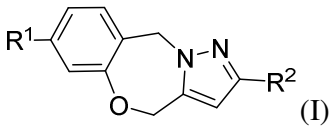
SUMMARY

LDC7559 and compounds of formula (I) have been found to agonize PFKL and suppress NOX2-dependent oxidative burst.

In a first example (Example 1; abbreviated as "E1") the disclosure provides a compound of the disclosure, which is a compound of formula (I):



(I)

or a prodrug thereof, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-NR^aR^b$ or a 5-10 membered heteroaryl that is optionally substituted with one or more groups R^c;

R^2 is a 6-10 membered aryl that is optionally substituted with one or more groups R^r; or R^2 is a 5-10 membered heteroaryl that is that is optionally substituted with one or more groups R^s; or R^2 is a 3-10 membered heterocycle that is that is optionally substituted with one or more groups R^z;

R^a is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkanoyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkynylcarbonyl, 3-6 membered heterocycle, or a 5-6 membered heteroaryl that is optionally substituted with one or more groups R^f; wherein each $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkanoyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkynylcarbonyl, and 3-6 membered heterocycle is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, cyano, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $C(=O)NR^mR^n$, and $(C_1\text{-}C_6)$alkyl that is optionally substituted with one or more groups independently selected form the group consisting of halo, hydroxy, cyano, $-NR^mR^n$, and $-C(=O)NR^mR^n$;

R^b is H or $(C_1\text{-}C_6)$alkyl;

each R^c is independently selected from the group consisting of cyano, $-NR^dR^e$, $-C(=O)NR^dR^e$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, and $(C_1\text{-}C_6)$alkanoyl, wherein each $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy and $(C_1\text{-}C_6)$alkanoyl is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, carboxy, and cyano;

R^d and R^e are each independently selected from the group consisting of H and $(C_1\text{-}C_6)$alkyl; or R^d and R^e taken together with the nitrogen to which they are attached form a 3-6

R^v and R^w are each independently selected from the group consisting of H, $(C_1$-$C_6)$alkyl, and $(C_1$-$C_6)$alkanoyl; or R^v and R^w taken together with the nitrogen to which they are attached form a 3-6 membered heterocyclic ring that is optionally substituted with one or more groups independently selected from the group consisting of halo and $(C_1$-$C_6)$alkyl;

R^x is H or $(C_1$-$C_6)$alkyl that is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, carboxy, cyano, and oxo;

R^y is H or $(C_1$-$C_6)$alkyl that is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, carboxy, cyano, and oxo; and

each R^z is independently selected from the group consisting of oxo, halo, hydroxy, and $(C_1$-$C_6)$alkyl that is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, carboxy, -NR^tR^u, -$C(=O)NR^tR^u$, $S(O)_2NR^vR^w$, -$S(O)_2R^y$, cyano, and oxo.

Further examples (E2-E81) of the first example of the disclosure are described below.

E2. The compound of E1, wherein R^1 is -NR^aR^b or a 5-10 membered heteroaryl that is optionally substituted with one or more groups R^c;

R^2 is a phenyl that is optionally substituted with one or more groups R^r; or R^2 is a 5- 9 membered heteroaryl that is that is optionally substituted with one or more groups R^s; or R^2 is a 9-membered heterocycle that is that is optionally substituted with one or more groups R^z;

R^a is $(C_1$-$C_6)$alkyl, $(C_3$-$C_6)$cycloalkyl, $(C_2$-$C_6)$alkynyl, $(C_1$-$C_6)$alkanoyl, $(C_2$-$C_6)$alkynylcarbonyl, 3-6 membered heterocycle, or a 5-membered heteroaryl that is optionally substituted with one or more groups R^f; wherein each $(C_1$-$C_6)$alkyl and $(C_3$-$C_6)$cycloalkyl is optionally substituted with one or more groups independently selected from the group consisting of halo, cyano, $(C_2$-$C_6)$alkynyl, $C(=O)NR^mR^n$, and $(C_1$-$C_6)$alkyl that is optionally substituted with one or more hydroxy;

R^b is H or $(C_1$-$C_6)$alkyl;

each R^c is independently selected from the group consisting of cyano, -NR^dR^e, and $(C_1$-$C_6)$alkyl that is optionally substituted with one or more cyano;

R^d and R^e are each H;

each R^f is independently selected from the group consisting of halo, hydroxy, cyano, -$C(=O)NR^gR^h$, and $(C_1$-$C_6)$alkyl that is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy and carboxy;

E72. The use of a compound, a prodrug, or a pharmaceutically acceptable salt of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E19, E20, E21, E22, E23, E24, E25, E36, E27, E28, E29, E30, E31, E32, E33, E34, E35, E36, E37, E38, E39, E40, E41, E42, E43, or E44 to prepare a medicament for treating a caspase-associated *auto-inflammatory condition* in an animal (e.g. a mammal such as a human).

E73. The use of E72, wherein the caspase-associated *auto-inflammatory condition* is sepsis or septic shock in an animal (e.g. a mammal such as a human).

E74. The use of a compound, a prodrug, or a pharmaceutically acceptable salt of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E19, E20, E21, E22, E23, E24, E25, E36, E27, E28, E29, E30, E31, E32, E33, E34, E35, E36, E37, E38, E39, E40, E41, E42, E43, or E44 to prepare a medicament for treating a disease or condition selected from the group consisting of pulmonary disease, a systemic autoimmune disease, atherosclerosis, thrombosis, multiple sclerosis, Alzheimer's disease, psoriasis, and pulmonary fibrosis in an animal (e.g. a mammal such as a human).

E75. The use of E74, wherein the pulmonary disease is acute respiratory distress syndrome ARDS, chronic obstructive pulmonary disease COPD, or bronchiectasis.

E76. The use of E74, wherein the disease or condition is thrombosis.

E77. The use of a compound, a prodrug, or a pharmaceutically acceptable salt of E1, E2, E3, E4, E5, E6, E7, E8, E9, E10, E11, E12, E13, E14, E15, E16, E17, E18, E19, E20, E21, E22, E23, E24, E25, E36, E27, E28, E29, E30, E31, E32, E33, E34, E35, E36, E37, E38, E39, E40, E41, E42, E43, or E44 to prepare a medicament for treating a disease or condition associated with the activity of a homologous PFK enzyme in an animal (e.g. a mammal such as a human).

E78. The use of E77, wherein the disease or condition is associated with the activity of PFKM (muscle-type).

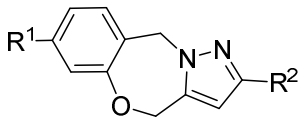
E79. The use of E77, wherein the disease or condition is associated with the activity of PFKP (platelet type).

E80. The method of E47, the compound, prodrug, or pharmaceutically acceptable salt of E59, or the use of claim E70, wherein the cancer is selected from the group consisting of: brain, breast, lung, urinary bladder, cervical, skin, oral cavity, pharynx, colon, liver, cecum, stomach, pancreatic, prostate, oesophageal, hematologic, thyroid, uterine, and head and neck cancer.

E81. A process or a synthetic intermediate disclosed herein that is useful for preparing a compound of formula (I) or prodrug thereof, or a pharmaceutically acceptable salt thereof.

E82. An invention as described herein.

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


(I)

or a prodrug thereof, or a pharmaceutically acceptable salt thereof, wherein:

R^1 is $-NR^aR^b$ or a 5-10 membered heteroaryl that is optionally substituted with one or more groups R^c;

R^2 is a 6-10 membered aryl that is optionally substituted with one or more groups R^r; or R^2 is a 5-10 membered heteroaryl that is that is optionally substituted with one or more groups R^s; or R^2 is a 3-10 membered heterocycle that is that is optionally substituted with one or more groups R^z;

R^a is $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkanoyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkynylcarbonyl, 3-6 membered heterocycle, or a 5-6 membered heteroaryl that is optionally substituted with one or more groups R^f; wherein each $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $(C_1\text{-}C_6)$alkanoyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_2\text{-}C_6)$alkynylcarbonyl, and 3-6 membered heterocycle is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, cyano, $(C_2\text{-}C_6)$alkenyl, $(C_2\text{-}C_6)$alkynyl, $C(=O)NR^mR^n$, and $(C_1\text{-}C_6)$alkyl that is optionally substituted with one or more groups independently selected form the group consisting of halo, hydroxy, cyano, $-NR^mR^n$, and $-C(=O)NR^mR^n$;

R^b is H or $(C_1\text{-}C_6)$alkyl;

each R^c is independently selected from the group consisting of cyano, $-NR^dR^e$, $-C(=O)NR^dR^e$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy, and $(C_1\text{-}C_6)$alkanoyl, wherein each $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_6)$cycloalkyl, $(C_3\text{-}C_6)$cycloalkyl$(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy and $(C_1\text{-}C_6)$alkanoyl is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, carboxy, and cyano;

R^d and R^e are each independently selected from the group consisting of H and $(C_1\text{-}C_6)$alkyl; or R^d and R^e taken together with the nitrogen to which they are attached form a 3-6 membered heterocyclic ring that is optionally substituted with one or more groups independently selected from the group consisting of halo and $(C_1\text{-}C_6)$alkyl;

each R^f is independently selected from the group consisting of halo, hydroxy, cyano, $-NR^gR^h$, $-C(=O)NR^gR^h$, and $(C_1\text{-}C_6)$alkyl that is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, carboxy, $-NR^gR^h$, $-C(=O)NR^gR^h$, and cyano;

R^g and R^h are each independently selected from the group consisting of H and (C_1-C_6)alkyl; or R^g and R^h taken together with the nitrogen to which they are attached form a 3-6 membered heterocyclic ring that is optionally substituted with one or more groups independently selected from the group consisting of halo and (C_1-C_6)alkyl;

R^m is H or (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, carboxy, cyano, and oxo;

R^n is H or (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, carboxy, cyano, and oxo;

each R^r is independently selected from the group consisting of halo, hydroxy, cyano, $-NR^tR^u$, $-C(=O)NR^tR^u$, $-S(O)_2NR^tR^u$, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, $-N(H)S(O)_2R^x$, $-S(O)_2R^x$, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl, wherein each (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkylthio, (C_2-C_6)alkenyl, and (C_2-C_6)alkynyl is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, carboxy, $-NR^tR^u$, $-C(=O)NR^tR^u$, $-S(O)_2NR^tR^u$, $-S(O)_2R^x$, and cyano;

each R^s is independently selected from the group consisting of halo, cyano, $-NR^vR^w$, $-C(=O)NR^vR^w$, $-S(O)_2NR^vR^w$, (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkylthio, 3-6 membered heterocycle, and $-S(O)_2R^y$, wherein each (C_1-C_6)alkyl, (C_3-C_6)cycloalkyl, (C_1-C_6)alkoxy, (C_1-C_6)alkanoyl, 3-6 membered heterocycle, and (C_1-C_6)alkylthio, is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, carboxy, $-NR^tR^u$, $-C(=O)NR^tR^u$, $S(O)_2NR^vR^w$, $-S(O)_2R^y$, and cyano;

R^t and R^u are each independently selected from the group consisting of H, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, and (C_2-C_6)alkynylcarbonyl; or R^t and R^u taken together with the nitrogen to which they are attached form a 3-6 membered heterocyclic ring that is optionally substituted with one or more groups independently selected from the group consisting of halo and (C_1-C_6)alkyl;

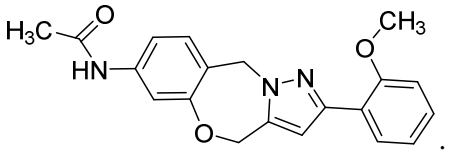
R^v and R^w are each independently selected from the group consisting of H, (C_1-C_6)alkyl, and (C_1-C_6)alkanoyl; or R^v and R^w taken together with the nitrogen to which they are attached form a 3-6 membered heterocyclic ring that is optionally substituted with one or more groups independently selected from the group consisting of halo and (C_1-C_6)alkyl;

R^x is H or (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, carboxy, cyano, and oxo;

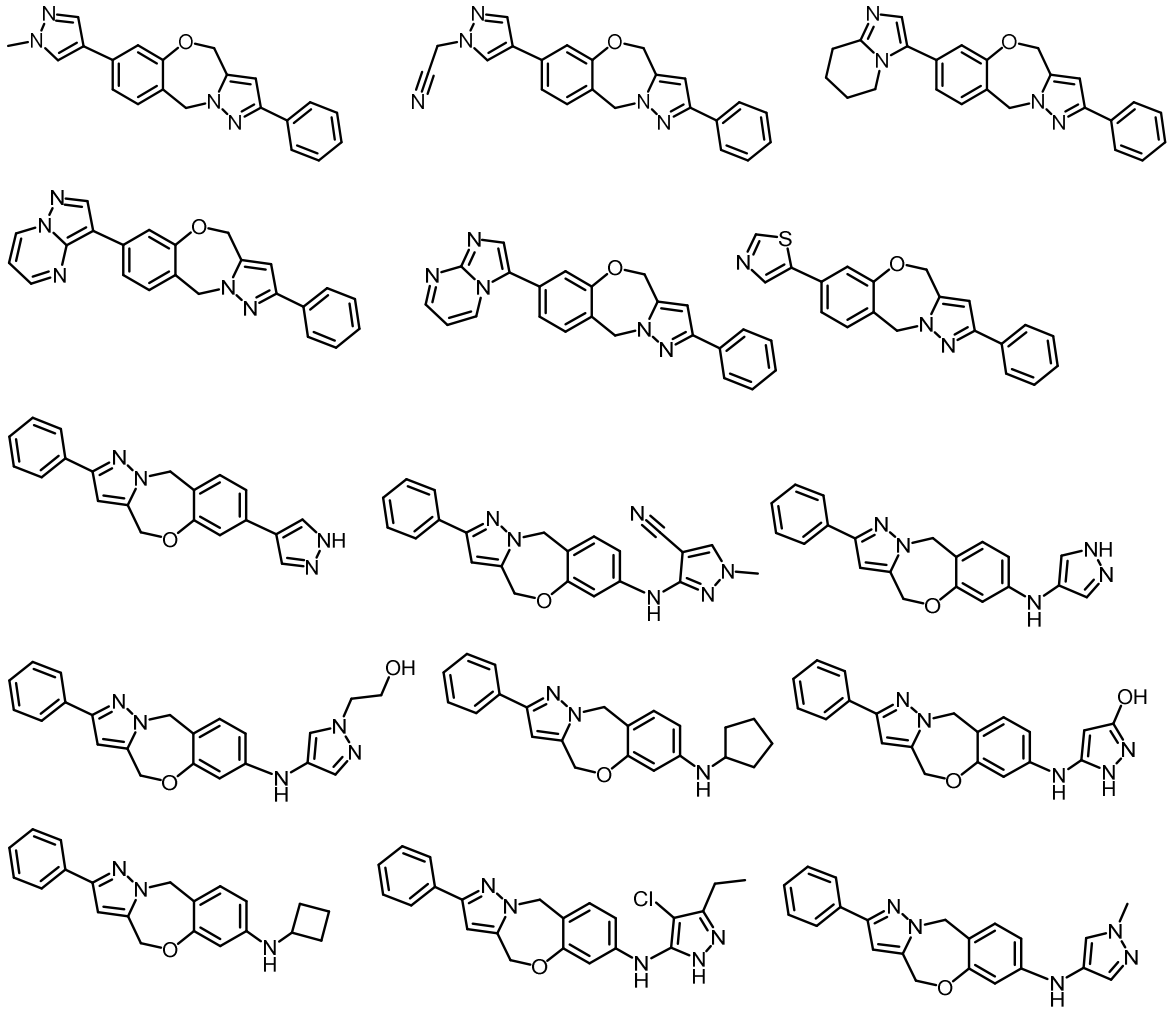
R^y is H or (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, carboxy, cyano, and oxo; and

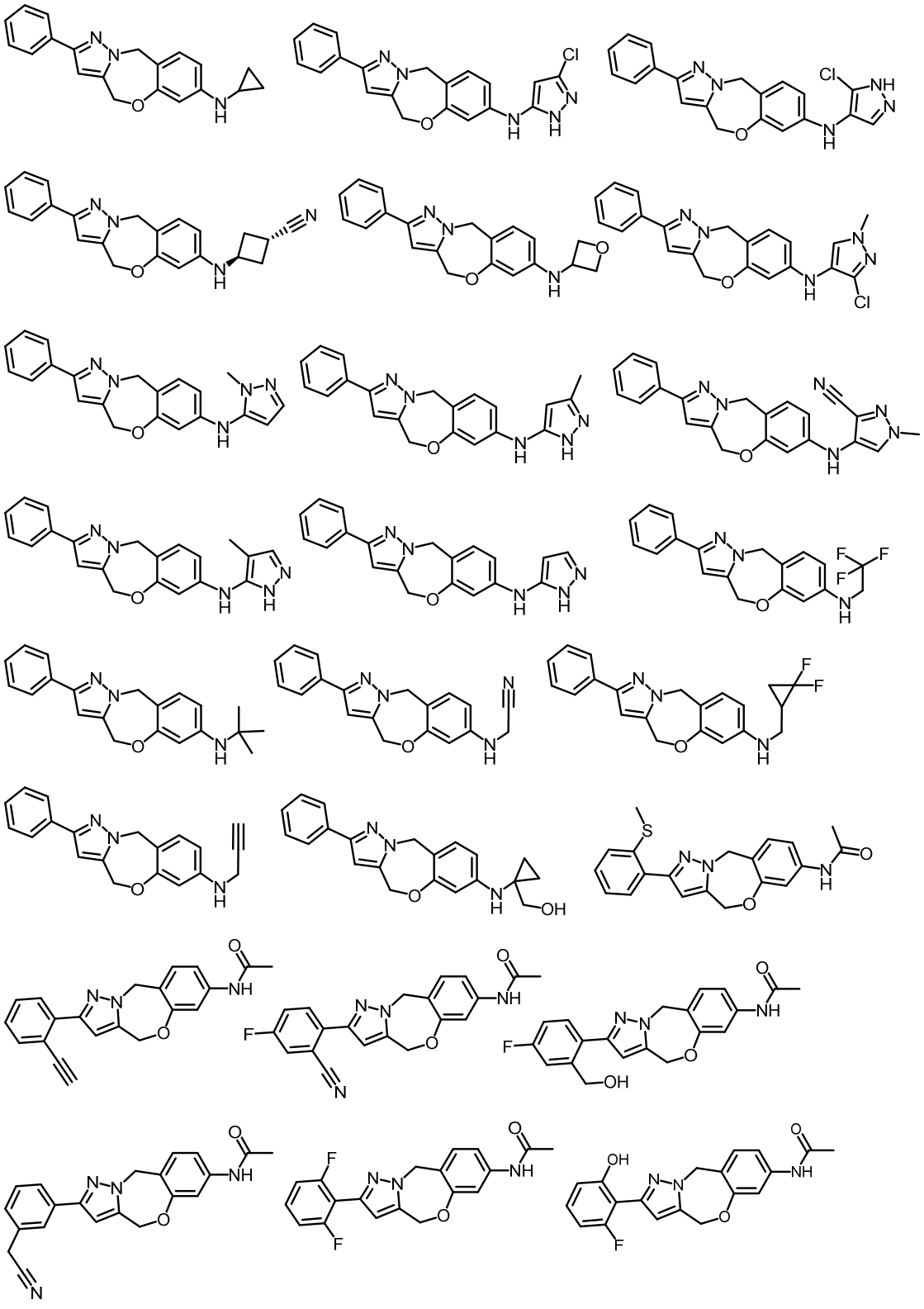
each R^z is independently selected from the group consisting of oxo, halo, hydroxy, and (C_1-C_6)alkyl that is optionally substituted with one or more groups independently selected from the group consisting of halo, hydroxy, carboxy, $-NR^tR^u$, $-C(=O)NR^tR^u$, $S(O)_2NR^vR^w$, $-S(O)_2R^y$, cyano, and oxo;

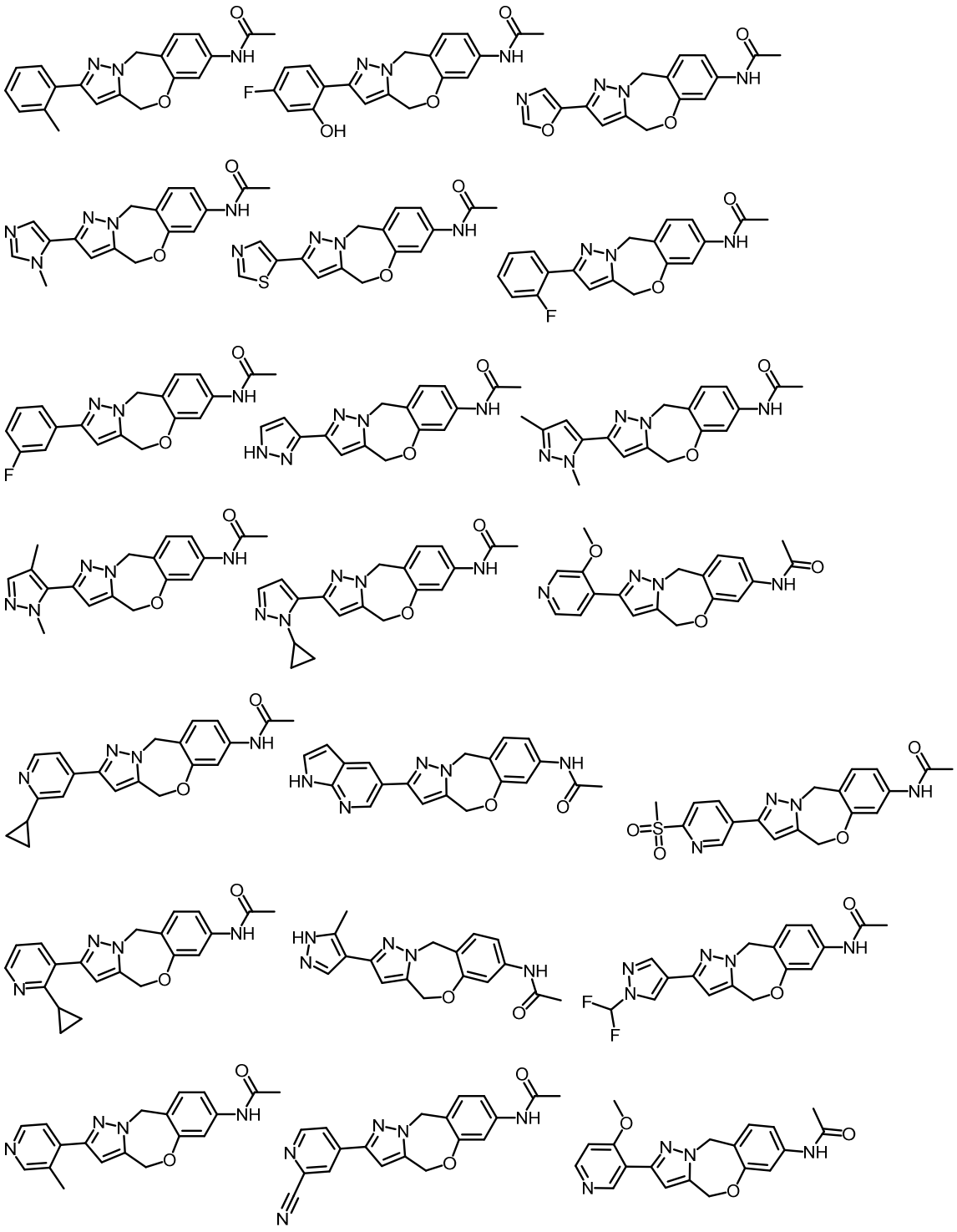
provided the compound is not:

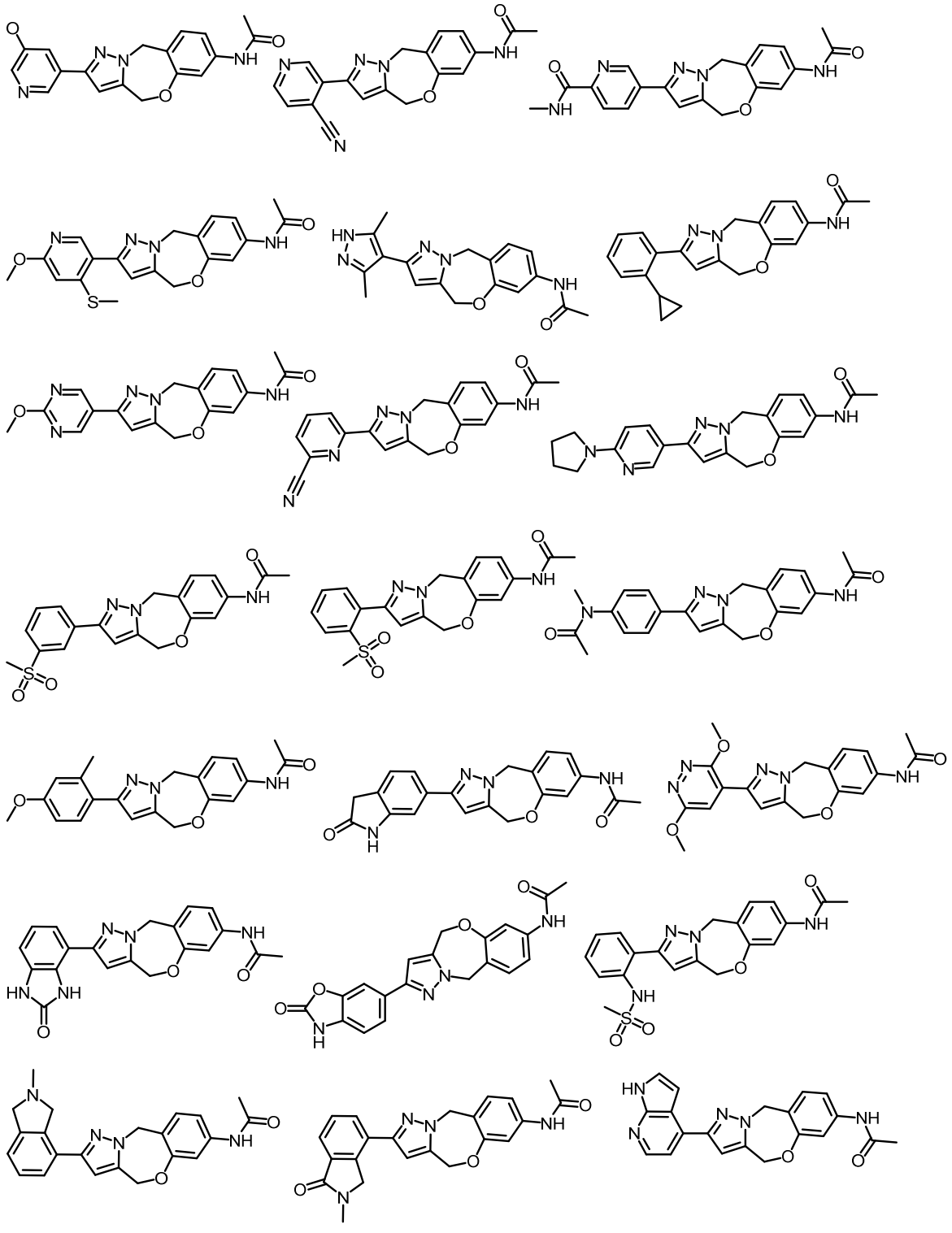


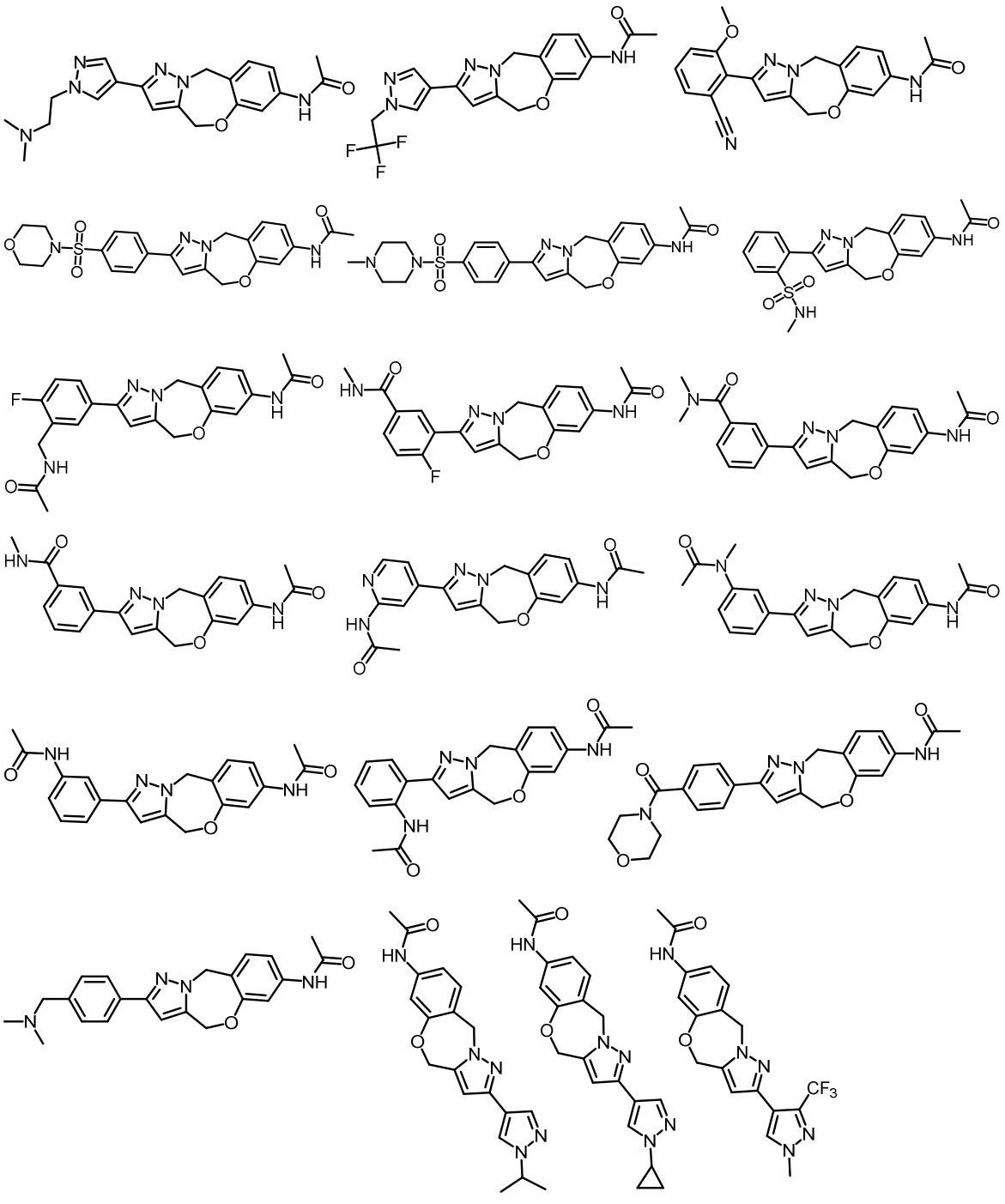
In one aspect, the disclosure provides a compound selected from the group consisting of:

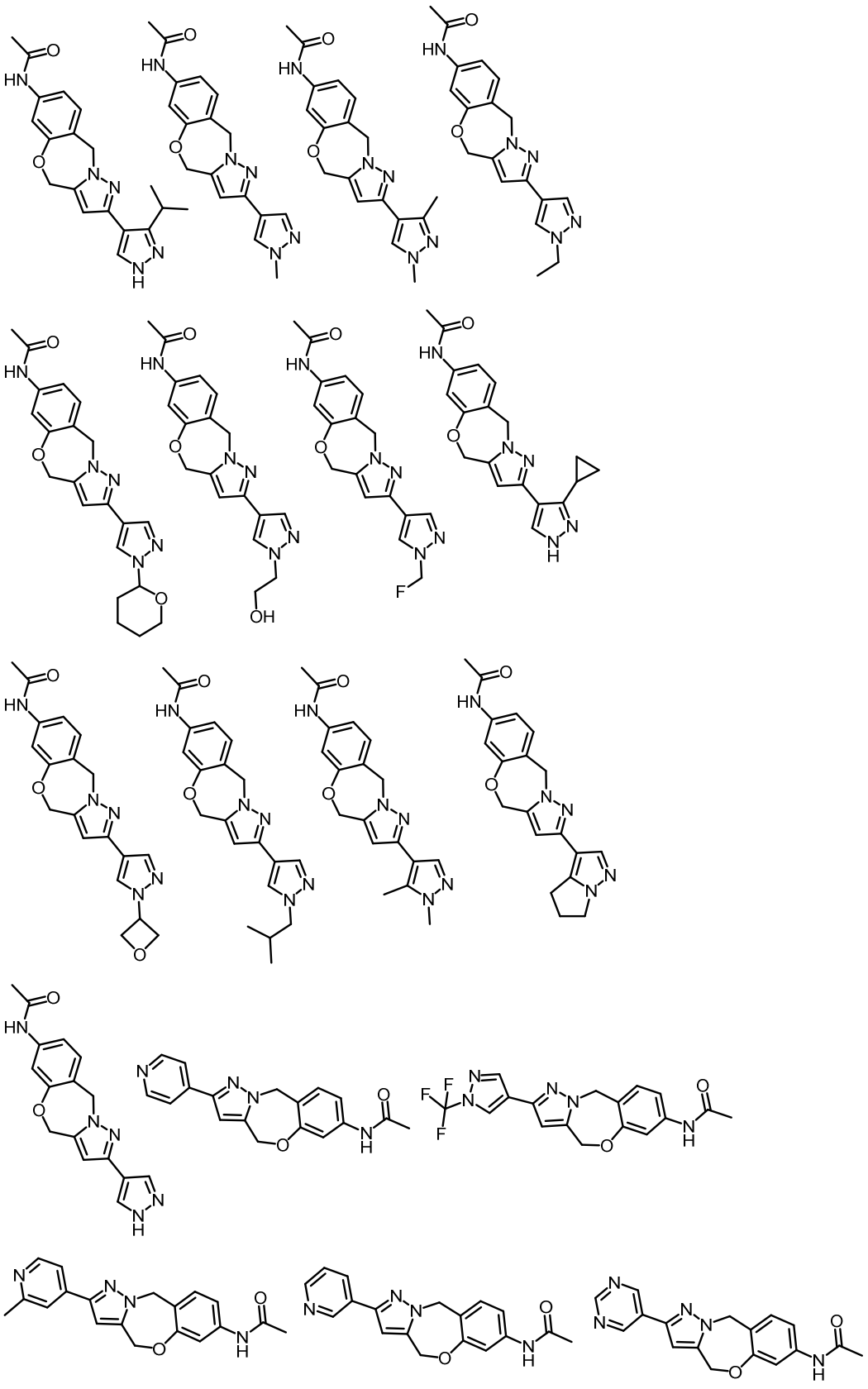


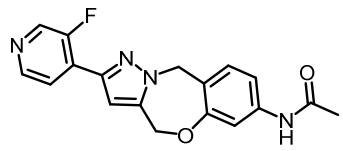










and 

or a pharmaceutically acceptable salt thereof.

In one aspect, the disclosure provides a pharmaceutical composition comprising a compound, prodrug, or pharmaceutically acceptable salt as disclosed herein and a pharmaceutically acceptable excipient.

In one aspect, the disclosure provides use of a compound of formula (I) as disclosed herein or a prodrug thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prophylactic or therapeutic treatment of a disease associated with the activity of glycolytic enzyme phosphofructokinase-1 liver type.

In one aspect, the disclosure provides use of a compound of formula (I) as disclosed herein or a prodrug thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prophylactic or therapeutic treatment of cancer, diabetes, or a caspase-associated auto-inflammatory condition.

In one aspect, the disclosure provides use of a compound of formula (I) as disclosed herein or a prodrug thereof, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the prophylactic or therapeutic treatment of a disease or condition selected from the group consisting of pulmonary disease, a systemic autoimmune disease, atherosclerosis, thrombosis, multiple sclerosis, Alzheimer's disease, psoriasis, and pulmonary fibrosis.