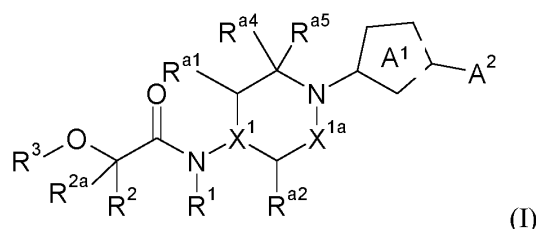


Patent Claims

1. A compound of formula (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 A¹ is optionally substituted with one or more R⁴, which are the same or different;

5 each R⁴ is independently oxo (=O) where the ring is at least partially saturated, thiooxo (=S) where the ring is at least partially saturated, halogen, CN, OR⁵, or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different;

10 R⁵ is H or C₁₋₆ alkyl, wherein C₁₋₆ alkyl is optionally substituted with one or more halogen, which are the same or different;

A² is R^{6a} or A^{2a};

15 R^{6a} is OR^{6a1}, SR^{6a1}, N(R^{6a1}R^{6a2}); C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ 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;

20 R^{6a1}, R^{6a2} are independently selected from the group consisting of H; C₁₋₆ alkyl; C₂₋₆ alkenyl; C₂₋₆ alkynyl; and A^{2a}, wherein C₁₋₆ alkyl; C₂₋₆ alkenyl; and C₂₋₆ 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;

25 R^{6a3} is H; or C₁₋₄ alkyl, wherein C₁₋₄ 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 R⁶, which are the same or different;

30

each R⁶ is independently R^{6b}, OH, OR^{6b}, halogen, or CN, wherein R^{6b} is cyclopropyl, C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl, and wherein R^{6b} is optionally substituted with one or more halogen, which are the same or different; or

two R⁶ 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 R⁷, which are the same or different;

each R⁷ is independently C₁₋₆ alkyl, C₂₋₆ alkenyl or C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are optionally substituted with one or more halogen, which are the same or different;

R¹ is H or C₁₋₄ alkyl, preferably H, wherein C₁₋₄ alkyl is optionally substituted with one or more halogen, which are the same or different;

R² is H; F; or C₁₋₄ alkyl, wherein C₁₋₄ alkyl is optionally substituted with one or more halogen, which are the same or different; and

R³ is A³, C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are optionally substituted with one or more R⁸, which are the same or different; or

R² and R³ 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 heterobicycyl, wherein 7 to 12 membered heterobicycyl is optionally substituted with one or more R¹⁰, which are the same or different;

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

each R⁸ is independently halogen; CN, C(O)OR⁹, OR⁹, C(O)R⁹, C(O)N(R⁹R^{9a}), S(O)₂N(R⁹R^{9a}), S(O)N(R⁹R^{9a}), S(O)₂R⁹, S(O)R⁹, N(R⁹)S(O)₂N(R^{9a}R^{9b}), SR⁹, N(R⁹R^{9a}), NO₂, OC(O)R⁹, N(R⁹)C(O)R^{9a}, N(R⁹)SO₂R^{9a}, N(R⁹)S(O)R^{9a}, N(R⁹)C(O)N(R^{9a}R^{9b}), N(R⁹)C(O)OR^{9a}, OC(O)N(R⁹R^{9a}), or A³;

R⁹, R^{9a}, R^{9b} are independently selected from the group consisting of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are

optionally substituted with one or more halogen, which are the same or different, or one OH, or one OC₁₋₄ alkyl, or one A³;

5 each A³ is independently phenyl, naphthyl, 3 to 7 membered heterocyclyl, or 7 to 12 membered heterobicyclyl, wherein A³ is optionally substituted with one or more R¹⁰, which are the same or different;

10 each R¹⁰ is independently halogen, CN, C(O)OR¹¹, OR¹¹, C(O)R¹¹, C(O)N(R^{11a}R^{11b}), S(O)₂N(R^{11a}R^{11b}), S(O)N(R^{11a}R^{11b}), S(O)₂R¹¹, S(O)R¹¹, N(R¹¹)S(O)₂N(R^{11a}R^{11b}), SR¹¹, N(R^{11a}R^{11b}), NO₂, OC(O)R¹¹, N(R¹¹)C(O)R^{11a}, N(R¹¹)S(O)₂R^{11a}, N(R¹¹)S(O)R^{11a}, N(R¹¹)C(O)OR^{11a}, N(R¹¹)C(O)N(R^{11a}R^{11b}), OC(O)N(R^{11a}R^{11b}), oxo (=O) where the ring is at least partially saturated, C₁₋₆ alkyl, C₂₋₆ alkenyl, or C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are optionally substituted with one or more R¹², which are the same or different;

15 R¹¹, R^{11a}, R^{11b} are independently selected from the group consisting of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are optionally substituted with one or more halogen, which are the same or different;

20 each R¹² is independently halogen, CN, C(O)OR¹³, OR¹³, C(O)R¹³, C(O)N(R^{13a}R^{13b}), S(O)₂N(R^{13a}R^{13b}), S(O)N(R^{13a}R^{13b}), S(O)₂R¹³, S(O)R¹³, N(R¹³)S(O)₂N(R^{13a}R^{13b}), SR¹³, N(R^{13a}R^{13b}), NO₂, OC(O)R¹³, N(R¹³)C(O)R^{13a}, N(R¹³)SO₂R^{13a}, N(R¹³)S(O)R^{13a}, N(R¹³)C(O)N(R^{13a}R^{13b}), N(R¹³)C(O)OR^{13a}, or OC(O)N(R^{13a}R^{13b});

25 R¹³, R^{13a}, R^{13b} are independently selected from the group consisting of H, C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl, wherein C₁₋₆ alkyl, C₂₋₆ alkenyl, and C₂₋₆ alkynyl are optionally substituted with one or more halogen, which are the same or different.

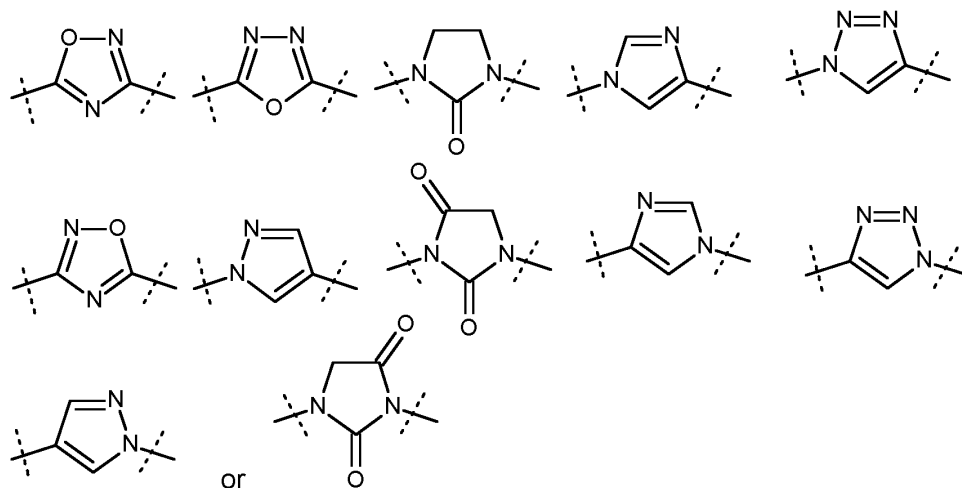
30 2. The compound of claim 1 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein X¹ is CH.

3. The compound of claim 1 or 2 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein X^{1a} is a covalent

single bond; $\text{CH}(\text{R}^{\text{a}3})$, or $\text{CH}(\text{R}^{\text{a}3})\text{CH}_2$, preferably $\text{CH}(\text{R}^{\text{a}3})$ or $\text{CH}(\text{R}^{\text{a}3})\text{CH}_2$, more preferably $\text{CH}(\text{R}^{\text{a}3})$.

4. The compound of any one of claims 1 to 3 or a pharmaceutically acceptable salt,
5 solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein $\text{R}^{\text{a}1}$, $\text{R}^{\text{a}2}$, $\text{R}^{\text{a}3}$, $\text{R}^{\text{a}4}$, $\text{R}^{\text{a}5}$, $\text{R}^{\text{a}6}$ are H; or $\text{R}^{\text{a}1}$ is OH and $\text{R}^{\text{a}2}$, $\text{R}^{\text{a}3}$, $\text{R}^{\text{a}4}$, $\text{R}^{\text{a}5}$, $\text{R}^{\text{a}6}$ are H; or $\text{R}^{\text{a}1}$, $\text{R}^{\text{a}3}$, $\text{R}^{\text{a}5}$, $\text{R}^{\text{a}6}$ are H and $\text{R}^{\text{a}2}$ and $\text{R}^{\text{a}4}$ form a methylene group; or $\text{R}^{\text{a}1}$ and $\text{R}^{\text{a}2}$ form a covalent single bond and $\text{R}^{\text{a}3}$, $\text{R}^{\text{a}4}$, $\text{R}^{\text{a}5}$, $\text{R}^{\text{a}6}$ are H.
- 10 5. The compound of any one of claims 1 to 4 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein $\text{R}^{\text{a}1}$, $\text{R}^{\text{a}2}$, $\text{R}^{\text{a}3}$, $\text{R}^{\text{a}4}$, $\text{R}^{\text{a}5}$, $\text{R}^{\text{a}6}$ are H.
- 15 6. The compound of any one of claims 1 to 5 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, 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.
- 20 7. The compound of any one of claims 1 to 6 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, 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.
- 25 8. The compound of any one of claims 1 to 7 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein A^1 is unsubstituted or substituted with one or two R^4 , which are the same or different, preferably A^1 is unsubstituted.
- 30 9. The compound of any one of claims 1 to 7 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein R^4 is oxo where the ring is at least partly saturated, or methyl.

10. The compound of any one of claims 1 to 9 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein A¹ is



5

11. The compound of any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein A² is R^{6a}.

10

12. The compound of claim 11 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein R^{6a} is OR^{6a1} and R^{6a1} is preferably A^{2a} or C₁₋₆ alkyl, optionally substituted with one or more halogen and/or one A^{2a} and/or one OR^{6a3}; or R^{6a} is C₁₋₆ alkyl, optionally substituted with one or more halogen and/or one A^{2a} and/or one OR^{6a3}.

15

13. The compound of claim 11 or 12 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein R^{6a} is OR^{6a1} and R^{6a1} is preferably C₁₋₆ alkyl, optionally substituted with one or more F and/or one OR^{6a3}; or R^{6a} is C₁₋₆ alkyl, optionally substituted with one or more halogen and/or one OR^{6a3}.

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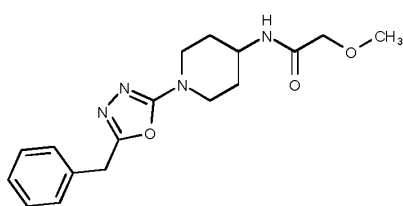
14. The compound of any one of claims 1 to 10 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein A² is A^{2a}.
- 5 15. The compound of claim 14 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, 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 R⁶, which are the same or different.
- 10 16. The compound of any one of claims 1 to 10, 14 and 15 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein A^{2a} is substituted with one or two R⁶, which are the same or different.
- 15 17. The compound of any one of claims 1 to 10, 14 to 16 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein each R⁶ is independently F, Cl, CF₃, OCH₃, OCF₃, CH₃, CH₂CH₃, or cyclopropyl.
- 20 18. The compound of any one of claims 1 to 17 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein R² is H.
- 25 19. The compound of any one of claims 1 to 18 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein R³ is A³.
- 30 20. The compound of any one of claims 1 to 19 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein A³ is phenyl, pyridyl, pyrazinyl or pyrimidazyl and wherein A³ is optionally substituted with one or more R¹⁰, which are the same or different.

21. The compound of any one of claims 1 to 20 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein A³ is substituted with one or two R¹⁰, which are the same or different.
- 5 22. The compound of any one of claims 1 to 17 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein R² and R³ 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 R¹⁰, which are the same or different, preferably the ring is substituted with one
10 or two R¹⁰.
23. The compound of any one of claims 1 to 22 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein R¹⁰ is independently F, Cl, CF₃, CH=O, CH₂OH or CH₃.
- 15 24. The compound of any one of claims 1 to 23 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof for use as a medicament, wherein the compound is
- 20 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;
25 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;
30 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;

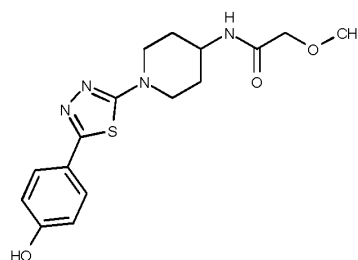
- 2-(4-Chloro-3-fluorophenoxy)-*N*-{1-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]azepan-4-yl}acetamide;
- 2-(4-Chloro-3-fluorophenoxy)-*N*-[(3*R*,4*R*)-1-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-3-hydroxypiperidin-4-yl]acetamide;
- 5 2-(4-Chloro-3-fluorophenoxy)-*N*-[(3*S*,4*S*)-1-[5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl]-3-hydroxypiperidin-4-yl]acetamide;
- 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;
- 10 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.
- 15
25. A pharmaceutical composition comprising at least one compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof as defined in any one of claims 1 to 24 together with a pharmaceutically acceptable carrier, optionally in combination with one or more other bioactive compounds or pharmaceutical compositions.
- 20
26. A compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof as defined in any one of claims 1 to 24 for use in a method of treating or preventing of one or more diseases or disorders associated with integrated stress response.
- 25
27. A compound or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof as defined in any one of claims 1 to 24 for use in a method of 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
- 30

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.

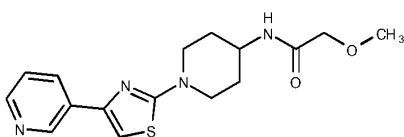
28. A compound as defined in any one of claims 1 to 24 or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof, provided that the following compounds or a pharmaceutically acceptable salt, solvate, hydrate, tautomer or stereoisomer thereof are excluded:



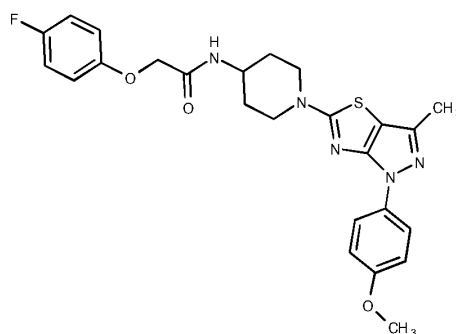
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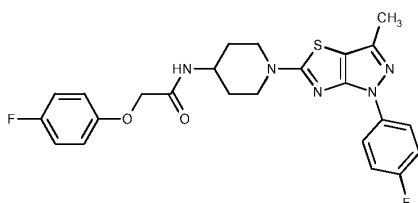
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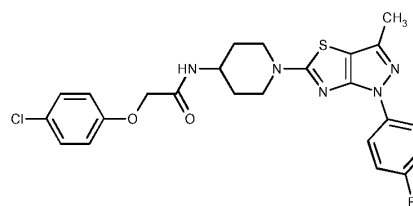
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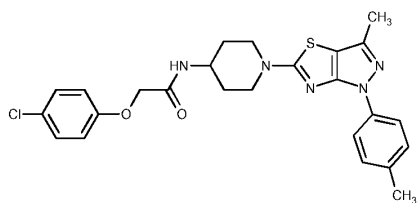
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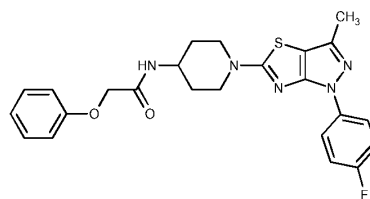
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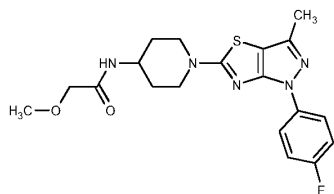
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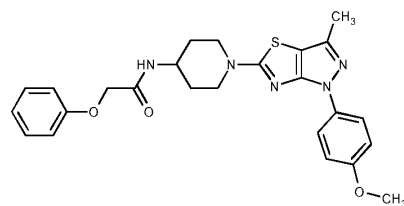
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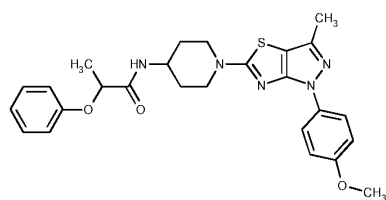
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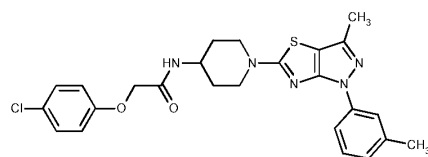
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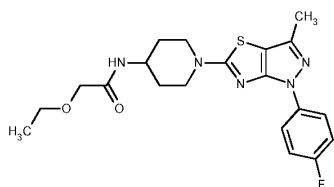
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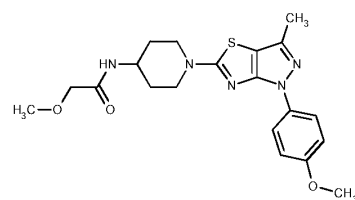
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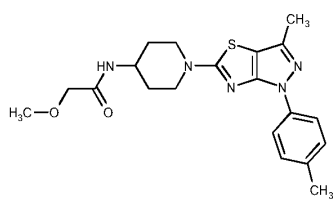
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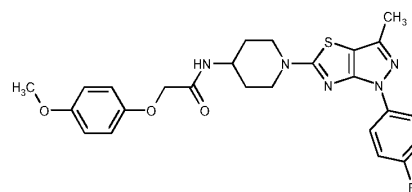
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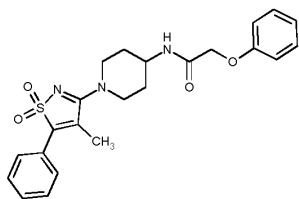
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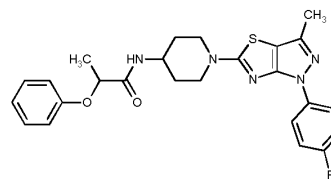
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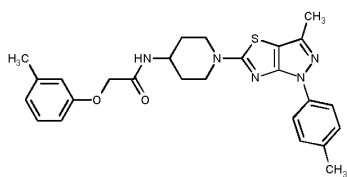
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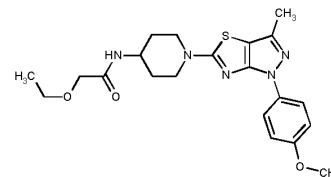
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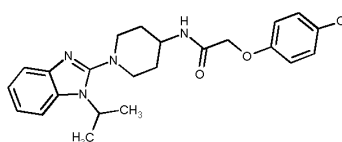
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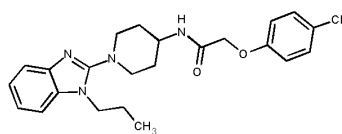
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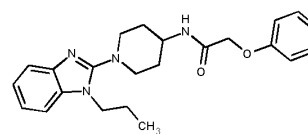
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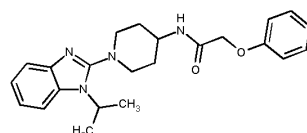
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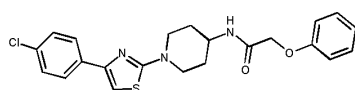
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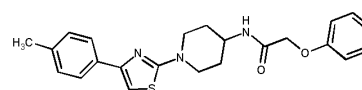
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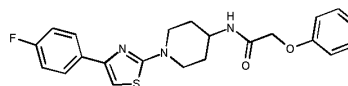
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CAS 878694-03-2,



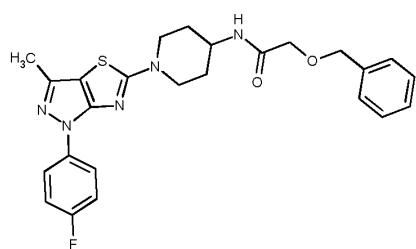
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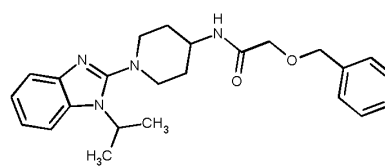
CAS 878693-72-2,

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CAS 1358737-82-2, and



CAS 1047557-93-6.