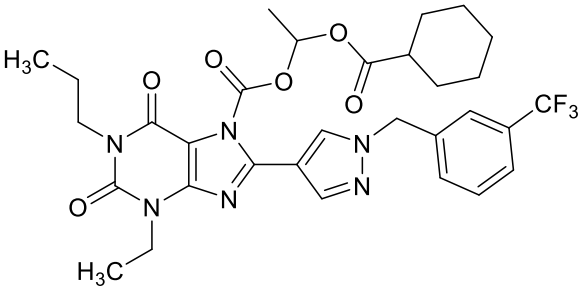
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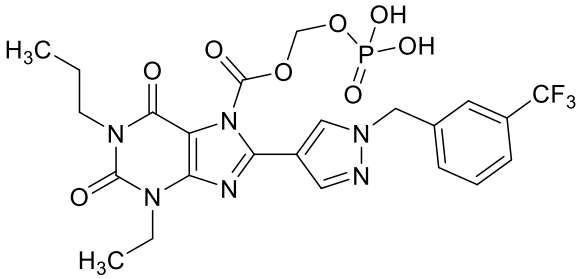
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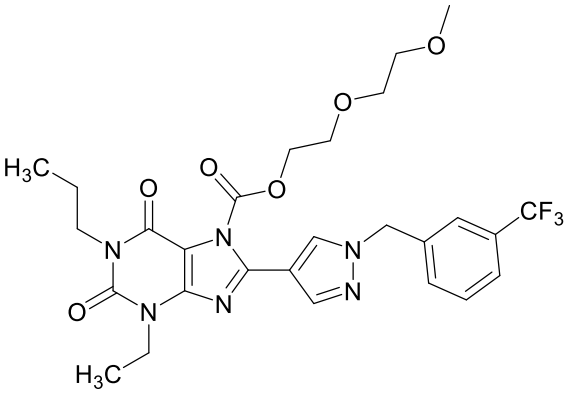
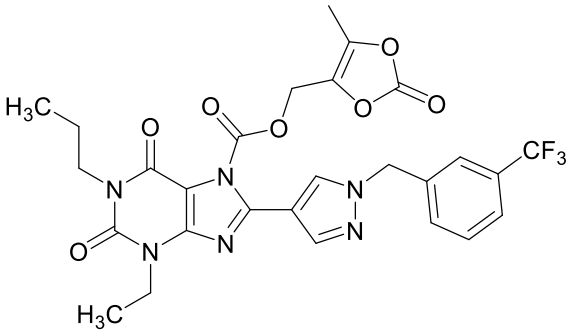
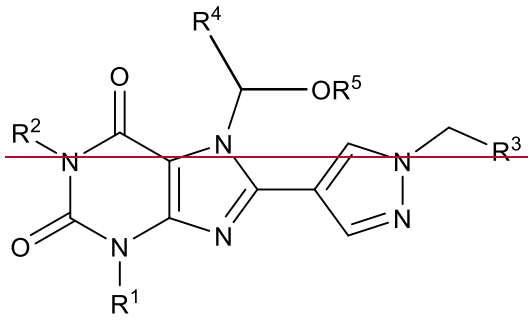

, or

;

or a pharmaceutically acceptable salt or solvate thereof.

~~13. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following structure of Formula (I):~~



Formula (I)

or a pharmaceutically acceptable salt or solvate thereof.

14. The compound of claim 13, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 and R^2 are each independently selected from substituted or unsubstituted C_1-C_6alkyl;

R^3 is selected from substituted or unsubstituted phenyl.

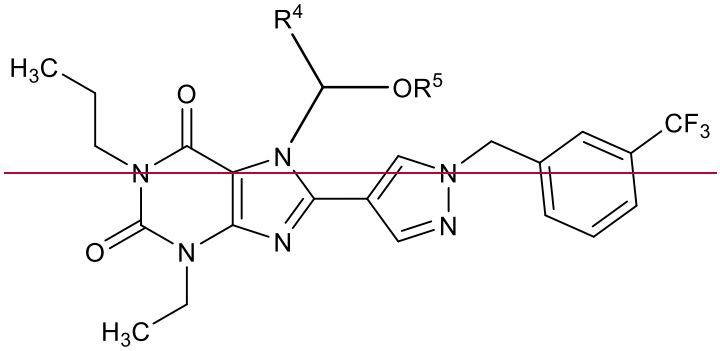
15. The compound of claim 13, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is ethyl;

R^2 is n-propyl; and

R^3 is 3-(trifluoromethyl)phenyl.

16. The compound of claim 13, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following structure:



or a pharmaceutically acceptable salt or solvate thereof.

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

R^4 is methyl or ethyl;

R^5 is hydrogen, R^7, $-C(=O)R^7$, $-C(=O)-OR^7$, $-C(=O)N(R^7)(R^8)$, $-C(=O)-SR^7$, or $-P(=O)(OR^9)_2$;

R^7 is C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted monocyclic C_3-C_8cycloalkyl, substituted or unsubstituted bicyclic C_5-C_{10}cycloalkyl, substituted or unsubstituted monocyclic C_2-C_8heterocycloalkyl, substituted or unsubstituted bicyclic C_5-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, $-CH_2$-(substituted or unsubstituted phenyl), $-CH_2$-(substituted or unsubstituted heteroaryl), $-CH_2$-(substituted or unsubstituted C_2-C_8heterocycloalkyl), $-CH(R^{10})O-R^{11}$, $-(CH_2CH_2O)_n-R^{11}$, or $-(C(R^{10})_2)_p-OR^{11}$;

each R^{10} is independently selected from hydrogen and methyl;

R^{11} is hydrogen, C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, $-C(=O)R^{12}$, $-C(=O)-OR^{12}$, $-C(=O)N(R^{12})(R^8)$, $-C(=O)-SR^{12}$, or $-P(=O)(OR^9)_2$.

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

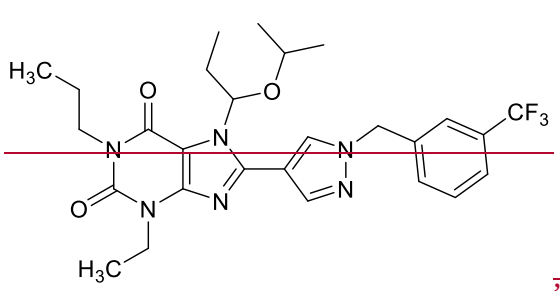
R^5 is R^7, $-C(=O)R^7$, $-C(=O)-OR^7$, $-C(=O)N(R^7)(R^8)$, $-C(=O)-SR^7$, or $-P(=O)(OH)_2$;

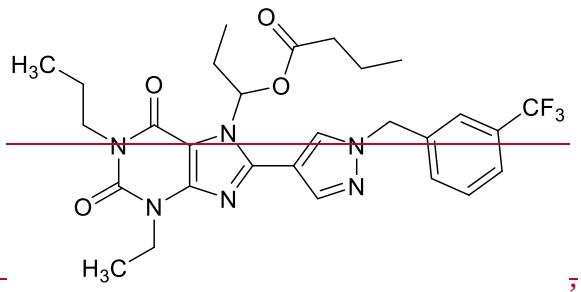
R^7 is C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted cyclohexyl, substituted or unsubstituted cyclopentyl, substituted or unsubstituted bicyclo[1.1.1]pentanyl, substituted or unsubstituted bicyclo[2.2.1]heptanyl, substituted or unsubstituted bicyclo[2.2.2]octanyl, substituted or unsubstituted bicyclo[3.2.1]octanyl, substituted or unsubstituted bicyclo[3.3.0]octanyl, substituted or unsubstituted bicyclo[4.3.0]nonanyl, or substituted or unsubstituted decalinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted azetidinyl, substituted or unsubstituted pyrrolidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted thiomorpholinyl, substituted or unsubstituted phenyl, substituted or unsubstituted monocyclic heteroaryl, $-CH_2$-(substituted or unsubstituted phenyl), $-CH_2$-(substituted or unsubstituted heteroaryl), $-CH_2$-(substituted or unsubstituted C_2-C_8heterocycloalkyl), $-CH(R^{10})O-R^{11}$, $-(CH_2CH_2O)_n-R^{11}$, or $-(C(R^{10})_2)_p-OR^{11}$;

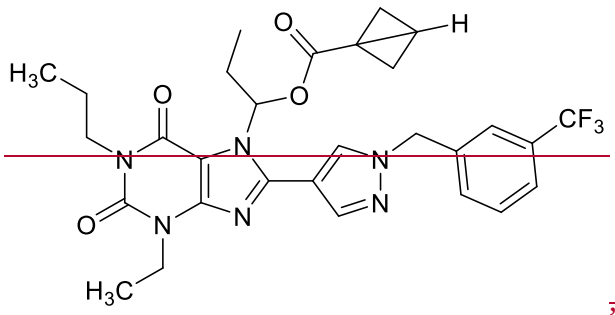
each R^{10} is independently selected from hydrogen and methyl;

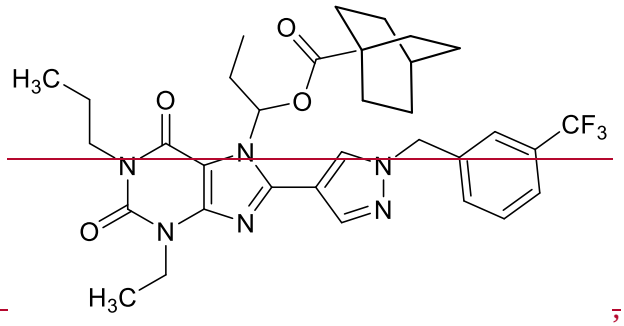
R^{11} is hydrogen, C_1-C_6alkyl, substituted or unsubstituted C_1-C_6heteroalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, $-C(=O)R^{12}$, $-C(=O)-OR^{12}$, $-C(=O)N(R^{12})(R^8)$, $-C(=O)-SR^{12}$, or $-P(=O)(OR^9)_2$.

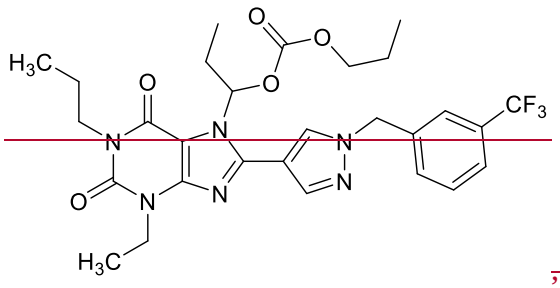
19. The compound of claim 16, wherein the compound has one of the following structures:

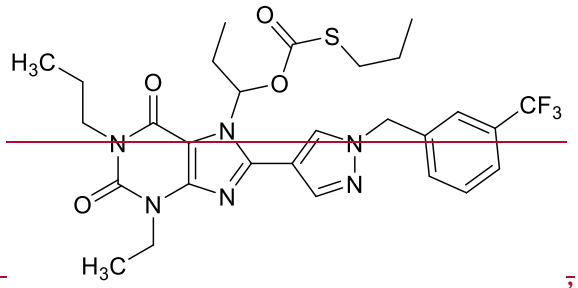


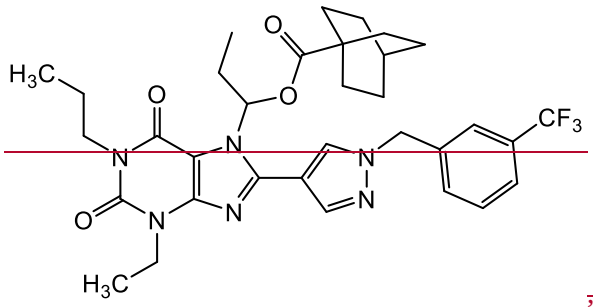


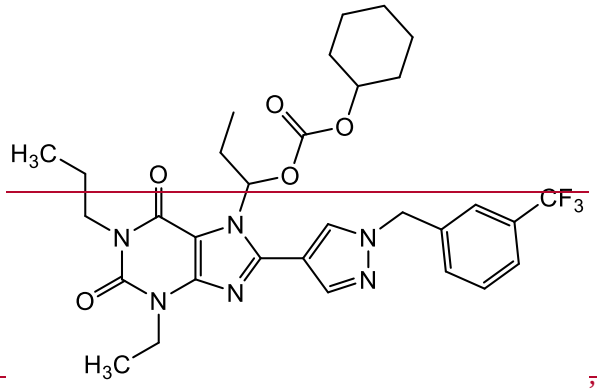


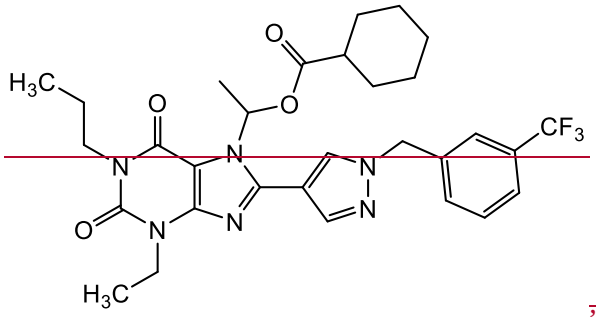












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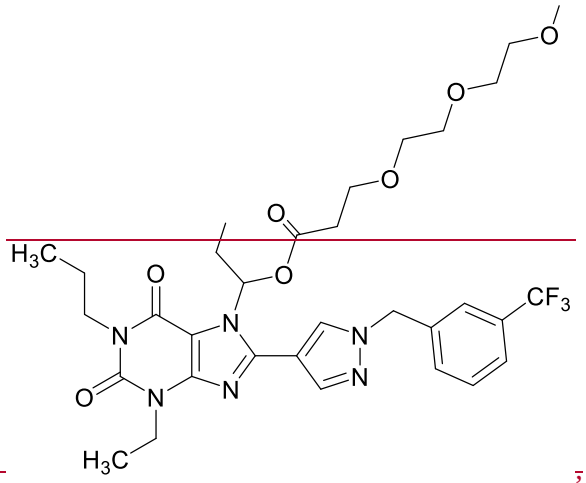

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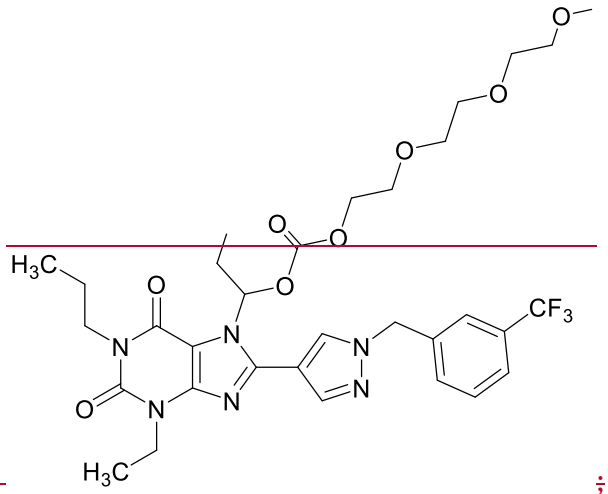
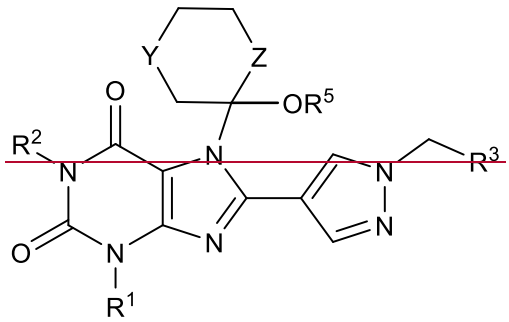


or ;

or a pharmaceutically acceptable salt or solvate thereof.

20. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following structure of Formula (II):



Formula (II)

wherein:

Y is selected from $-CH_2-$, O, S, $-NR^{15}-$, and $-S(O)_2-$;

Z is O or S;

or a pharmaceutically acceptable salt or solvate thereof.

21. The compound of claim 20, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 and R^2 are each independently selected from substituted or unsubstituted C_1-C_6alkyl;

R^3 is selected from substituted or unsubstituted phenyl.

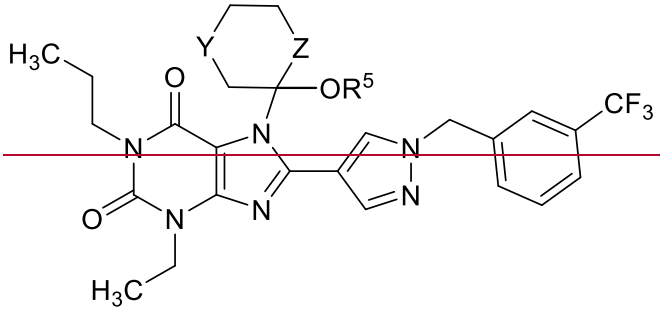
22. The compound of claim 20, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is ethyl;

R^2 is n-propyl; and

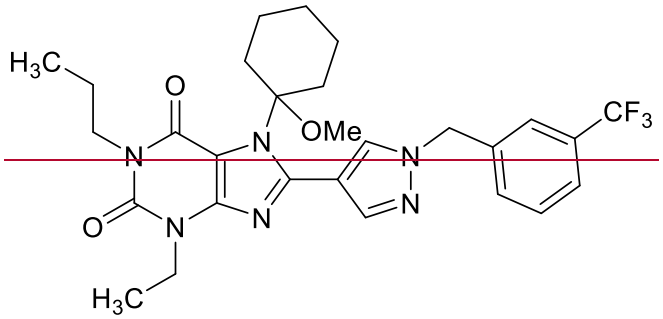
R^3 is 3-(trifluoromethyl)phenyl.

23. The compound of claim 20, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following structure:



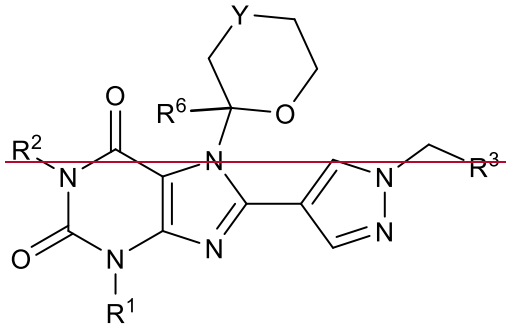
or a pharmaceutically acceptable salt or solvate thereof.

24. The compound of claim 1, wherein the compound has the following structure:



or a pharmaceutically acceptable salt or solvate thereof.

25. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, wherein the compound has the following structure of Formula (IIa):



Formula (IIa)

wherein:

Y is selected from -CH_2-, O, S, -NR^{15}-, and -$S(O)_2$-;

or a pharmaceutically acceptable salt or solvate thereof.

26. The compound of claim 25, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 and R^2 are each independently selected from substituted or unsubstituted C_1-C_6alkyl;

R^3 is selected from substituted or unsubstituted phenyl.

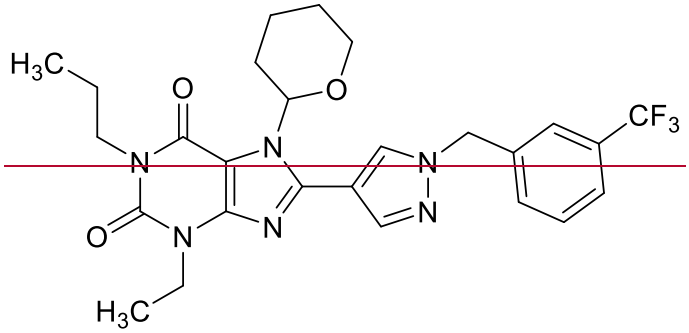
27. The compound of claim 25, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is ethyl;

R^2 is n-propyl; and

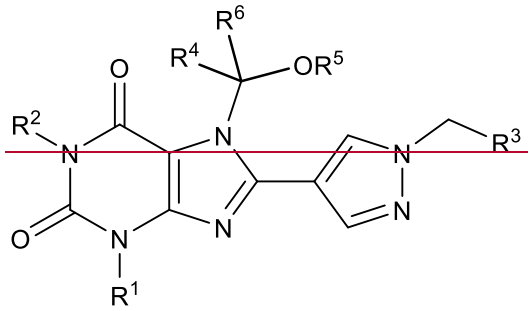
R^3 is 3-(trifluoromethyl)phenyl.

28. The compound of claim 25, wherein the compound has the following structure:



or a pharmaceutically acceptable salt or solvate thereof.

29. A compound represented by Formula (B):



Formula (B)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 and R^2 are each independently selected from hydrogen, and substituted or unsubstituted alkyl;

R^3 is selected from substituted or unsubstituted phenyl, and substituted or unsubstituted heteroaryl, wherein if R^3 is substituted then R^3 is substituted with one or more groups selected from halogen, -CN, -OH, C_1-C_4alkyl, C_2-C_4alkenyl, C_2-C_4alkynyl, C_1-

C_4alkoxy, C_1-C_4fluoroalkyl, C_1-C_4fluoroalkoxy, and substituted or unsubstituted C_1-C_4heteroalkyl;

R^4 is hydrogen or substituted or unsubstituted alkyl;

R^6 is hydrogen or substituted or unsubstituted alkyl;

or R^4 and R^6 are taken together with the carbon atom to which they are attached to form a carbonyl (C=O);

or R^4 and R^6 are taken together with the carbon atom to which they are attached to form a ring that is a substituted or unsubstituted C_3-C_{10}cycloalkyl, or substituted or unsubstituted C_2-C_{10}heterocycloalkyl, wherein if the ring is substituted then it is substituted with one or more R^{15};

R^{15} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, -alkyl-(substituted or unsubstituted phenyl), -alkyl-(substituted or unsubstituted heteroaryl), $-C(=O)R^{16}$, $-C(=O)-OR^{16}$, $-C(=O)N(R^{16})_2$;

each R^{16} is independently selected from hydrogen and substituted or unsubstituted alkyl;

R^5 is substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, -alkyl-(substituted or unsubstituted phenyl), -alkyl-(substituted or unsubstituted heteroaryl), -alkyl-(substituted or unsubstituted cycloalkyl), alkyl-(substituted or unsubstituted heterocycloalkyl), $-(C(R^{10})_2O)_m-R^{11}$, $-C(=O)-(C(R^{10})_2O)_m-R^{11}$, $-C(=O)-(CH_2CH_2O)_n-R^{11}$, $-C(=O)-R^a$ or $-C(=O)-OR^7$;

R^a is substituted or unsubstituted bicyclic cycloalkyl, substituted or unsubstituted bicyclic heterocycloalkyl, substituted or unsubstituted bicyclic heteroaryl, (substituted or unsubstituted heterocycloalkyl containing at least one O atom in the ring), substituted or unsubstituted azetidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted azapenyl, substituted or unsubstituted 5-membered heteroaryl, substituted or unsubstituted pyridin-2-yl, substituted or unsubstituted pyridin-4-yl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl;

or R^4 and R^5 are taken together with the atoms to which they are attached to form a substituted or unsubstituted C_2-C_{10}heterocycloalkyl;

R^7 is substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted

heteroaryl, -alkyl-(substituted or unsubstituted phenyl), -alkyl-(substituted or unsubstituted heteroaryl), -alkyl-(substituted or unsubstituted cycloalkyl), -alkyl-(substituted or unsubstituted heterocycloalkyl), $-(C(R^{10})_2O)_m-R^{11}$, $-(CH_2CH_2O)_n-R^{11}$, or $-(C(R^{10})_2)_p-OR^{11}$;

each R^9 is independently selected from hydrogen and alkyl;

each R^{10} is independently selected from hydrogen and alkyl;

R^{11} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, $-C(=O)R^{12}$, $-C(=O)-OR^{12}$, $-C(=O)N(R^{12})(R^8)$, $-C(=O)-SR^{12}$, or $-P(=O)(OR^9)_2$;

R^{12} is hydrogen, substituted or unsubstituted alkyl, substituted or unsubstituted heteroalkyl, substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, -alkyl-(substituted or unsubstituted phenyl), or -alkyl-(substituted or unsubstituted heteroaryl);

m is 1, 2, 3, 4, 5, or 6;

n is 1, 2, 3, 4, 5, or 6.

p is 1, 2, 3, 4, 5, or 6;

wherein substituted means that the referenced group is substituted with one or more additional groups individually and independently selected from halogen, -CN, $-NH_2$, -NH(alkyl), $-N(alkyl)_2$, -OH, $-CO_2H$, $-CO_2$alkyl, $-C(=O)NH_2$, -C(=O)NH(alkyl), $-C(=O)N(alkyl)_2$, $-S(=O)_2NH_2$, $-S(=O)_2NH(alkyl)$, $-S(=O)_2N(alkyl)_2$, alkyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone.

30. The compound of claim 29, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^4 is hydrogen;

R^6 is hydrogen;

R^5 is substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, -alkyl-(substituted or unsubstituted phenyl), -alkyl-(substituted or unsubstituted heteroaryl), -alkyl-(substituted or unsubstituted cycloalkyl), -alkyl-(substituted or unsubstituted heterocycloalkyl), $-(C(R^{10})_2O)_m-R^{11}$, $-C(=O)-(C(R^{10})_2O)_m-R^{11}$, $-C(=O)-(CH_2CH_2O)_n-R^{11}$, $-C(=O)-R^a$ or $-C(=O)-OR^7$.

31. The compound of claim 29 or claim 30, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 and R^2 are each independently selected from substituted or unsubstituted C_1-C_6alkyl;

R^3 is selected from substituted or unsubstituted phenyl.

32. The compound of claim 29 or claim 30, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 and R^2 are each independently selected from methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, tert-pentyl, neopentyl, isopentyl, sec-pentyl, 3-pentyl, n-hexyl, isohexyl, 3-methylpentyl, 2,3-dimethylbutyl, and neohexyl.

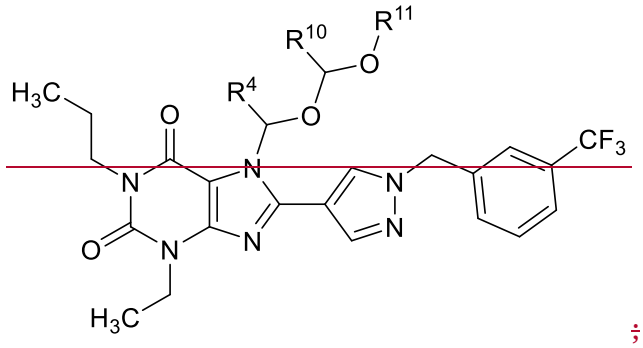
33. The compound of claim 29 or claim 30, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^1 is ethyl;

R^2 is n-propyl; and

R^3 is 3-(trifluoromethyl)phenyl.

34. The compound of claim 29 or claim 30, wherein the compound has the following structure:



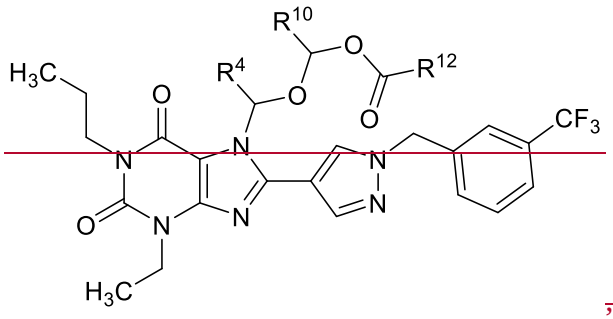
;

or a pharmaceutically acceptable salt or solvate thereof.

35. The compound of claim 34, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^{11} is hydrogen, substituted or unsubstituted alkyl, $-C(=O)R^{12}$, $-C(=O)-OR^{12}$, $-C(=O)N(R^{12})(R^8)$, or $-P(=O)(OR^9)_2$.

36. The compound of claim 35, wherein the compound has one of the following structures:



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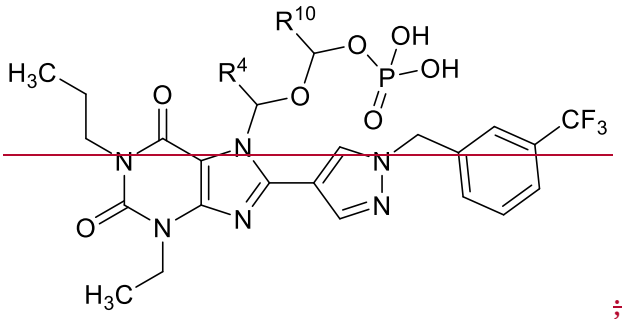
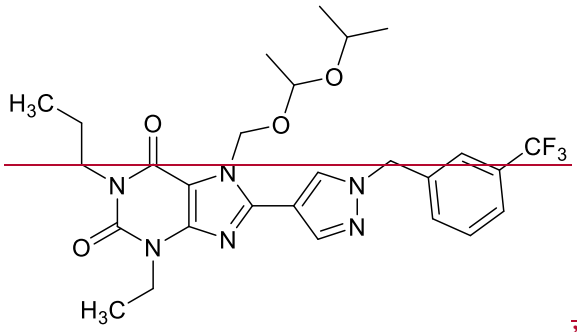


;

or a pharmaceutically acceptable salt or solvate thereof.

37. The compound of claim 35, wherein the compound has one of the following structures:



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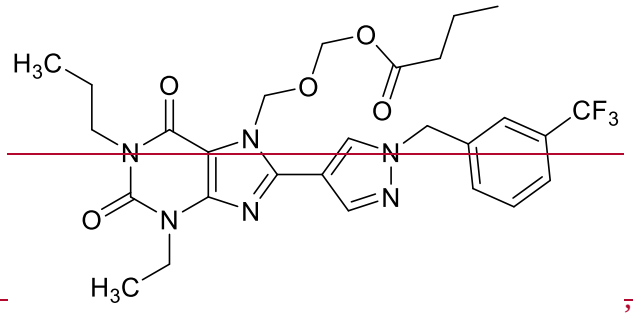

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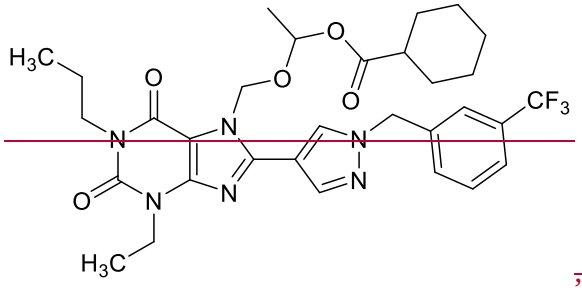
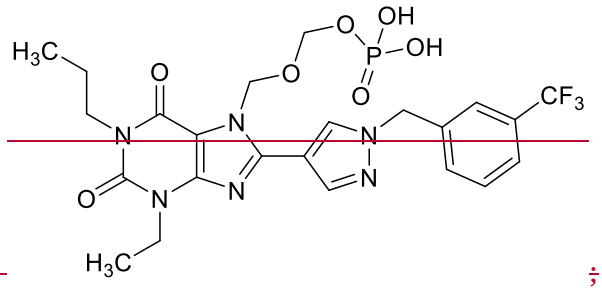


, or



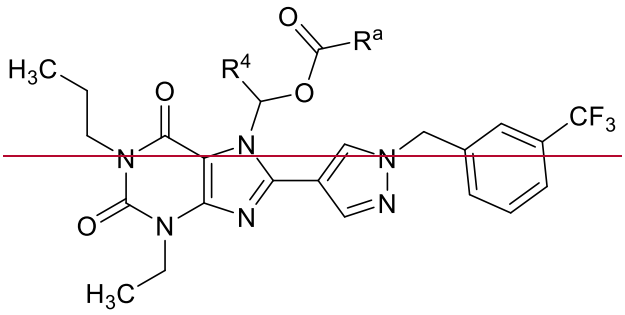
;

or a pharmaceutically acceptable salt or solvate thereof.

38. The compound of claim 29 or claim 30, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^5 is $-C(=O)-(C(R^{10})_2O)_m-R^{11}$, $-C(=O)-(CH_2CH_2O)_n-R^{11}$, $-C(=O)-R^a$ or $-C(=O)-OR^7$.

39. The compound of claim 38, wherein the compound has the following structure:



or a pharmaceutically acceptable salt or solvate thereof.

40. The compound of claim 39, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^a is substituted or unsubstituted bicyclic cycloalkyl that is a fused bicyclic cycloalkyl, bridged bicyclic cycloalkyl, or spiro bicyclic cycloalkyl;

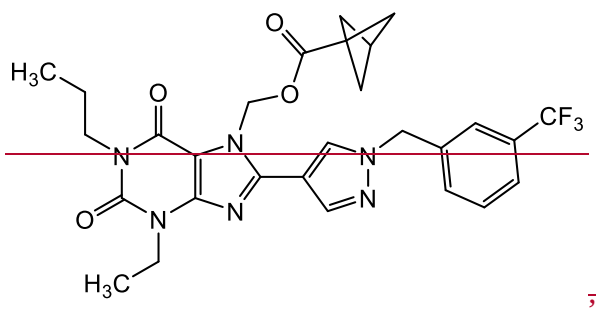
or R^a is substituted or unsubstituted bicyclic heterocycloalkyl that is a fused bicyclic heterocycloalkyl, bridged bicyclic heterocycloalkyl, or spiro bicyclic heterocycloalkyl;

or R^a is substituted or unsubstituted bicyclic heteroaryl.

41. The compound of claim 39, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^a is substituted or unsubstituted bicyclo[1.1.1]pentanyl, substituted or unsubstituted bicyclo[2.2.1]heptanyl, substituted or unsubstituted bicyclo[2.2.2]octanyl, substituted or unsubstituted bicyclo[3.2.1]octanyl, substituted or unsubstituted bicyclo[3.3.0]octanyl, substituted or unsubstituted bicyclo[4.3.0]nonanyl, or substituted or unsubstituted decalinyl.

42. The compound of claim 40, wherein the compound has one of the following structures:



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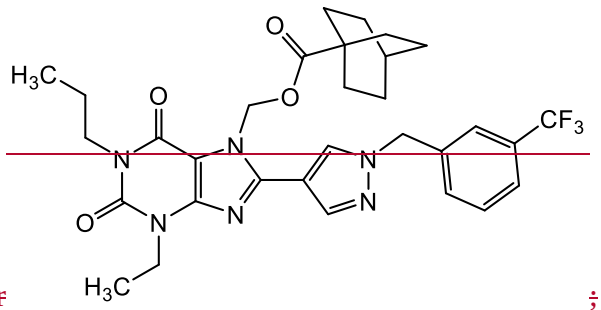


;

or a pharmaceutically acceptable salt or solvate thereof.

43. The compound of claim 39, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^a is substituted or unsubstituted heterocycloalkyl containing at least one O atom in the ring, substituted or unsubstituted azetidinyl, substituted or unsubstituted piperidinyl, substituted or unsubstituted azapenyl, substituted or unsubstituted 5-membered

heteroaryl, substituted or unsubstituted pyridin-2-yl, substituted or unsubstituted pyridin-4-yl, substituted or unsubstituted pyrimidinyl, substituted or unsubstituted pyrazinyl, substituted or unsubstituted pyridazinyl, substituted or unsubstituted triazinyl.

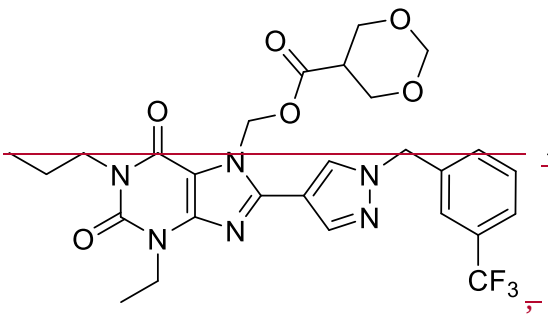
44. The compound of claim 43, or a pharmaceutically acceptable salt or solvate thereof, wherein:

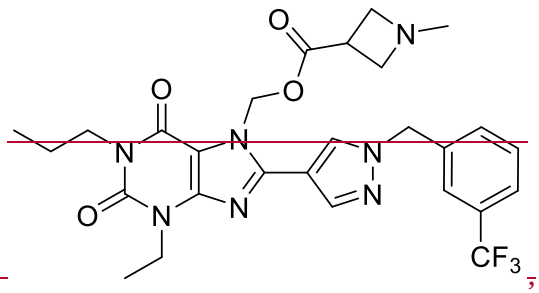
R^a is a substituted or unsubstituted heterocycloalkyl containing at least one O atom in the ring that is substituted or unsubstituted tetrahydrofuranyl, substituted or unsubstituted dihydrofuranyl, substituted or unsubstituted oxazolidinonyl, substituted or unsubstituted tetrahydropyranyl, substituted or unsubstituted dihydropyranyl, substituted or unsubstituted tetrahydrothiopyranyl, substituted or unsubstituted morpholinyl, substituted or unsubstituted oxetanyl, substituted or unsubstituted oxepanyl, substituted or unsubstituted oxazepinyl, or substituted or unsubstituted dioxanyl.

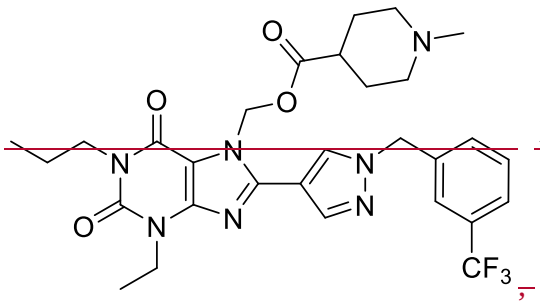
45. The compound of claim 43, or a pharmaceutically acceptable salt or solvate thereof, wherein:

R^a is a substituted or unsubstituted 5-membered heteroaryl that is substituted or unsubstituted furanyl, substituted or unsubstituted thienyl, substituted or unsubstituted pyrrolyl, substituted or unsubstituted oxazolyl, substituted or unsubstituted thiazolyl, substituted or unsubstituted imidazolyl, substituted or unsubstituted pyrazolyl, substituted or unsubstituted triazolyl, substituted or unsubstituted tetrazolyl, substituted or unsubstituted isoxazolyl, substituted or unsubstituted isothiazolyl, substituted or unsubstituted oxadiazolyl, or substituted or unsubstituted thiadiazolyl,

46. The compound of claim 43, wherein the compound has one of the following structures:







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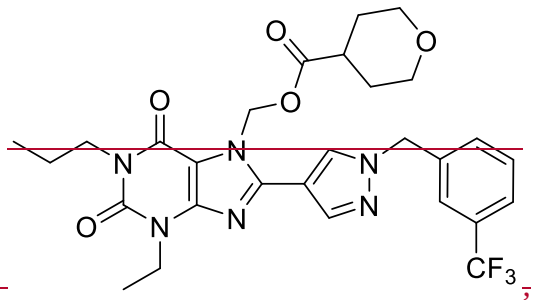

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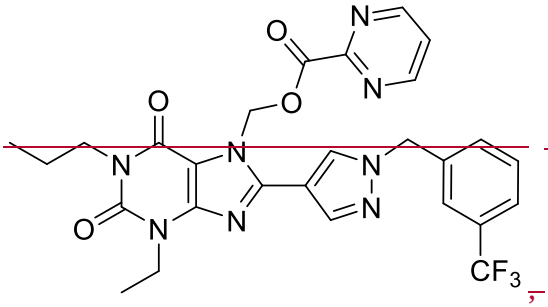

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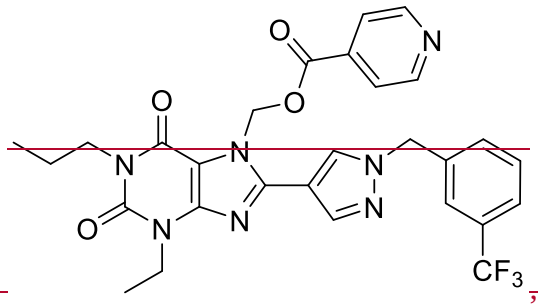

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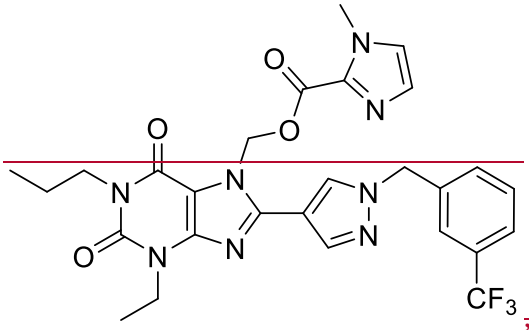
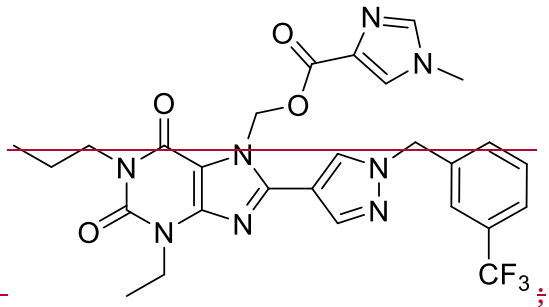


, or



;

or a pharmaceutically acceptable salt or solvate thereof.

47. The compound of claim 29 or claim 30, or a pharmaceutically acceptable salt or solvate thereof, wherein:

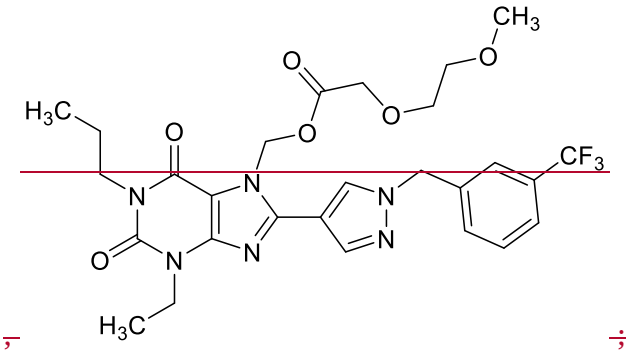
R^1 is ethyl;

R^2 is n-propyl;

R^3 is 3-(trifluoromethyl)phenyl;

R^5 is -C(=O)-$(C(R^{10})_2O)_m$-R^{11}, -C(=O)-$(CH_2CH_2O)_n$-R^{11}, or -C(=O)-OR^7.

48. The compound of claim 47, wherein the compound has one of the following structures:



,

;

or a pharmaceutically acceptable salt or solvate thereof.

~~49. The compound of claim 29 or claim 30, or a pharmaceutically acceptable salt or solvate thereof, wherein:~~

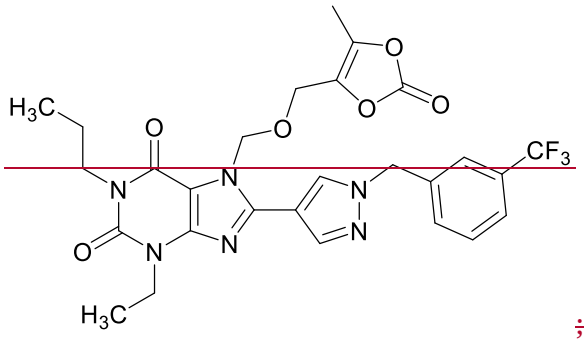
~~R^1 is ethyl;~~

~~R^2 is n-propyl;~~

~~R^3 is 3-(trifluoromethyl)phenyl;~~

~~R^5 is substituted or unsubstituted C_3-C_{10}cycloalkyl, substituted or unsubstituted C_2-C_{10}heterocycloalkyl, substituted or unsubstituted phenyl, substituted or unsubstituted heteroaryl, -alkyl-(substituted or unsubstituted phenyl), -alkyl-(substituted or unsubstituted heteroaryl), -alkyl-(substituted or unsubstituted cycloalkyl), -alkyl-(substituted or unsubstituted heterocycloalkyl).~~

~~50. The compound of claim 49, wherein the compound has the following structure:~~



~~;~~

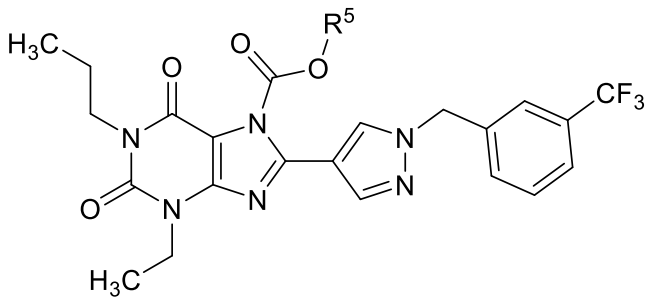
~~or a pharmaceutically acceptable salt or solvate thereof.~~

~~51.~~9. A pharmaceutical composition~~formulation~~, comprising a compound of claim ~~any one of claims~~ 1~~-50~~, or any pharmaceutically acceptable salt or solvate thereof; and at least one pharmaceutically acceptable excipient.

~~52.~~10. The pharmaceutical composition of claim 9~~51~~, wherein the pharmaceutical composition is formulated for administration to a mammal by oral administration, intravenous administration, or subcutaneous administration.

~~53.~~11. The pharmaceutical composition of claim 10~~51~~, wherein 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.

12. The compound of claim 3, wherein the compound has the following structure:



or a pharmaceutically acceptable salt thereof.

13. The compound of claim 12, or a pharmaceutically acceptable salt thereof, wherein:

R^5 is R^7;

R^7 is C_1-C_6alkyl, -$(CH_2CH_2O)_n$-R^{11}, or -$(C(R^{10})_2)_p$-OR^{11};

each R^{10} is independently selected from hydrogen and methyl;

R^{11} is hydrogen, C_1-C_6alkyl, -$C(=O)R^{12}$, or -$P(=O)(OR^9)_2$;

R^{12} is substituted or unsubstituted C_1-C_6alkyl, or substituted or unsubstituted C_3-C_{10}cycloalkyl;

n is 1, 2, 3, 4, 5, or 6; and

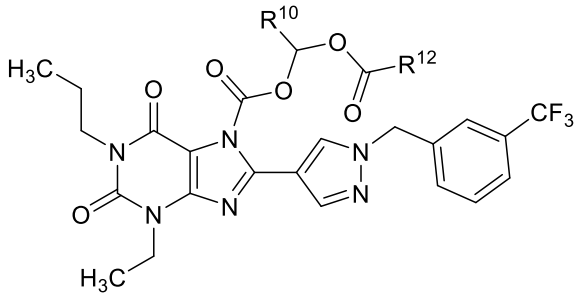
p is 1, 2, 3, 4, 5, or 6;

wherein substituted means that the referenced group is substituted with one or more additional groups individually and independently selected from C_1-C_6alkyl.

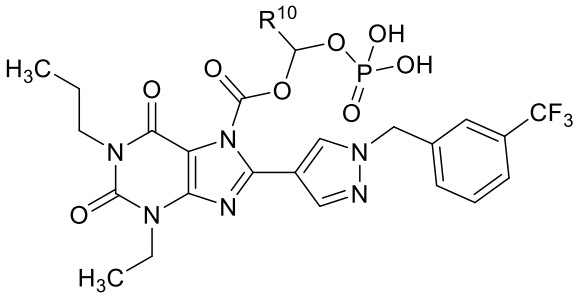
14. The compound of claim 13, or a pharmaceutically acceptable salt thereof, wherein:

R^7 is C_1-C_6alkyl.

15. The compound of claim 1, wherein the compound has one of the following structures:

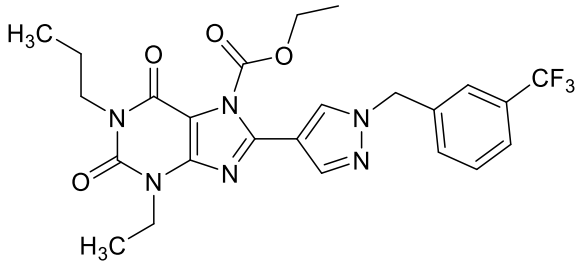
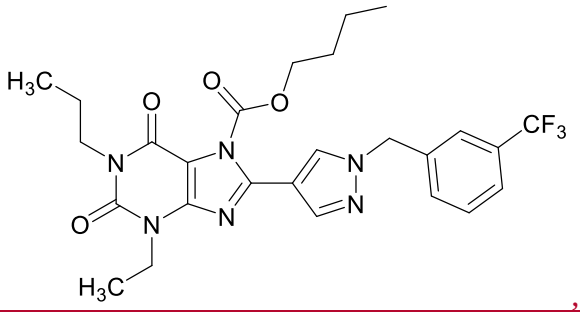
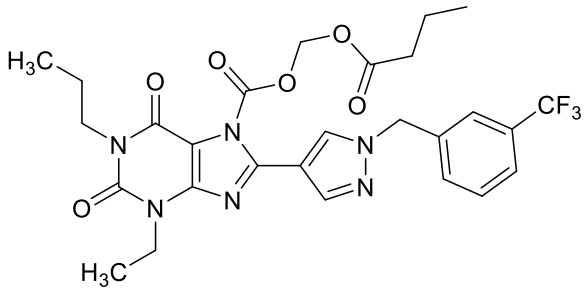


or



or a pharmaceutically acceptable salt thereof.

16. A compound of structure:


,

,

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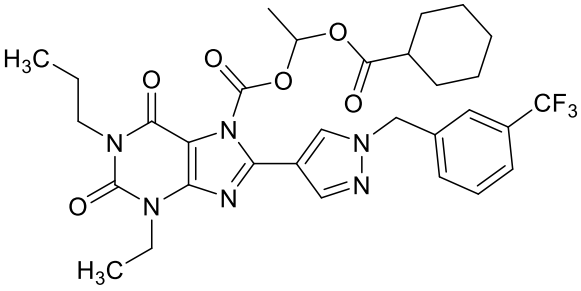
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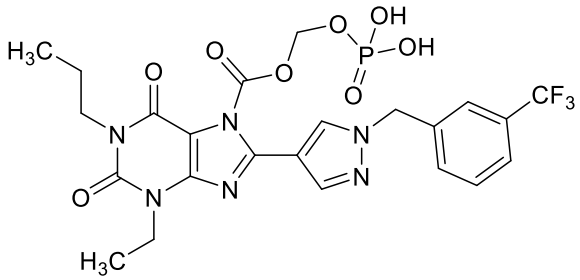
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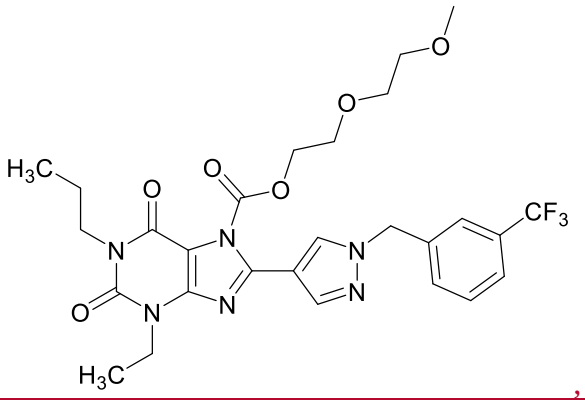
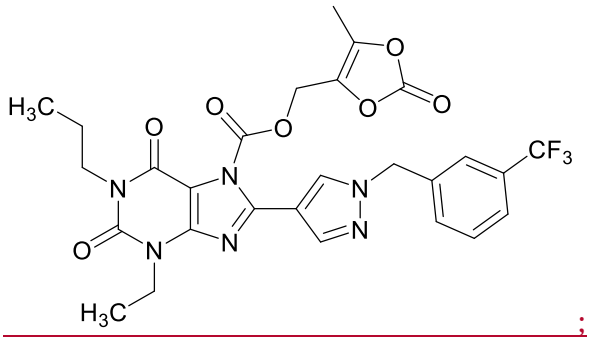
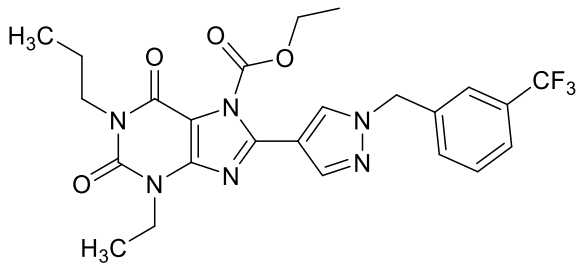

, or

;

or a pharmaceutically acceptable salt thereof.

17. A pharmaceutical composition, comprising a compound of claim 1, or any pharmaceutically acceptable salt thereof; and at least one pharmaceutically acceptable excipient.

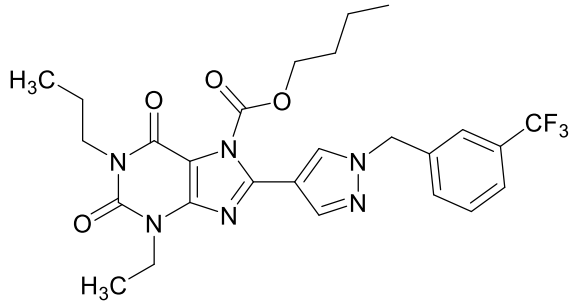
18. A compound of structure:



,

or a pharmaceutically acceptable salt thereof.

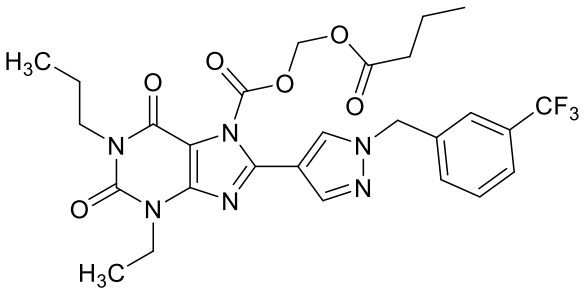
19. A compound of structure:



,

or a pharmaceutically acceptable salt thereof.

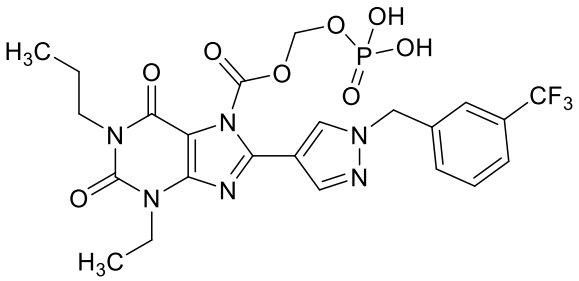
20. A compound of structure:



,

or a pharmaceutically acceptable salt thereof.

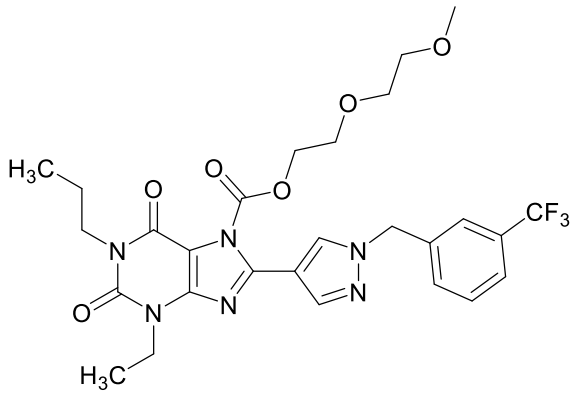
21. A compound of structure:



,

or a pharmaceutically acceptable salt thereof.

22. A compound of structure:



,

or a pharmaceutically acceptable salt thereof.

54. A method of modulating the A_{2B} adenosine receptor in a mammal comprising administering to the mammal a compound of any one of claims 1-50, or any pharmaceutically acceptable salt or solvate thereof.

55. A method of treating a disease or disorder in a mammal comprising administering to the mammal in need thereof a therapeutically effective amount of a compound of any one of claims 1-50, or a pharmaceutically acceptable salt or solvate thereof, wherein the condition is selected from the group consisting of cardiovascular diseases, fibrosis, neurological disorders, type I hypersensitivity disorders, chronic and acute liver diseases, lung diseases, renal diseases, diabetes, obesity, and cancer.

56. The method of claim 55, wherein the condition is cancer.

57. The method of any one of claims 54-56, wherein the subject is human.