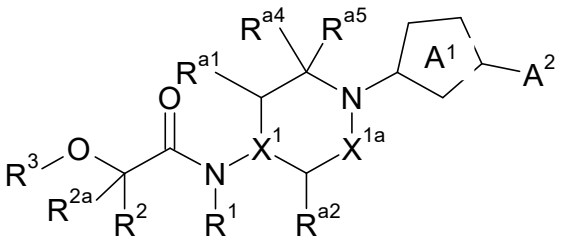
pathway. Heteroaryl derivatives as ATF4 inhibitors are described in WO 2019/193540 A1. Bicyclic aromatic ring derivatives as ATF4 inhibitors are described in WO 2019/193541 A1.

However, there is a continuing need for new compounds useful as modulators of the integrated stress response pathway with good pharmacokinetic properties.

Thus, an object of the present disclosure is to provide a new class of compounds as modulators of the integrated stress response pathway, which may be effective in the treatment of integrated stress response pathway related diseases and which may show improved pharmaceutically relevant properties including activity, solubility, selectivity, ADMET properties and/or reduced side effects.

In an aspect of the present disclosure, there is provided a use of a compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof in the manufacture of a medicament, wherein

X^1 is $C(R^{a6})$ or N;

X^{1a} is a covalent single bond; $CH(R^{a3})$, O, $N(R^{a7})$, or $CH(R^{a3})CH_2$;

R^{a1}, R^{a2}, R^{a3} are independently selected from the group consisting of H; halogen; OH; O-C_{1-4} alkyl; C_{1-4} alkyl; and A^{2a},
and R^{a4}, R^{a5}, R^{a6} are independently selected from the group consisting of H; halogen; C_{1-4} alkyl; and A^{2a}, provided that only one of R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6} is A^{2a};
optionally R^{a1} and R^{a2} form a covalent single bond;
optionally R^{a2} and R^{a4} form a methylene group;
optionally R^{a4} and R^{a6} form an ethylene group;

optionally R^{a4} and R^{a5} are joined to form an oxo group;

R^{a7} is H, $C(O)OC_{1-4}$ alkyl, or C_{1-4} alkyl, wherein $C(O)OC_{1-4}$ alkyl and C_{1-4} alkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, OH, and $O\text{-}C_{1-3}$ alkyl, wherein the substituents are the same or different, preferably R^{a7} is H;

A^1 is C_5 cycloalkylene, C_5 cycloalkenylene, a nitrogen ring atom containing 5-membered heterocyclene or a 7- to 12- membered heterobicyclene, which includes a nitrogen ring atom containing 5-membered heterocycle, wherein said heterocycle is attached to the nitrogen ring atom shown in formula (I) and wherein A^1 is optionally substituted with one or more R^4, which are the same or different;

each R^4 is independently oxo (=O) where the ring is at least partially saturated, thiooxo (=S) where the ring is at least partially saturated, halogen, CN, OR^5, or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^5 is H or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^2 is R^{6a} or A^{2a};

R^{6a} is OR^{6a1}, SR^{6a1}, $N(R^{6a1}R^{6a2})$; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a1}, R^{6a2} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; and A^{2a}, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a3} is H; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^{2a} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2a} is optionally substituted with one or more R^6, which are the same or different;

each R^6 is independently R^{6b}, OH, OR^{6b}, halogen, or CN, wherein R^{6b} is cyclopropyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, and wherein R^{6b} is optionally substituted with one or more halogen, which are the same or different; or
two R^6 are joined to form together with the atoms to which they are attached a ring A^{2b};

A^{2b} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2b} is optionally substituted with one or more R^7, which are the same or different;

each R^7 is independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

R^1 is H or C_{1-4} alkyl, preferably H, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^2 is H; F; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different; and
R^3 is A^3, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^8, which are the same or different; or
R^2 and R^3 are joined to form together with the oxygen atom and carbon atom to which they are attached a ring A^{3a}, wherein A^{3a} is a 7 to 12 membered heterobicyclyl, wherein 7 to 12 membered heterobicyclyl is optionally substituted with one or more R^{10}, which are the same or different;

R^{2a} is H or F, preferably H;

each R^8 is independently halogen; CN, $C(O)OR^9$, OR^9, $C(O)R^9$, $C(O)N(R^9R^{9a})$, $S(O)_2N(R^9R^{9a})$, $S(O)N(R^9R^{9a})$, $S(O)_2R^9$, $S(O)R^9$, $N(R^9)S(O)_2N(R^{9a}R^{9b})$, SR^9, $N(R^9R^{9a})$, NO_2, $OC(O)R^9$, $N(R^9)C(O)R^{9a}$, $N(R^9)SO_2R^{9a}$, $N(R^9)S(O)R^{9a}$, $N(R^9)C(O)N(R^{9a}R^{9b})$, $N(R^9)C(O)OR^{9a}$, $OC(O)N(R^9R^{9a})$, or A^3;

R^9, R^{9a}, R^{9b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different, or one OH, or one OC_{1-4} alkyl, or one A^3;

each A^3 is independently phenyl, naphthyl, 3 to 7 membered heterocyclyl, or 7 to 12 membered heterobicyclyl, wherein A^3 is optionally substituted with one or more R^{10}, which are the same or different;

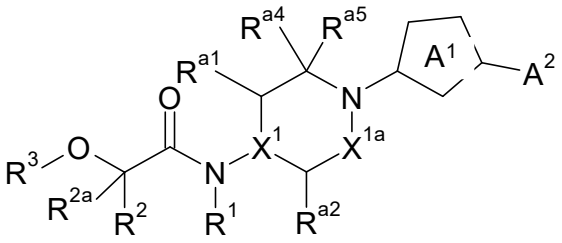
each R^{10} is independently halogen, CN, $C(O)OR^{11}$, OR^{11}, $C(O)R^{11}$, $C(O)N(R^{11}R^{11a})$, $S(O)_2N(R^{11}R^{11a})$, $S(O)N(R^{11}R^{11a})$, $S(O)_2R^{11}$, $S(O)R^{11}$, $N(R^{11})S(O)_2N(R^{11a}R^{11b})$, SR^{11}, $N(R^{11}R^{11a})$, NO_2, $OC(O)R^{11}$, $N(R^{11})C(O)R^{11a}$, $N(R^{11})S(O)_2R^{11a}$, $N(R^{11})S(O)R^{11a}$, $N(R^{11})C(O)OR^{11a}$, $N(R^{11})C(O)N(R^{11a}R^{11b})$, $OC(O)N(R^{11}R^{11a})$, oxo (=O) where the ring is at least partially saturated, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{12}, which are the same or different;

R^{11}, R^{11a}, R^{11b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

each R^{12} is independently halogen, CN, $C(O)OR^{13}$, OR^{13}, $C(O)R^{13}$, $C(O)N(R^{13}R^{13a})$, $S(O)_2N(R^{13}R^{13a})$, $S(O)N(R^{13}R^{13a})$, $S(O)_2R^{13}$, $S(O)R^{13}$, $N(R^{13})S(O)_2N(R^{13a}R^{13b})$, SR^{13}, $N(R^{13}R^{13a})$, NO_2, $OC(O)R^{13}$, $N(R^{13})C(O)R^{13a}$, $N(R^{13})SO_2R^{13a}$, $N(R^{13})S(O)R^{13a}$, $N(R^{13})C(O)N(R^{13a}R^{13b})$, $N(R^{13})C(O)OR^{13a}$, or $OC(O)N(R^{13}R^{13a})$;

R^{13}, R^{13a}, R^{13b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different.

In another aspect, there is provided a compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein

X^1 is $C(R^{a6})$ or N;

X^{1a} is a covalent single bond; $CH(R^{a3})$, O, $N(R^{a7})$, or $CH(R^{a3})CH_2$;

R^{a1}, R^{a2}, R^{a3} are independently selected from the group consisting of H; halogen; OH; O-C_{1-4} alkyl; C_{1-4} alkyl; and A^{2a},
and R^{a4}, R^{a5}, R^{a6} are independently selected from the group consisting of H; halogen; C_{1-4} alkyl; and A^{2a}, provided that only one of R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6} is A^{2a};
optionally R^{a1} and R^{a2} form a covalent single bond;
optionally R^{a2} and R^{a4} form a methylene group;
optionally R^{a4} and R^{a6} form an ethylene group;
optionally R^{a4} and R^{a5} are joined to form an oxo group;

R^{a7} is H, $C(O)OC_{1-4}$ alkyl, or C_{1-4} alkyl, wherein $C(O)OC_{1-4}$ alkyl and C_{1-4} alkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, OH, and O-C_{1-3} alkyl, wherein the substituents are the same or different, preferably R^{a7} is H;

A^1 is C_5 cycloalkylene, C_5 cycloalkenylene, a nitrogen ring atom containing 5-membered heterocyclene or a 7- to 12- membered heterobicyclene, which includes a nitrogen ring atom containing 5-membered heterocycle, wherein said heterocycle is attached to the nitrogen ring atom shown in formula (I) and wherein A^1 is optionally substituted with one or more R^4, which are the same or different;

each R^4 is independently oxo (=O) where the ring is at least partially saturated, thiooxo (=S) where the ring is at least partially saturated, halogen, CN, OR^5, or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^5 is H or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^2 is R^{6a} or A^{2a};

R^{6a} is OR^{6a1}, SR^{6a1}, $N(R^{6a1}R^{6a2})$; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a1}, R^{6a2} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; and A^{2a}, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a3} is H; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^{2a} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2a} is optionally substituted with one or more R^6, which are the same or different;

each R^6 is independently R^{6b}, OH, OR^{6b}, halogen, or CN, wherein R^{6b} is cyclopropyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, and wherein R^{6b} is optionally substituted with one or more halogen, which are the same or different; or
two R^6 are joined to form together with the atoms to which they are attached a ring A^{2b};

A^{2b} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2b} is optionally substituted with one or more R^7, which are the same or different;

each R^7 is independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

R^1 is H or C_{1-4} alkyl, preferably H, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^2 is H; F; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different; and

R^3 is A^3, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^8, which are the same or different; or

R^2 and R^3 are joined to form together with the oxygen atom and carbon atom to which they are attached a ring A^{3a}, wherein A^{3a} is a 7 to 12 membered heterobicyclyl, wherein 7 to 12 membered heterobicyclyl is optionally substituted with one or more R^{10}, which are the same or different;

R^{2a} is H or F, preferably H;

each R^8 is independently halogen; CN, $C(O)OR^9$, OR^9, $C(O)R^9$, $C(O)N(R^9R^{9a})$, $S(O)_2N(R^9R^{9a})$, $S(O)N(R^9R^{9a})$, $S(O)_2R^9$, $S(O)R^9$, $N(R^9)S(O)_2N(R^{9a}R^{9b})$, SR^9, $N(R^9R^{9a})$, NO_2, $OC(O)R^9$, $N(R^9)C(O)R^{9a}$, $N(R^9)SO_2R^{9a}$, $N(R^9)S(O)R^{9a}$, $N(R^9)C(O)N(R^{9a}R^{9b})$, $N(R^9)C(O)OR^{9a}$, $OC(O)N(R^9R^{9a})$, or A^3;

R^9, R^{9a}, R^{9b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different, or one OH, or one OC_{1-4} alkyl, or one A^3;

each A^3 is independently phenyl, naphthyl, 3 to 7 membered heterocyclyl, or 7 to 12 membered heterobicyclyl, wherein A^3 is optionally substituted with one or more R^{10}, which are the same or different;

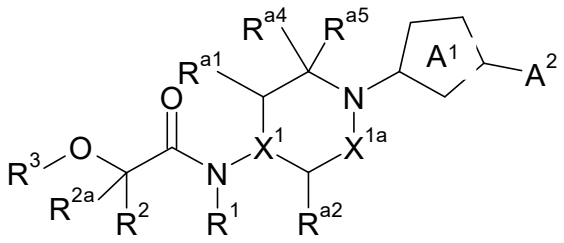
each R^{10} is independently halogen, CN, $C(O)OR^{11}$, OR^{11}, $C(O)R^{11}$, $C(O)N(R^{11}R^{11a})$, $S(O)_2N(R^{11}R^{11a})$, $S(O)N(R^{11}R^{11a})$, $S(O)_2R^{11}$, $S(O)R^{11}$, $N(R^{11})S(O)_2N(R^{11a}R^{11b})$, SR^{11}, $N(R^{11}R^{11a})$, NO_2, $OC(O)R^{11}$, $N(R^{11})C(O)R^{11a}$, $N(R^{11})S(O)_2R^{11a}$, $N(R^{11})S(O)R^{11a}$, $N(R^{11})C(O)OR^{11a}$, $N(R^{11})C(O)N(R^{11a}R^{11b})$, $OC(O)N(R^{11}R^{11a})$, oxo (=O) where the ring is at least partially saturated, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{12}, which are the same or different;

R^{11}, R^{11a}, R^{11b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

each R^{12} is independently halogen, CN, $C(O)OR^{13}$, OR^{13}, $C(O)R^{13}$, $C(O)N(R^{13}R^{13a})$, $S(O)_2N(R^{13}R^{13a})$, $S(O)N(R^{13}R^{13a})$, $S(O)_2R^{13}$, $S(O)R^{13}$, $N(R^{13})S(O)_2N(R^{13a}R^{13b})$, SR^{13}, $N(R^{13}R^{13a})$, NO_2, $OC(O)R^{13}$, $N(R^{13})C(O)R^{13a}$, $N(R^{13})SO_2R^{13a}$, $N(R^{13})S(O)R^{13a}$, $N(R^{13})C(O)N(R^{13a}R^{13b})$, $N(R^{13})C(O)OR^{13a}$, or $OC(O)N(R^{13}R^{13a})$;

R^{13}, R^{13a}, R^{13b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different.

In another aspect, there is provided a pharmaceutical composition comprising at least one compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein

X^1 is $C(R^{a6})$ or N;

X^{1a} is a covalent single bond; $CH(R^{a3})$, O, $N(R^{a7})$, or $CH(R^{a3})CH_2$;

R^{a1}, R^{a2}, R^{a3} are independently selected from the group consisting of H; halogen; OH; O-C_{1-4} alkyl; C_{1-4} alkyl; and A^{2a},
and R^{a4}, R^{a5}, R^{a6} are independently selected from the group consisting of H; halogen; C_{1-4} alkyl; and A^{2a}, provided that only one of R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6} is A^{2a};
optionally R^{a1} and R^{a2} form a covalent single bond;
optionally R^{a2} and R^{a4} form a methylene group;
optionally R^{a4} and R^{a6} form an ethylene group;
optionally R^{a4} and R^{a5} are joined to form an oxo group;

R^{a7} is H, $C(O)OC_{1-4}$ alkyl, or C_{1-4} alkyl, wherein $C(O)OC_{1-4}$ alkyl and C_{1-4} alkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, OH, and O-C_{1-3} alkyl, wherein the substituents are the same or different, preferably R^{a7} is H;

A^1 is C_5 cycloalkylene, C_5 cycloalkenylene, a nitrogen ring atom containing 5-membered heterocyclene or a 7- to 12- membered heterobicyclene, which includes a nitrogen ring atom containing 5-membered heterocycle, wherein said heterocycle is attached to the nitrogen ring atom shown in formula (I) and wherein A^1 is optionally substituted with one or more R^4, which are the same or different;

each R^4 is independently oxo (=O) where the ring is at least partially saturated, thiooxo (=S) where the ring is at least partially saturated, halogen, CN, OR^5, or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^5 is H or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^2 is R^{6a} or A^{2a};

R^{6a} is OR^{6a1}, SR^{6a1}, $N(R^{6a1}R^{6a2})$; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more

substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a1}, R^{6a2} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; and A^{2a}, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a3} is H; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^{2a} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2a} is optionally substituted with one or more R^6, which are the same or different;

each R^6 is independently R^{6b}, OH, OR^{6b}, halogen, or CN, wherein R^{6b} is cyclopropyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, and wherein R^{6b} is optionally substituted with one or more halogen, which are the same or different; or
two R^6 are joined to form together with the atoms to which they are attached a ring A^{2b};

A^{2b} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2b} is optionally substituted with one or more R^7, which are the same or different;

each R^7 is independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

R^1 is H or C_{1-4} alkyl, preferably H, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^2 is H; F; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different; and

R^3 is A^3, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^8, which are the same or different; or

R^2 and R^3 are joined to form together with the oxygen atom and carbon atom to which they are attached a ring A^{3a}, wherein A^{3a} is a 7 to 12 membered heterobicyclyl, wherein 7 to 12 membered heterobicyclyl is optionally substituted with one or more R^{10}, which are the same or different;

R^{2a} is H or F, preferably H;

each R^8 is independently halogen; CN, $C(O)OR^9$, OR^9, $C(O)R^9$, $C(O)N(R^9R^{9a})$, $S(O)_2N(R^9R^{9a})$, $S(O)N(R^9R^{9a})$, $S(O)_2R^9$, $S(O)R^9$, $N(R^9)S(O)_2N(R^{9a}R^{9b})$, SR^9, $N(R^9R^{9a})$, NO_2, $OC(O)R^9$, $N(R^9)C(O)R^{9a}$, $N(R^9)SO_2R^{9a}$, $N(R^9)S(O)R^{9a}$, $N(R^9)C(O)N(R^{9a}R^{9b})$, $N(R^9)C(O)OR^{9a}$, $OC(O)N(R^9R^{9a})$, or A^3;

R^9, R^{9a}, R^{9b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different, or one OH, or one OC_{1-4} alkyl, or one A^3;

each A^3 is independently phenyl, naphthyl, 3 to 7 membered heterocyclyl, or 7 to 12 membered heterobicyclyl, wherein A^3 is optionally substituted with one or more R^{10}, which are the same or different;

each R^{10} is independently halogen, CN, $C(O)OR^{11}$, OR^{11}, $C(O)R^{11}$, $C(O)N(R^{11}R^{11a})$, $S(O)_2N(R^{11}R^{11a})$, $S(O)N(R^{11}R^{11a})$, $S(O)_2R^{11}$, $S(O)R^{11}$, $N(R^{11})S(O)_2N(R^{11a}R^{11b})$, SR^{11}, $N(R^{11}R^{11a})$, NO_2, $OC(O)R^{11}$, $N(R^{11})C(O)R^{11a}$, $N(R^{11})S(O)_2R^{11a}$, $N(R^{11})S(O)R^{11a}$, $N(R^{11})C(O)OR^{11a}$, $N(R^{11})C(O)N(R^{11a}R^{11b})$, $OC(O)N(R^{11}R^{11a})$, oxo (=O) where the ring is at least partially saturated, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{12}, which are the same or different;

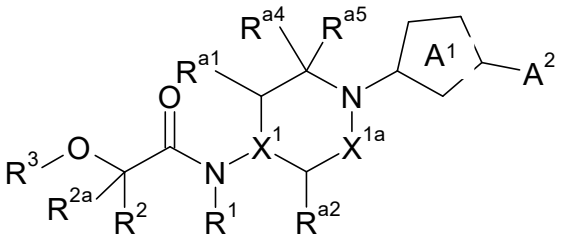
R^{11}, R^{11a}, R^{11b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

each R^{12} is independently halogen, CN, $C(O)OR^{13}$, OR^{13}, $C(O)R^{13}$, $C(O)N(R^{13}R^{13a})$, $S(O)_2N(R^{13}R^{13a})$, $S(O)N(R^{13}R^{13a})$, $S(O)_2R^{13}$, $S(O)R^{13}$, $N(R^{13})S(O)_2N(R^{13a}R^{13b})$, SR^{13}, $N(R^{13}R^{13a})$, NO_2, $OC(O)R^{13}$, $N(R^{13})C(O)R^{13a}$, $N(R^{13})SO_2R^{13a}$, $N(R^{13})S(O)R^{13a}$, $N(R^{13})C(O)N(R^{13a}R^{13b})$, $N(R^{13})C(O)OR^{13a}$, or $OC(O)N(R^{13}R^{13a})$;

R^{13}, R^{13a}, R^{13b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

together with a pharmaceutically acceptable carrier, optionally in combination with one or more other bioactive compounds or pharmaceutical compositions.

In another aspect, there is provided a compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein

X^1 is $C(R^{a6})$ or N;

X^{1a} is a covalent single bond; $CH(R^{a3})$, O, $N(R^{a7})$, or $CH(R^{a3})CH_2$;

R^{a1}, R^{a2}, R^{a3} are independently selected from the group consisting of H; halogen; OH; O-C_{1-4} alkyl; C_{1-4} alkyl; and A^{2a},
and R^{a4}, R^{a5}, R^{a6} are independently selected from the group consisting of H; halogen; C_{1-4} alkyl; and A^{2a}, provided that only one of R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6} is A^{2a};

optionally R^{a1} and R^{a2} form a covalent single bond;
optionally R^{a2} and R^{a4} form a methylene group;
optionally R^{a4} and R^{a6} form an ethylene group;
optionally R^{a4} and R^{a5} are joined to form an oxo group;

R^{a7} is H, $C(O)OC_{1-4}$ alkyl, or C_{1-4} alkyl, wherein $C(O)OC_{1-4}$ alkyl and C_{1-4} alkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, OH, and $O\text{-}C_{1-3}$ alkyl, wherein the substituents are the same or different, preferably R^{a7} is H;

A^1 is C_5 cycloalkylene, C_5 cycloalkenylene, a nitrogen ring atom containing 5-membered heterocyclene or a 7- to 12- membered heterobicyclene, which includes a nitrogen ring atom containing 5-membered heterocycle, wherein said heterocycle is attached to the nitrogen ring atom shown in formula (I) and wherein A^1 is optionally substituted with one or more R^4, which are the same or different;

each R^4 is independently oxo (=O) where the ring is at least partially saturated, thiooxo (=S) where the ring is at least partially saturated, halogen, CN, OR^5, or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^5 is H or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^2 is R^{6a} or A^{2a};

R^{6a} is OR^{6a1}, SR^{6a1}, $N(R^{6a1}R^{6a2})$; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a1}, R^{6a2} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; and A^{2a}, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are

optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a3} is H; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^{2a} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2a} is optionally substituted with one or more R^6, which are the same or different;

each R^6 is independently R^{6b}, OH, OR^{6b}, halogen, or CN, wherein R^{6b} is cyclopropyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, and wherein R^{6b} is optionally substituted with one or more halogen, which are the same or different; or
two R^6 are joined to form together with the atoms to which they are attached a ring A^{2b};

A^{2b} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2b} is optionally substituted with one or more R^7, which are the same or different;

each R^7 is independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

R^1 is H or C_{1-4} alkyl, preferably H, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^2 is H; F; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different; and
R^3 is A^3, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^8, which are the same or different; or
R^2 and R^3 are joined to form together with the oxygen atom and carbon atom to which they are attached a ring A^{3a}, wherein A^{3a} is a 7 to 12 membered heterobicyclyl, wherein 7 to 12 membered heterobicyclyl is optionally substituted with one or more R^{10}, which are the same or different;

R^{2a} is H or F, preferably H;

each R^8 is independently halogen; CN, $C(O)OR^9$, OR^9, $C(O)R^9$, $C(O)N(R^9R^{9a})$, $S(O)_2N(R^9R^{9a})$, $S(O)N(R^9R^{9a})$, $S(O)_2R^9$, $S(O)R^9$, $N(R^9)S(O)_2N(R^{9a}R^{9b})$, SR^9, $N(R^9R^{9a})$, NO_2, $OC(O)R^9$, $N(R^9)C(O)R^{9a}$, $N(R^9)SO_2R^{9a}$, $N(R^9)S(O)R^{9a}$, $N(R^9)C(O)N(R^{9a}R^{9b})$, $N(R^9)C(O)OR^{9a}$, $OC(O)N(R^9R^{9a})$, or A^3;

R^9, R^{9a}, R^{9b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different, or one OH, or one OC_{1-4} alkyl, or one A^3;

each A^3 is independently phenyl, naphthyl, 3 to 7 membered heterocyclyl, or 7 to 12 membered heterobicyclyl, wherein A^3 is optionally substituted with one or more R^{10}, which are the same or different;

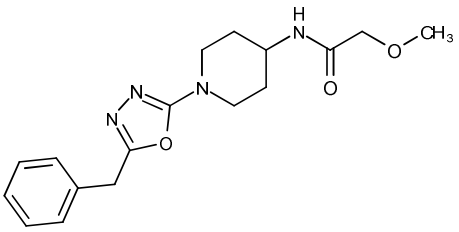
each R^{10} is independently halogen, CN, $C(O)OR^{11}$, OR^{11}, $C(O)R^{11}$, $C(O)N(R^{11}R^{11a})$, $S(O)_2N(R^{11}R^{11a})$, $S(O)N(R^{11}R^{11a})$, $S(O)_2R^{11}$, $S(O)R^{11}$, $N(R^{11})S(O)_2N(R^{11a}R^{11b})$, SR^{11}, $N(R^{11}R^{11a})$, NO_2, $OC(O)R^{11}$, $N(R^{11})C(O)R^{11a}$, $N(R^{11})S(O)_2R^{11a}$, $N(R^{11})S(O)R^{11a}$, $N(R^{11})C(O)OR^{11a}$, $N(R^{11})C(O)N(R^{11a}R^{11b})$, $OC(O)N(R^{11}R^{11a})$, oxo (=O) where the ring is at least partially saturated, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{12}, which are the same or different;

R^{11}, R^{11a}, R^{11b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

each R^{12} is independently halogen, CN, $C(O)OR^{13}$, OR^{13}, $C(O)R^{13}$, $C(O)N(R^{13}R^{13a})$, $S(O)_2N(R^{13}R^{13a})$, $S(O)N(R^{13}R^{13a})$, $S(O)_2R^{13}$, $S(O)R^{13}$, $N(R^{13})S(O)_2N(R^{13a}R^{13b})$, SR^{13}, $N(R^{13}R^{13a})$, NO_2, $OC(O)R^{13}$, $N(R^{13})C(O)R^{13a}$, $N(R^{13})SO_2R^{13a}$, $N(R^{13})S(O)R^{13a}$, $N(R^{13})C(O)N(R^{13a}R^{13b})$, $N(R^{13})C(O)OR^{13a}$, or $OC(O)N(R^{13}R^{13a})$;

R^{13}, R^{13a}, R^{13b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

provided that the following compounds or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof are excluded:



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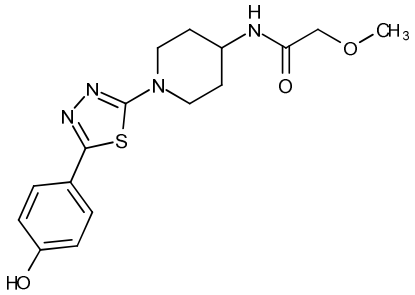

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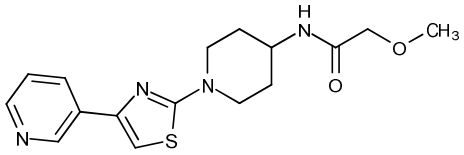

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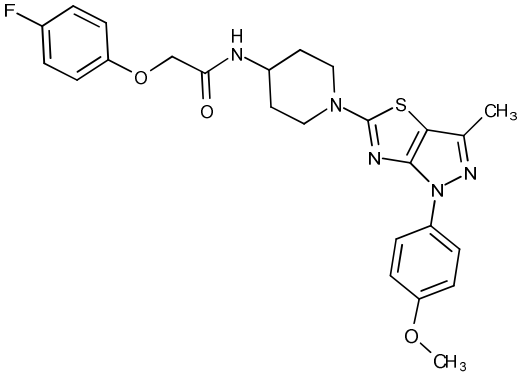

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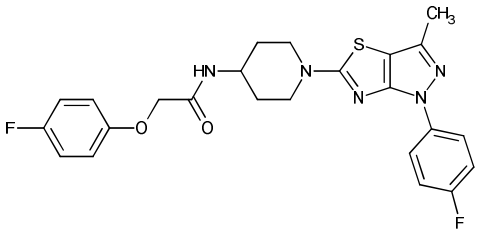

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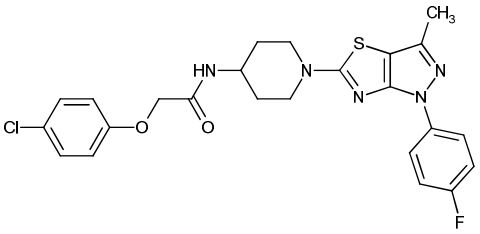

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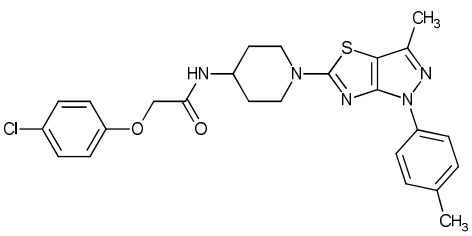

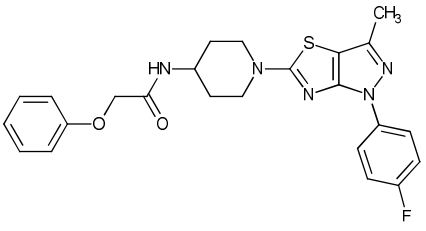

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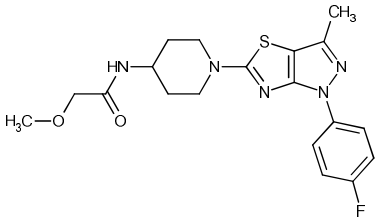

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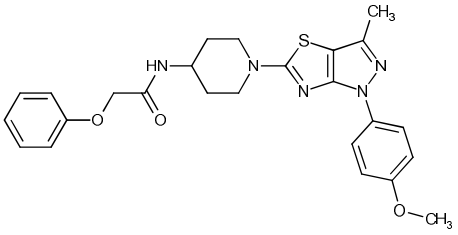

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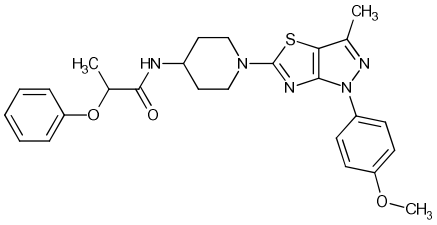

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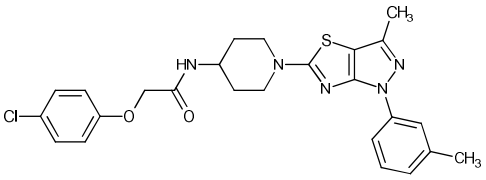

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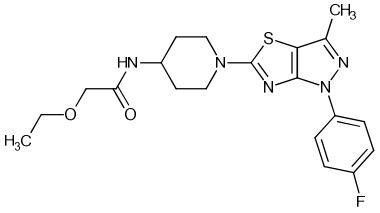

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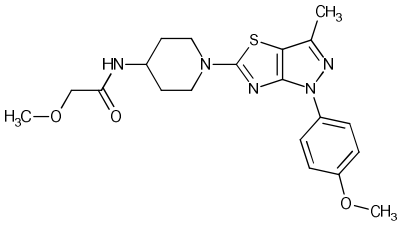

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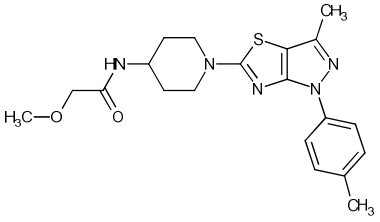

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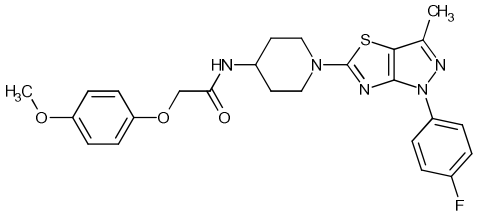

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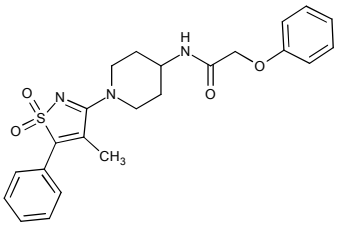

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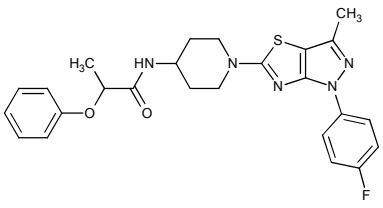

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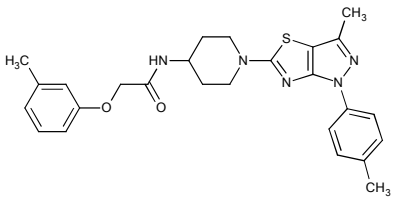

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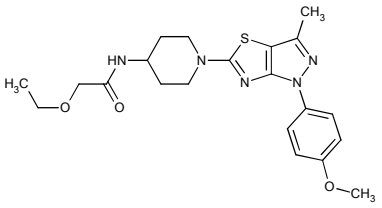

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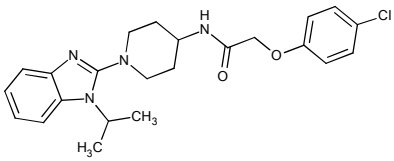

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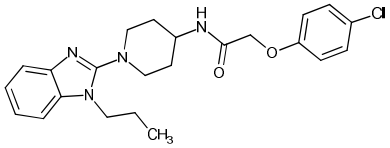

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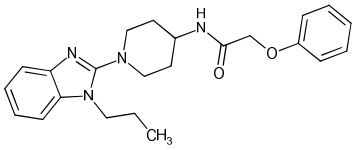

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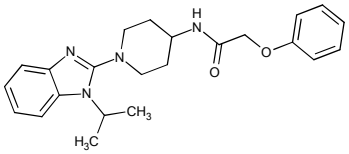

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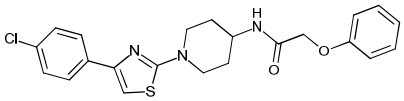

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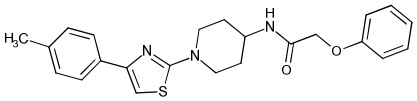

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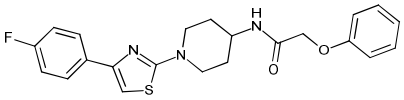

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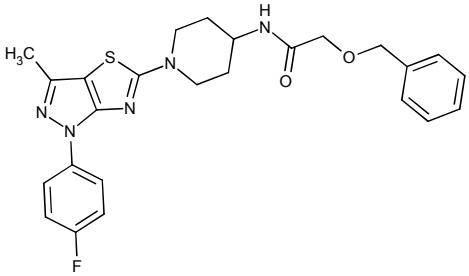

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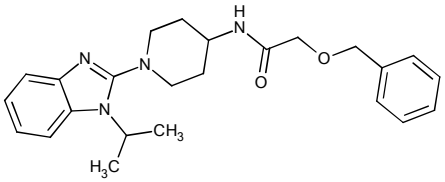

CAS 1047557-93-6.

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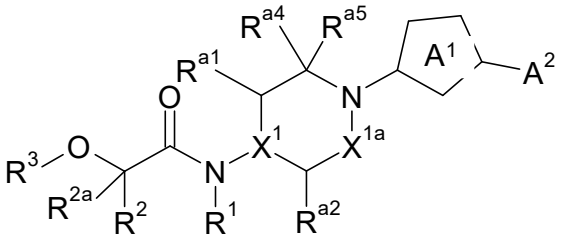
Accordingly, the present disclosure provides a compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein

X^1 is $C(R^{a6})$ or N;

X^{1a} is a covalent single bond; $CH(R^{a3})$, O, $N(R^{a7})$, or $CH(R^{a3})CH_2$;

R^{a1}, R^{a2}, R^{a3} are independently selected from the group consisting of H; halogen; OH; O-C_{1-4} alkyl; C_{1-4} alkyl; and A^{2a},

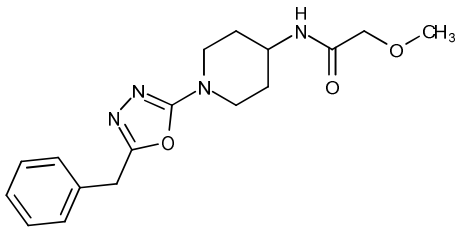
and R^{a4}, R^{a5}, R^{a6} are independently selected from the group consisting of H; halogen; C_{1-4} alkyl; and A^{2a}, provided that only one of R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6} is A^{2a};

optionally R^{a1} and R^{a2} form a covalent single bond;

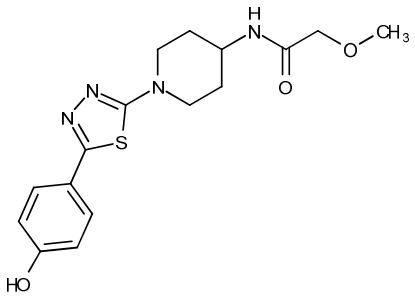
optionally R^{a2} and R^{a4} form a methylene group;

R^{13}, R^{13a}, R^{13b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different.

A compound not restricted to the use as a medicament as defined above with preferences as defined below and a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, is also within the scope of the present disclosure provided that the following compounds or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof are excluded:



CAS 2249353-57-7,



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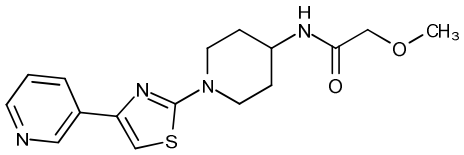
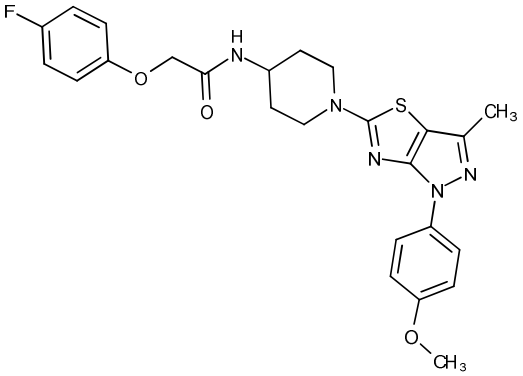
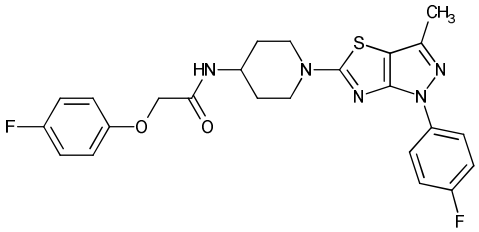


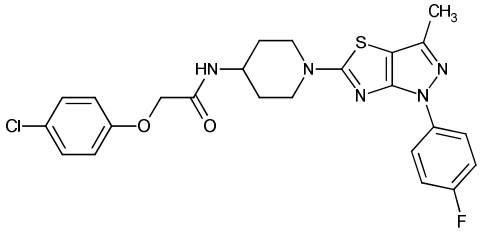
CAS 1787882-10-3,



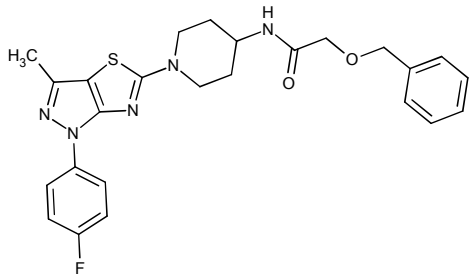
CAS 1359473-07-6,



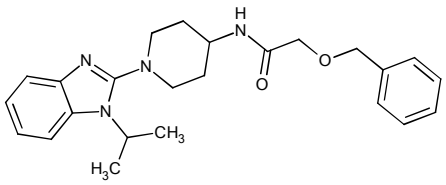
CAS 1359350-08-5,



CAS 1359344-31-2,



CAS 1358737-82-2, and



CAS 1047557-93-6.

The excluded compounds represent commercial compounds without indication of the use.

In case a variable or substituent can be selected from a group of different variants and such variable or substituent occurs more than once the respective variants can be the same or different.

Within the meaning of the present disclosure the terms are used as follows:

The term “optionally substituted” means unsubstituted or substituted. Generally -but not limited to-, “one or more substituents” means one, two or three, preferably one or two substituents and more preferably one substituent. Generally these substituents can be the same or different.

“Alkyl” means a straight-chain or branched hydrocarbon chain. Each hydrogen of an alkyl carbon may be replaced by a substituent as further specified.

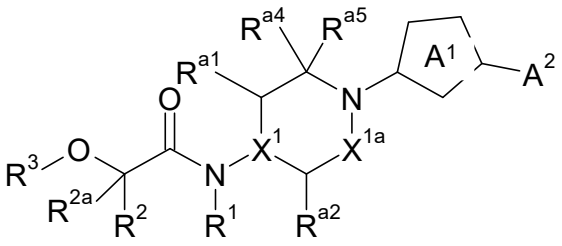
“Alkenyl” means a straight-chain or branched hydrocarbon chain that contains at least one carbon-carbon double bond. Each hydrogen of an alkenyl carbon may be replaced by a substituent as further specified.

“Alkynyl” means a straight-chain or branched hydrocarbon chain that contains at least one carbon-carbon triple bond. Each hydrogen of an alkynyl carbon may be replaced by a substituent as further specified.

“C_{1-4} alkyl” means an alkyl chain having 1 - 4 carbon atoms, e.g. if present at the end of a molecule: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, or e.g. -

Patent Claims

1. Use of a compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof in the manufacture of a medicament, wherein

X^1 is $C(R^{a6})$ or N;

X^{1a} is a covalent single bond; $CH(R^{a3})$, O, $N(R^{a7})$, or $CH(R^{a3})CH_2$;

R^{a1}, R^{a2}, R^{a3} are independently selected from the group consisting of H; halogen; OH; O-C_{1-4} alkyl; C_{1-4} alkyl; and A^{2a},
and R^{a4}, R^{a5}, R^{a6} are independently selected from the group consisting of H; halogen; C_{1-4} alkyl; and A^{2a}, provided that only one of R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6} is A^{2a};
optionally R^{a1} and R^{a2} form a covalent single bond;
optionally R^{a2} and R^{a4} form a methylene group;
optionally R^{a4} and R^{a6} form an ethylene group;
optionally R^{a4} and R^{a5} are joined to form an oxo group;

R^{a7} is H, $C(O)OC_{1-4}$ alkyl, or C_{1-4} alkyl, wherein $C(O)OC_{1-4}$ alkyl and C_{1-4} alkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, OH, and O-C_{1-3} alkyl, wherein the substituents are the same or different, preferably R^{a7} is H;

A^1 is C_5 cycloalkylene, C_5 cycloalkenylene, a nitrogen ring atom containing 5-membered heterocyclene or a 7- to 12- membered heterobicyclene, which includes a nitrogen ring atom containing 5-membered heterocycle, wherein said heterocycle is

attached to the nitrogen ring atom shown in formula (I) and wherein A^1 is optionally substituted with one or more R^4, which are the same or different;

each R^4 is independently oxo (=O) where the ring is at least partially saturated, thiooxo (=S) where the ring is at least partially saturated, halogen, CN, OR^5, or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^5 is H or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^2 is R^{6a} or A^{2a};

R^{6a} is OR^{6a1}, SR^{6a1}, $N(R^{6a1}R^{6a2})$; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a1}, R^{6a2} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; and A^{2a}, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a3} is H; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^{2a} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2a} is optionally substituted with one or more R^6, which are the same or different;

each R^6 is independently R^{6b}, OH, OR^{6b}, halogen, or CN, wherein R^{6b} is cyclopropyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, and wherein R^{6b} is optionally substituted with one or more halogen, which are the same or different; or
two R^6 are joined to form together with the atoms to which they are attached a ring A^{2b};

A^{2b} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2b} is optionally substituted with one or more R^7, which are the same or different;

each R^7 is independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

R^1 is H or C_{1-4} alkyl, preferably H, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^2 is H; F; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different; and

R^3 is A^3, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^8, which are the same or different; or

R^2 and R^3 are joined to form together with the oxygen atom and carbon atom to which they are attached a ring A^{3a}, wherein A^{3a} is a 7 to 12 membered heterobicyclyl, wherein 7 to 12 membered heterobicyclyl is optionally substituted with one or more R^{10}, which are the same or different;

R^{2a} is H or F, preferably H;

each R^8 is independently halogen; CN, $C(O)OR^9$, OR^9, $C(O)R^9$, $C(O)N(R^9R^{9a})$, $S(O)_2N(R^9R^{9a})$, $S(O)N(R^9R^{9a})$, $S(O)_2R^9$, $S(O)R^9$, $N(R^9)S(O)_2N(R^{9a}R^{9b})$, SR^9, $N(R^9R^{9a})$, NO_2, $OC(O)R^9$, $N(R^9)C(O)R^{9a}$, $N(R^9)SO_2R^{9a}$, $N(R^9)S(O)R^{9a}$, $N(R^9)C(O)N(R^{9a}R^{9b})$, $N(R^9)C(O)OR^{9a}$, $OC(O)N(R^9R^{9a})$, or A^3;

R^9, R^{9a}, R^{9b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different, or one OH, or one OC_{1-4} alkyl, or one A^3;

each A^3 is independently phenyl, naphthyl, 3 to 7 membered heterocyclyl, or 7 to 12 membered heterobicyclyl, wherein A^3 is optionally substituted with one or more R^{10}, which are the same or different;

each R^{10} is independently halogen, CN, $C(O)OR^{11}$, OR^{11}, $C(O)R^{11}$, $C(O)N(R^{11}R^{11a})$, $S(O)_2N(R^{11}R^{11a})$, $S(O)N(R^{11}R^{11a})$, $S(O)_2R^{11}$, $S(O)R^{11}$, $N(R^{11})S(O)_2N(R^{11a}R^{11b})$, SR^{11}, $N(R^{11}R^{11a})$, NO_2, $OC(O)R^{11}$, $N(R^{11})C(O)R^{11a}$, $N(R^{11})S(O)_2R^{11a}$, $N(R^{11})S(O)R^{11a}$, $N(R^{11})C(O)OR^{11a}$, $N(R^{11})C(O)N(R^{11a}R^{11b})$, $OC(O)N(R^{11}R^{11a})$, oxo (=O) where the ring is at least partially saturated, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{12}, which are the same or different;

R^{11}, R^{11a}, R^{11b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

each R^{12} is independently halogen, CN, $C(O)OR^{13}$, OR^{13}, $C(O)R^{13}$, $C(O)N(R^{13}R^{13a})$, $S(O)_2N(R^{13}R^{13a})$, $S(O)N(R^{13}R^{13a})$, $S(O)_2R^{13}$, $S(O)R^{13}$, $N(R^{13})S(O)_2N(R^{13a}R^{13b})$, SR^{13}, $N(R^{13}R^{13a})$, NO_2, $OC(O)R^{13}$, $N(R^{13})C(O)R^{13a}$, $N(R^{13})SO_2R^{13a}$, $N(R^{13})S(O)R^{13a}$, $N(R^{13})C(O)N(R^{13a}R^{13b})$, $N(R^{13})C(O)OR^{13a}$, or $OC(O)N(R^{13}R^{13a})$;

R^{13}, R^{13a}, R^{13b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different.

2. The use of claim 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein X^1 is CH.

3. The use of claim 1 or 2 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein X^{1a} is a covalent single bond; $CH(R^{a3})$, or $CH(R^{a3})CH_2$, preferably $CH(R^{a3})$ or $CH(R^{a3})CH_2$, more preferably $CH(R^{a3})$.

4. The use of any one of claims 1 to 3 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6} are H; or

R^{a1} is OH and R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6} are H; or R^{a1}, R^{a3}, R^{a5}, R^{a6} are H and R^{a2} and R^{a4} form a methylene group; or R^{a1} and R^{a2} form a covalent single bond and R^{a3}, R^{a4}, R^{a5}, R^{a6} are H.

5. The use of any one of claims 1 to 4 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6} are H.

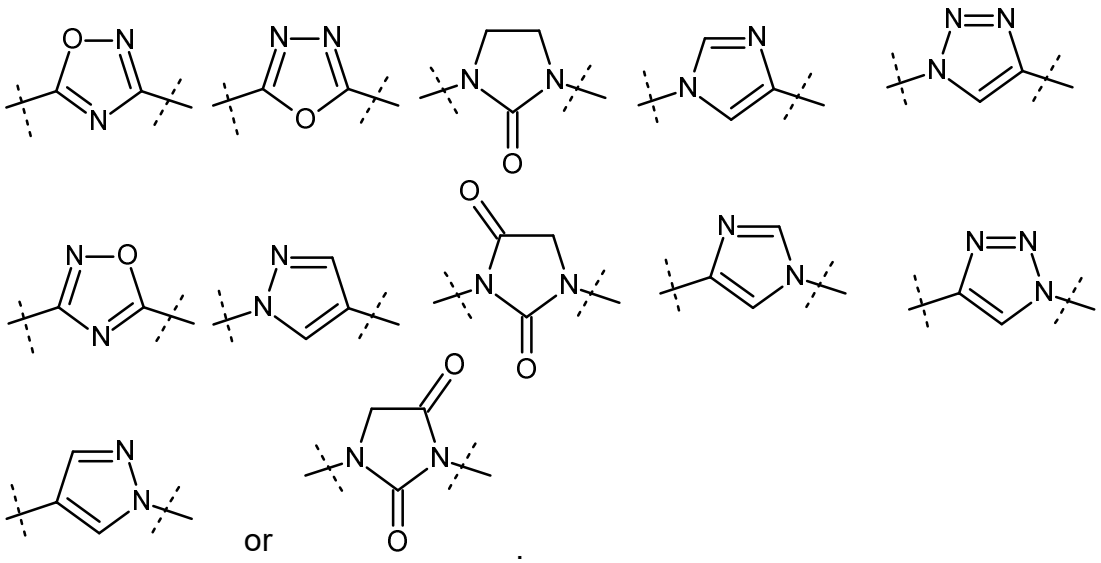
6. The use of any one of claims 1 to 5 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^1 is a nitrogen ring atom containing 5-membered heterocyclene and wherein A^1 is optionally substituted with one or more R^4, which are the same or different.

7. The use of any one of claims 1 to 6 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^1 is a nitrogen ring atom containing 5-membered heterocyclene selected from the group of bivalent heterocycles consisting of oxadiazole, imidazole, imidazolidine, pyrazole and triazole, preferably oxadiazole, and wherein A^1 is optionally substituted with one or more R^4, which are the same or different.

8. The use of any one of claims 1 to 7 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^1 is unsubstituted or substituted with one or two R^4, which are the same or different, preferably A^1 is unsubstituted.

9. The use of any one of claims 1 to 7 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^4 is oxo where the ring is at least partly saturated, or methyl.

10. The use of any one of claims 1 to 9 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^1 is



11. The use of any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^2 is R^{6a}.

12. The use of claim 11 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^{6a} is OR^{6a1} and R^{6a1} is preferably A^{2a} or C_{1-6} alkyl, optionally substituted with one or more halogen and/or one A^{2a} and/or one OR^{6a3}; or R^{6a} is C_{1-6} alkyl, optionally substituted with one or more halogen and/or one A^{2a} and/or one OR^{6a3}.

13. The use of claim 11 or 12 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^{6a} is OR^{6a1} and R^{6a1} is preferably C_{1-6} alkyl, optionally substituted with one or more F and/or one OR^{6a3}; or R^{6a} is C_{1-6} alkyl, optionally substituted with one or more halogen and/or one OR^{6a3}.

14. The use of any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^2 is A^{2a}.

15. The use of claim 14 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^{2a} is phenyl, or 5- to 6-membered aromatic heterocyclyl, preferably pyridyl, pyrazinyl, pyridazinyl, pyrazolyl or 1,2,4-

oxadiazolyl, and wherein A^{2a} is optionally substituted with one or more R^6, which are the same or different.

16. The use of any one of claims 1 to 10, 14 and 15 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^{2a} is substituted with one or two R^6, which are the same or different.

17. The use of any one of claims 1 to 10, 14 to 16 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein each R^6 is independently F, Cl, CF_3, OCH_3, OCF_3, CH_3, CH_2CH_3, or cyclopropyl.

18. The use of any one of claims 1 to 17 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^2 is H.

19. The use of any one of claims 1 to 18 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^3 is A^3.

20. The use of any one of claims 1 to 19 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^3 is phenyl, pyridyl, pyrazinyl or pyrimidazyl and wherein A^3 is optionally substituted with one or more R^{10}, which are the same or different.

21. The use of any one of claims 1 to 20 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein A^3 is substituted with one or two R^{10}, which are the same or different.

22. The use of any one of claims 1 to 17 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^2 and R^3 are joined together with the oxygen and carbon atom to which they are attached to form a dihydrobenzopyran ring, wherein the ring is optionally substituted with one or more R^{10}, which are the same or different, preferably the ring is substituted with one or two R^{10}.

23. The use of any one of claims 1 to 22 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein R^{10} is independently F, Cl, CF_3, CH=O, CH_2OH or CH_3.

24. The use of any one of claims 1 to 23 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein the compound is

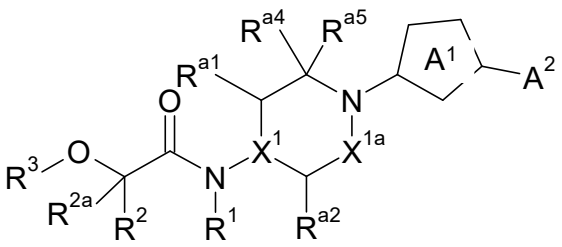
2-(4-chloro-3-fluorophenoxy)-*N*-{1-[5-(5-chloropyridin-2-yl)-1,3,4-oxadiazol-2-yl]piperidin-4-yl}acetamide;
2-[(6-chloro-5-fluoropyridin-3-yl)oxy]-*N*-{1-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]piperidin-4-yl}acetamide;
2-(4-chloro-3-fluorophenoxy)-*N*-[(3*R**,4*R**)-1-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-3-hydroxypiperidin-4-yl]acetamide;
2-(4-chloro-3-fluoro-phenoxy)-*N*-[1-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-4-piperidyl]acetamide;
2-(4-Chloro-3-fluorophenoxy)-*N*-{1-[5-(4,4,4-trifluorobutyl)-1,3,4-oxadiazol-2-yl]piperidin-4-yl}acetamide;
2-(4-Chloro-3-fluorophenoxy)-*N*-[(1*R*,5*S*,6*R*)-3-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-3-azabicyclo[3.1.0]hexan-6-yl]acetamide;
2-(4-Chloro-3-fluorophenoxy)-*N*-{4-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]piperazin-1-yl}acetamide;
2-(4-Chloro-3-fluorophenoxy)-*N*-{1-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]azepan-4-yl}acetamide;
2-(4-Chloro-3-fluorophenoxy)-*N*-[(3*R*,4*R*)-1-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-3-hydroxypiperidin-4-yl]acetamide;
2-(4-Chloro-3-fluorophenoxy)-*N*-[(3*S*,4*S*)-1-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-3-hydroxypiperidin-4-yl]acetamide;
2-(4-Chloro-3-fluorophenoxy)-*N*-[(4*S*)-1-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]azepan-4-yl]acetamide;
2-(4-chloro-3-fluorophenoxy)-*N*-[(4*R*)-1-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]azepan-4-yl]acetamide;
2-(4-chloro-3-fluorophenoxy)-*N*-(1-{5-[3-(trifluoromethoxy)azetidin-1-yl]-1,3,4-oxadiazol-2-yl}piperidin-4-yl)acetamide; or

2-(4-chloro-3-fluorophenoxy)-*N*-(1-{5-[2-(trifluoromethoxy)ethoxy]-1,3,4-oxadiazol-2-yl}piperidin-4-yl)acetamide.

25. The use of any one of claims 1 to 24, in the manufacture of a medicament for treating or preventing of one or more diseases or disorders associated with integrated stress response.

26. The use of any one of claims 1 to 24, in the manufacture of a medicament for treating or preventing of one or more diseases or disorders selected from the group consisting of leukodystrophies, intellectual disability syndrome, neurodegenerative diseases and disorders, neoplastic diseases, infectious diseases, inflammatory diseases, musculoskeletal diseases, metabolic diseases, ocular diseases as well as diseases selected from the group consisting of organ fibrosis, chronic and acute diseases of the liver, chronic and acute diseases of the lung, chronic and acute diseases of the kidney, myocardial infarction, cardiovascular disease, arrhythmias, atherosclerosis, spinal cord injury, ischemic stroke, and neuropathic pain.

27. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein

X^1 is $C(R^{a6})$ or N;

X^{1a} is a covalent single bond; $CH(R^{a3})$, O, $N(R^{a7})$, or $CH(R^{a3})CH_2$;

R^{a1}, R^{a2}, R^{a3} are independently selected from the group consisting of H; halogen; OH; O-C_{1-4} alkyl; C_{1-4} alkyl; and A^{2a},

and R^{a4}, R^{a5}, R^{a6} are independently selected from the group consisting of H; halogen; C_{1-4} alkyl; and A^{2a}, provided that only one of R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6} is A^{2a};
optionally R^{a1} and R^{a2} form a covalent single bond;
optionally R^{a2} and R^{a4} form a methylene group;
optionally R^{a4} and R^{a6} form an ethylene group;
optionally R^{a4} and R^{a5} are joined to form an oxo group;

R^{a7} is H, $C(O)OC_{1-4}$ alkyl, or C_{1-4} alkyl, wherein $C(O)OC_{1-4}$ alkyl and C_{1-4} alkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, OH, and $O\text{-}C_{1-3}$ alkyl, wherein the substituents are the same or different, preferably R^{a7} is H;

A^1 is C_5 cycloalkylene, C_5 cycloalkenylene, a nitrogen ring atom containing 5-membered heterocyclene or a 7- to 12- membered heterobicyclene, which includes a nitrogen ring atom containing 5-membered heterocycle, wherein said heterocycle is attached to the nitrogen ring atom shown in formula (I) and wherein A^1 is optionally substituted with one or more R^4, which are the same or different;

each R^4 is independently oxo (=O) where the ring is at least partially saturated, thiooxo (=S) where the ring is at least partially saturated, halogen, CN, OR^5, or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^5 is H or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^2 is R^{6a} or A^{2a};

R^{6a} is OR^{6a1}, SR^{6a1}, $N(R^{6a1}R^{6a2})$; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a1}, R^{6a2} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; and A^{2a}, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a3} is H; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^{2a} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2a} is optionally substituted with one or more R^6, which are the same or different;

each R^6 is independently R^{6b}, OH, OR^{6b}, halogen, or CN, wherein R^{6b} is cyclopropyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, and wherein R^{6b} is optionally substituted with one or more halogen, which are the same or different; or
two R^6 are joined to form together with the atoms to which they are attached a ring A^{2b};

A^{2b} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2b} is optionally substituted with one or more R^7, which are the same or different;

each R^7 is independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

R^1 is H or C_{1-4} alkyl, preferably H, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^2 is H; F; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different; and
R^3 is A^3, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^8, which are the same or different; or
R^2 and R^3 are joined to form together with the oxygen atom and carbon atom to which they are attached a ring A^{3a}, wherein A^{3a} is a 7 to 12 membered heterobicyclyl,

wherein 7 to 12 membered heterobicyclyl is optionally substituted with one or more R^{10}, which are the same or different;

R^{2a} is H or F, preferably H;

each R^8 is independently halogen; CN, $C(O)OR^9$, OR^9, $C(O)R^9$, $C(O)N(R^9R^{9a})$, $S(O)_2N(R^9R^{9a})$, $S(O)N(R^9R^{9a})$, $S(O)_2R^9$, $S(O)R^9$, $N(R^9)S(O)_2N(R^{9a}R^{9b})$, SR^9, $N(R^9R^{9a})$, NO_2, $OC(O)R^9$, $N(R^9)C(O)R^{9a}$, $N(R^9)SO_2R^{9a}$, $N(R^9)S(O)R^{9a}$, $N(R^9)C(O)N(R^{9a}R^{9b})$, $N(R^9)C(O)OR^{9a}$, $OC(O)N(R^9R^{9a})$, or A^3;

R^9, R^{9a}, R^{9b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different, or one OH, or one OC_{1-4} alkyl, or one A^3;

each A^3 is independently phenyl, naphthyl, 3 to 7 membered heterocyclyl, or 7 to 12 membered heterobicyclyl, wherein A^3 is optionally substituted with one or more R^{10}, which are the same or different;

each R^{10} is independently halogen, CN, $C(O)OR^{11}$, OR^{11}, $C(O)R^{11}$, $C(O)N(R^{11}R^{11a})$, $S(O)_2N(R^{11}R^{11a})$, $S(O)N(R^{11}R^{11a})$, $S(O)_2R^{11}$, $S(O)R^{11}$, $N(R^{11})S(O)_2N(R^{11a}R^{11b})$, SR^{11}, $N(R^{11}R^{11a})$, NO_2, $OC(O)R^{11}$, $N(R^{11})C(O)R^{11a}$, $N(R^{11})S(O)_2R^{11a}$, $N(R^{11})S(O)R^{11a}$, $N(R^{11})C(O)OR^{11a}$, $N(R^{11})C(O)N(R^{11a}R^{11b})$, $OC(O)N(R^{11}R^{11a})$, oxo (=O) where the ring is at least partially saturated, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{12}, which are the same or different;

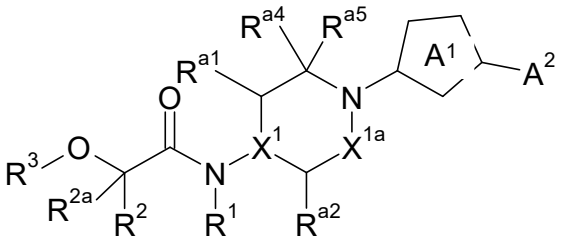
R^{11}, R^{11a}, R^{11b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

each R^{12} is independently halogen, CN, $C(O)OR^{13}$, OR^{13}, $C(O)R^{13}$, $C(O)N(R^{13}R^{13a})$, $S(O)_2N(R^{13}R^{13a})$, $S(O)N(R^{13}R^{13a})$, $S(O)_2R^{13}$, $S(O)R^{13}$, $N(R^{13})S(O)_2N(R^{13a}R^{13b})$, SR^{13},

$N(R^{13}R^{13a})$, NO_2, $OC(O)R^{13}$, $N(R^{13})C(O)R^{13a}$, $N(R^{13})SO_2R^{13a}$, $N(R^{13})S(O)R^{13a}$, $N(R^{13})C(O)N(R^{13a}R^{13b})$, $N(R^{13})C(O)OR^{13a}$, or $OC(O)N(R^{13}R^{13a})$;

R^{13}, R^{13a}, R^{13b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different.

28. A pharmaceutical composition comprising at least one compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein

X^1 is $C(R^{a6})$ or N;

X^{1a} is a covalent single bond; $CH(R^{a3})$, O, $N(R^{a7})$, or $CH(R^{a3})CH_2$;

R^{a1}, R^{a2}, R^{a3} are independently selected from the group consisting of H; halogen; OH; O-C_{1-4} alkyl; C_{1-4} alkyl; and A^{2a},

and R^{a4}, R^{a5}, R^{a6} are independently selected from the group consisting of H; halogen; C_{1-4} alkyl; and A^{2a}, provided that only one of R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6} is A^{2a};
optionally R^{a1} and R^{a2} form a covalent single bond;
optionally R^{a2} and R^{a4} form a methylene group;
optionally R^{a4} and R^{a6} form an ethylene group;
optionally R^{a4} and R^{a5} are joined to form an oxo group;

R^{a7} is H, $C(O)OC_{1-4}$ alkyl, or C_{1-4} alkyl, wherein $C(O)OC_{1-4}$ alkyl and C_{1-4} alkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, OH, and O-C_{1-3} alkyl, wherein the substituents are the same or different, preferably R^{a7} is H;

A^1 is C_5 cycloalkylene, C_5 cycloalkenylene, a nitrogen ring atom containing 5-membered heterocyclene or a 7- to 12- membered heterobicyclene, which includes a nitrogen ring atom containing 5-membered heterocycle, wherein said heterocycle is attached to the nitrogen ring atom shown in formula (I) and wherein A^1 is optionally substituted with one or more R^4, which are the same or different;

each R^4 is independently oxo (=O) where the ring is at least partially saturated, thiooxo (=S) where the ring is at least partially saturated, halogen, CN, OR^5, or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^5 is H or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^2 is R^{6a} or A^{2a};

R^{6a} is OR^{6a1}, SR^{6a1}, $N(R^{6a1}R^{6a2})$; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a1}, R^{6a2} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; and A^{2a}, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a3} is H; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^{2a} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2a} is optionally substituted with one or more R^6, which are the same or different;

each R^6 is independently R^{6b}, OH, OR^{6b}, halogen, or CN, wherein R^{6b} is cyclopropyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, and wherein R^{6b} is optionally substituted with one or more halogen, which are the same or different; or
two R^6 are joined to form together with the atoms to which they are attached a ring A^{2b};

A^{2b} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2b} is optionally substituted with one or more R^7, which are the same or different;

each R^7 is independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

R^1 is H or C_{1-4} alkyl, preferably H, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^2 is H; F; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different; and
R^3 is A^3, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^8, which are the same or different; or
R^2 and R^3 are joined to form together with the oxygen atom and carbon atom to which they are attached a ring A^{3a}, wherein A^{3a} is a 7 to 12 membered heterobicyclyl, wherein 7 to 12 membered heterobicyclyl is optionally substituted with one or more R^{10}, which are the same or different;

R^{2a} is H or F, preferably H;

each R^8 is independently halogen; CN, $C(O)OR^9$, OR^9, $C(O)R^9$, $C(O)N(R^9R^{9a})$, $S(O)_2N(R^9R^{9a})$, $S(O)N(R^9R^{9a})$, $S(O)_2R^9$, $S(O)R^9$, $N(R^9)S(O)_2N(R^{9a}R^{9b})$, SR^9, $N(R^9R^{9a})$, NO_2, $OC(O)R^9$, $N(R^9)C(O)R^{9a}$, $N(R^9)SO_2R^{9a}$, $N(R^9)S(O)R^{9a}$, $N(R^9)C(O)N(R^{9a}R^{9b})$, $N(R^9)C(O)OR^{9a}$, $OC(O)N(R^9R^{9a})$, or A^3;

R^9, R^{9a}, R^{9b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different, or one OH, or one OC_{1-4} alkyl, or one A^3;

each A^3 is independently phenyl, naphthyl, 3 to 7 membered heterocyclyl, or 7 to 12 membered heterobicyclyl, wherein A^3 is optionally substituted with one or more R^{10}, which are the same or different;

each R^{10} is independently halogen, CN, $C(O)OR^{11}$, OR^{11}, $C(O)R^{11}$, $C(O)N(R^{11}R^{11a})$, $S(O)_2N(R^{11}R^{11a})$, $S(O)N(R^{11}R^{11a})$, $S(O)_2R^{11}$, $S(O)R^{11}$, $N(R^{11})S(O)_2N(R^{11a}R^{11b})$, SR^{11}, $N(R^{11}R^{11a})$, NO_2, $OC(O)R^{11}$, $N(R^{11})C(O)R^{11a}$, $N(R^{11})S(O)_2R^{11a}$, $N(R^{11})S(O)R^{11a}$, $N(R^{11})C(O)OR^{11a}$, $N(R^{11})C(O)N(R^{11a}R^{11b})$, $OC(O)N(R^{11}R^{11a})$, oxo (=O) where the ring is at least partially saturated, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{12}, which are the same or different;

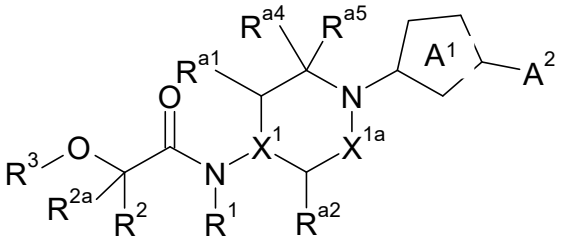
R^{11}, R^{11a}, R^{11b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

each R^{12} is independently halogen, CN, $C(O)OR^{13}$, OR^{13}, $C(O)R^{13}$, $C(O)N(R^{13}R^{13a})$, $S(O)_2N(R^{13}R^{13a})$, $S(O)N(R^{13}R^{13a})$, $S(O)_2R^{13}$, $S(O)R^{13}$, $N(R^{13})S(O)_2N(R^{13a}R^{13b})$, SR^{13}, $N(R^{13}R^{13a})$, NO_2, $OC(O)R^{13}$, $N(R^{13})C(O)R^{13a}$, $N(R^{13})SO_2R^{13a}$, $N(R^{13})S(O)R^{13a}$, $N(R^{13})C(O)N(R^{13a}R^{13b})$, $N(R^{13})C(O)OR^{13a}$, or $OC(O)N(R^{13}R^{13a})$;

R^{13}, R^{13a}, R^{13b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

together with a pharmaceutically acceptable carrier, optionally in combination with one or more other bioactive compounds or pharmaceutical compositions.

29. A compound of formula (I)



(I)

or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, wherein

X^1 is $C(R^{a6})$ or N;

X^{1a} is a covalent single bond; $CH(R^{a3})$, O, $N(R^{a7})$, or $CH(R^{a3})CH_2$;

R^{a1}, R^{a2}, R^{a3} are independently selected from the group consisting of H; halogen; OH; O-C_{1-4} alkyl; C_{1-4} alkyl; and A^{2a},
and R^{a4}, R^{a5}, R^{a6} are independently selected from the group consisting of H; halogen; C_{1-4} alkyl; and A^{2a}, provided that only one of R^{a1}, R^{a2}, R^{a3}, R^{a4}, R^{a5}, R^{a6} is A^{2a};
optionally R^{a1} and R^{a2} form a covalent single bond;
optionally R^{a2} and R^{a4} form a methylene group;
optionally R^{a4} and R^{a6} form an ethylene group;
optionally R^{a4} and R^{a5} are joined to form an oxo group;

R^{a7} is H, $C(O)OC_{1-4}$ alkyl, or C_{1-4} alkyl, wherein $C(O)OC_{1-4}$ alkyl and C_{1-4} alkyl are optionally substituted with one or more substituents selected from the group consisting of halogen, OH, and O-C_{1-3} alkyl, wherein the substituents are the same or different, preferably R^{a7} is H;

A^1 is C_5 cycloalkylene, C_5 cycloalkenylene, a nitrogen ring atom containing 5-membered heterocyclene or a 7- to 12- membered heterobicyclene, which includes a nitrogen ring atom containing 5-membered heterocycle, wherein said heterocycle is attached to the nitrogen ring atom shown in formula (I) and wherein A^1 is optionally substituted with one or more R^4, which are the same or different;

each R^4 is independently oxo (=O) where the ring is at least partially saturated, thiooxo (=S) where the ring is at least partially saturated, halogen, CN, OR^5, or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^5 is H or C_{1-6} alkyl, wherein C_{1-6} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^2 is R^{6a} or A^{2a};

R^{6a} is OR^{6a1}, SR^{6a1}, $N(R^{6a1}R^{6a2})$; C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a1}, R^{6a2} are independently selected from the group consisting of H; C_{1-6} alkyl; C_{2-6} alkenyl; C_{2-6} alkynyl; and A^{2a}, wherein C_{1-6} alkyl; C_{2-6} alkenyl; and C_{2-6} alkynyl are optionally substituted with one or more substituents selected from the group consisting of halogen; CN; OR^{6a3}; and A^{2a}, wherein the substituents are the same or different;

R^{6a3} is H; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

A^{2a} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2a} is optionally substituted with one or more R^6, which are the same or different;

each R^6 is independently R^{6b}, OH, OR^{6b}, halogen, or CN, wherein R^{6b} is cyclopropyl, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, and wherein R^{6b} is optionally substituted with one or more halogen, which are the same or different; or
two R^6 are joined to form together with the atoms to which they are attached a ring A^{2b};

A^{2b} is phenyl; or 3 to 7 membered heterocyclyl, wherein A^{2b} is optionally substituted with one or more R^7, which are the same or different;

each R^7 is independently C_{1-6} alkyl, C_{2-6} alkenyl or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

R^1 is H or C_{1-4} alkyl, preferably H, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different;

R^2 is H; F; or C_{1-4} alkyl, wherein C_{1-4} alkyl is optionally substituted with one or more halogen, which are the same or different; and

R^3 is A^3, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^8, which are the same or different; or

R^2 and R^3 are joined to form together with the oxygen atom and carbon atom to which they are attached a ring A^{3a}, wherein A^{3a} is a 7 to 12 membered heterobicyclyl, wherein 7 to 12 membered heterobicyclyl is optionally substituted with one or more R^{10}, which are the same or different;

R^{2a} is H or F, preferably H;

each R^8 is independently halogen; CN, $C(O)OR^9$, OR^9, $C(O)R^9$, $C(O)N(R^9R^{9a})$, $S(O)_2N(R^9R^{9a})$, $S(O)N(R^9R^{9a})$, $S(O)_2R^9$, $S(O)R^9$, $N(R^9)S(O)_2N(R^{9a}R^{9b})$, SR^9, $N(R^9R^{9a})$, NO_2, $OC(O)R^9$, $N(R^9)C(O)R^{9a}$, $N(R^9)SO_2R^{9a}$, $N(R^9)S(O)R^{9a}$, $N(R^9)C(O)N(R^{9a}R^{9b})$, $N(R^9)C(O)OR^{9a}$, $OC(O)N(R^9R^{9a})$, or A^3;

R^9, R^{9a}, R^{9b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different, or one OH, or one OC_{1-4} alkyl, or one A^3;

each A^3 is independently phenyl, naphthyl, 3 to 7 membered heterocyclyl, or 7 to 12 membered heterobicyclyl, wherein A^3 is optionally substituted with one or more R^{10}, which are the same or different;

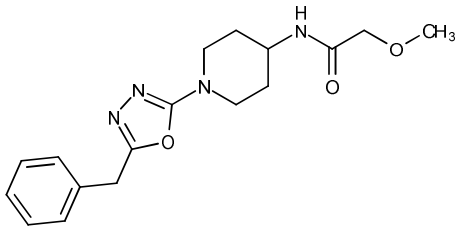
each R^{10} is independently halogen, CN, $C(O)OR^{11}$, OR^{11}, $C(O)R^{11}$, $C(O)N(R^{11}R^{11a})$, $S(O)_2N(R^{11}R^{11a})$, $S(O)N(R^{11}R^{11a})$, $S(O)_2R^{11}$, $S(O)R^{11}$, $N(R^{11})S(O)_2N(R^{11a}R^{11b})$, SR^{11}, $N(R^{11}R^{11a})$, NO_2, $OC(O)R^{11}$, $N(R^{11})C(O)R^{11a}$, $N(R^{11})S(O)_2R^{11a}$, $N(R^{11})S(O)R^{11a}$, $N(R^{11})C(O)OR^{11a}$, $N(R^{11})C(O)N(R^{11a}R^{11b})$, $OC(O)N(R^{11}R^{11a})$, oxo (=O) where the ring is at least partially saturated, C_{1-6} alkyl, C_{2-6} alkenyl, or C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more R^{12}, which are the same or different;

R^{11}, R^{11a}, R^{11b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

each R^{12} is independently halogen, CN, $C(O)OR^{13}$, OR^{13}, $C(O)R^{13}$, $C(O)N(R^{13}R^{13a})$, $S(O)_2N(R^{13}R^{13a})$, $S(O)N(R^{13}R^{13a})$, $S(O)_2R^{13}$, $S(O)R^{13}$, $N(R^{13})S(O)_2N(R^{13a}R^{13b})$, SR^{13}, $N(R^{13}R^{13a})$, NO_2, $OC(O)R^{13}$, $N(R^{13})C(O)R^{13a}$, $N(R^{13})SO_2R^{13a}$, $N(R^{13})S(O)R^{13a}$, $N(R^{13})C(O)N(R^{13a}R^{13b})$, $N(R^{13})C(O)OR^{13a}$, or $OC(O)N(R^{13}R^{13a})$;

R^{13}, R^{13a}, R^{13b} are independently selected from the group consisting of H, C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, and C_{2-6} alkynyl are optionally substituted with one or more halogen, which are the same or different;

provided that the following compounds or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof are excluded:



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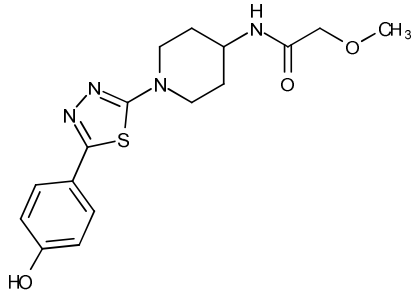

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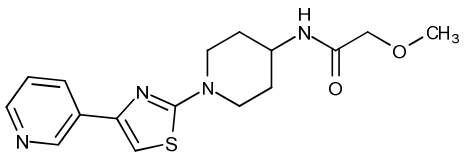

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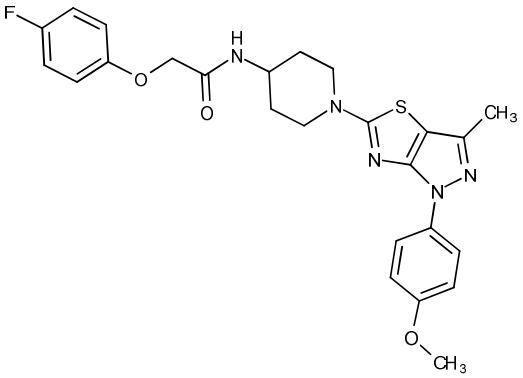

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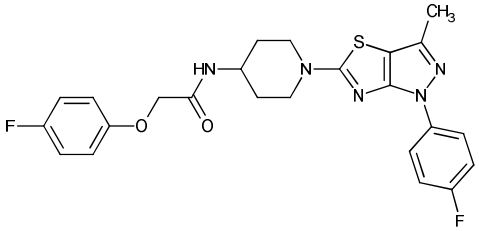

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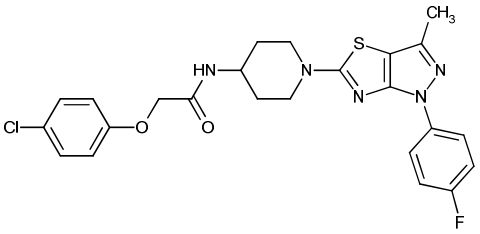

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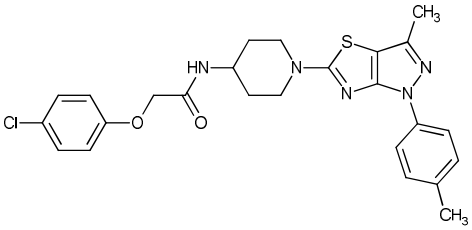

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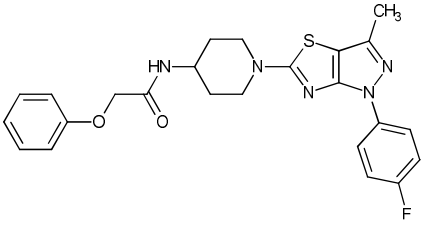

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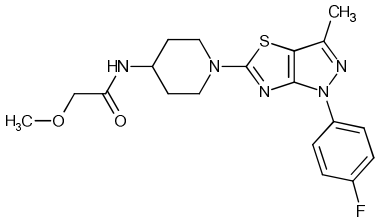

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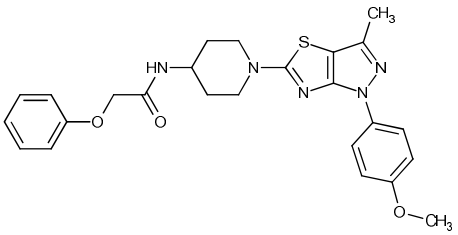

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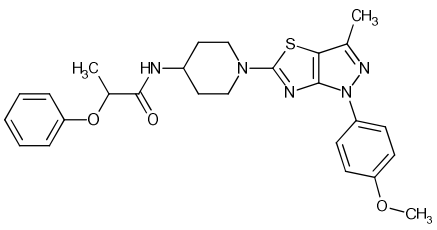

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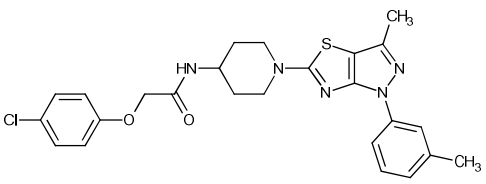

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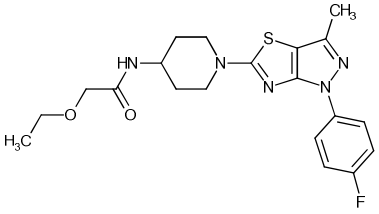

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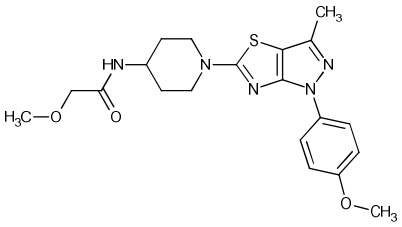

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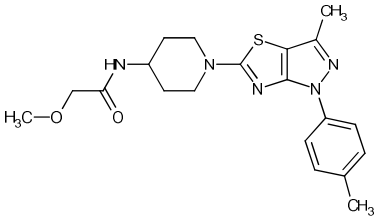

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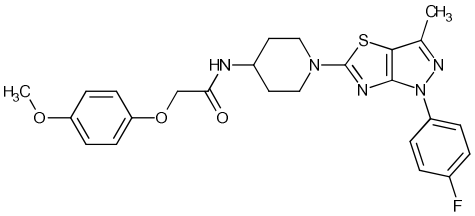

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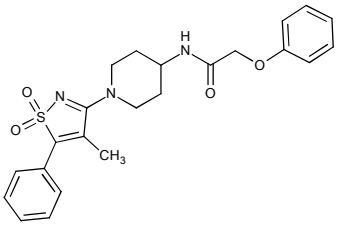

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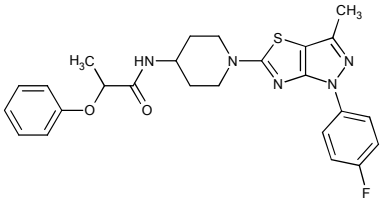

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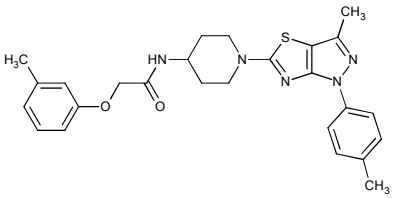

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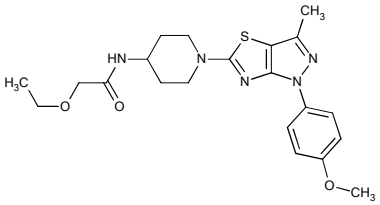

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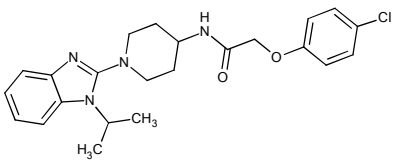

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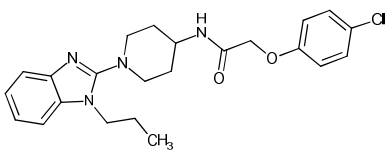

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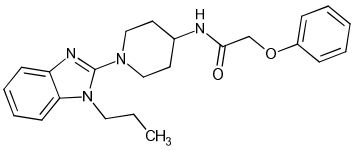

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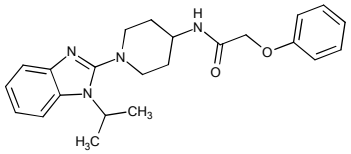

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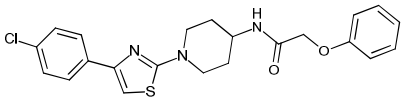

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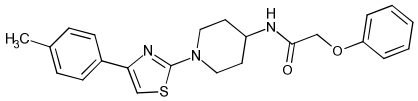

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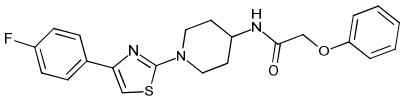

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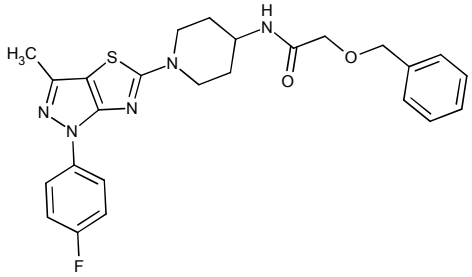

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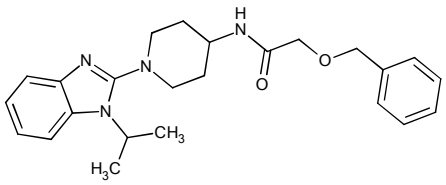

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