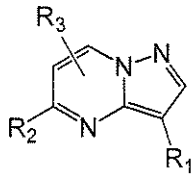
inhibition of AAK1 activity may have utility in the treatment of schizophrenia, cognitive deficits in schizophrenia, Parkinson's disease, bipolar disorder, and Alzheimer's disease.

3. SUMMARY ~~OF THE INVENTION~~

This ~~invention~~ disclosure is directed, in part, to AAK1 inhibitors of the formula:



and pharmaceutically acceptable salt thereof, wherein: R_1 is R_{1A} or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1A}; each R_{1A} is independently -OR_{1C}, $-N(R_{1C})_2$, -$C(O)R_{1C}$, -$C(O)OR_{1C}$, -$C(O)N(R_{1C})_2$, -$N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B}; each R_{1B} is independently -OR_{1C}, $-N(R_{1C})_2$, -$C(O)R_{1C}$, -$C(O)OR_{1C}$, -$C(O)N(R_{1C})_2$, -$N(R_{1C})C(O)OR_{1C}$, cyano or halo; each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; R_2 is $-NR_{2A}R_{2B}$, wherein R_{2A} is hydrogen and R_{2B} is optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{2C}; or R_{2A} and R_{2B} are taken together to form a 4-7-membered heterocycle optionally substituted with one or more R_{2C}; each R_{2C} is independently $-OR_{2D}$, $-N(R_{2D})_2$, -$C(O)R_{2D}$, -$C(O)OR_{2D}$, -$C(O)N(R_{2D})_2$, -$N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more R_{2D}; each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl; and R_3 is hydrogen or C_{1-6} alkyl optionally substituted with one or more of cyano, halo or hydroxyl.

One embodiment of the ~~invention~~ disclosure encompasses pharmaceutical compositions and dosage forms comprising a compound disclosed herein (*i.e.*, a compound of the ~~invention~~disclosure).

Another embodiment of this ~~invention~~ disclosure encompasses methods of inhibiting adaptor associated kinase 1 (AAK1), both *in vitro* and *in vivo*, which comprise contacting AAK1 with a compound ~~offe~~ the ~~invention~~disclosure.

In one aspect, there is provided a method of inhibiting adaptor associated kinase 1 (AAK1) activity, comprising contacting AAK1 with a compound of the formula:

or a pharmaceutically acceptable salt thereof, wherein:

R_1 is R_{1A} or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1A};

each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B};

each R_{1B} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano or halo;

each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl;

R_2 is $-NR_{2A}R_{2B}$, wherein R_{2A} is hydrogen and R_{2B} is optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{2C};

or R_{2A} and R_{2B} are taken together to form a 4-7-membered heterocycle optionally substituted with one or more R_{2C};

each R_{2C} is independently $-OR_{2D}$, $-N(R_{2D})_2$, $-C(O)R_{2D}$, $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, $-N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more amino, cyano, halo, hydroxyl, or R_{2D};

each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more amino, cyano, halo, or hydroxyl; and

R_3 is hydrogen or C_{1-6} alkyl optionally substituted with one or more cyano, halo or hydroxyl.

In one aspect, there is provided the use of a therapeutically effective amount of a compound of the formula:

or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or managing a disease or disorder mediated by AAK1 activity, wherein:

R_1 is R_{1A} or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1A};

each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B};

each R_{1B} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano or halo;

each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more cyano, halo or hydroxyl;

R_2 is $-NR_{2A}R_{2B}$, wherein R_{2A} is hydrogen and R_{2B} is optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{2C};

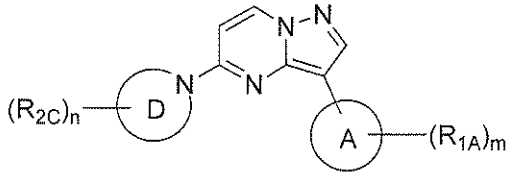
or R_{2A} and R_{2B} are taken together to form a 4-7-membered heterocycle optionally substituted with one or more R_{2C};

each R_{2C} is independently $-OR_{2D}$, $-N(R_{2D})_2$, $-C(O)R_{2D}$, $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, $-N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more amino, cyano, halo, hydroxyl, or R_{2D};

each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more amino, cyano, halo, or hydroxyl; and

R_3 is hydrogen or C_{1-6} alkyl optionally substituted with one or more of cyano, halo or hydroxyl.

In one aspect, there is provided a compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is cyclic C_{1-12} hydrocarbyl or 4-7-membered heterocycle;

D is 4-7-membered heterocycle;

each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B};

each R_{1B} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano or halo;

each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl;

each R_{2C} is independently $-OR_{2D}$, $-N(R_{2D})_2$, $-C(O)R_{2D}$, $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, $-N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more amino, cyano, halo, hydroxyl, or R_{2D};

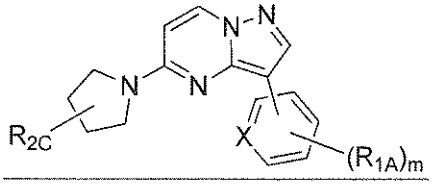
each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of amino, cyano, halo, hydroxyl;

n is 1-3; and

m is 0-3;

with the proviso that when D is piperidinyl, A is phenyl, and R_{2C} is $-N(R_{2D})_2$, R_{2D} is not ethyl.

In one aspect, there is provided a compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

X is CH or N;

each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B};

each R_{1B} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano or halo;

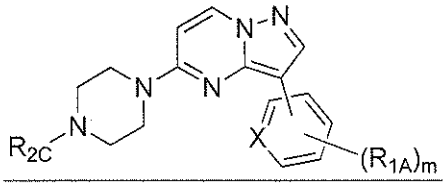
each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl;

each R_{2C} is independently $-OR_{2D}$, $-N(R_{2D})_2$, $-C(O)R_{2D}$, $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, $-N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more amino, cyano, halo, hydroxyl, or R_{2D};

each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of amino, cyano, halo, or hydroxyl; and

m is 0-3.

In one aspect, there is provided a compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

X is CH or N;

each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B};

each R_{1B} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano or halo;

each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl;

each R_{2C} is independently $-OR_{2D}$, $-N(R_{2D})_2$, $-C(O)R_{2D}$, $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, $-N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more amino, cyano, halo, hydroxyl, or R_{2D};

each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of amino, cyano, halo, hydroxyl; and

m is 0-3.

In one aspect, there is provided a pharmaceutical composition comprising a compound as described above and a pharmaceutically acceptable excipient or diluent.

In one aspect, there is provided method of inhibiting AAK1 activity, which comprises contacting AAK1 with a compound as described above.

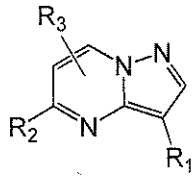
In one aspect, there is provided the use of a therapeutically effective amount of a compound as described above, or a pharmaceutical composition as described above in the manufacture of a medicament for treating or managing a disease or disorder mediated by AAK1 activity.

Another embodiment encompasses methods of treating and managing diseases and disorders mediated by AAK1 activity. Examples of such diseases and disorders are believed to include Alzheimer's disease, bipolar disorder, pain, Parkinson's disease, and schizophrenia (including cognitive deficits in schizophrenia).

CLAIMS

What is claimed is:

1. A method of inhibiting adaptor associated kinase 1 (AAK1) activity, comprising contacting AAK1 with a compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

R_1 is R_{1A} or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1A};

each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B};

each R_{1B} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, cyano or halo;

each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl;

R_2 is $-NR_{2A}R_{2B}$, wherein R_{2A} is hydrogen and R_{2B} is optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{2C};

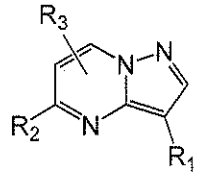
or R_{2A} and R_{2B} are taken together to form a 4-7-membered heterocycle optionally substituted with one or more R_{2C};

each R_{2C} is independently $-OR_{2D}$, $-N(R_{2D})_2$, $-C(O)R_{2D}$, $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, $-N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more amino, cyano, halo, hydroxyl, or R_{2D};

each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more amino, cyano, halo, or hydroxyl; and

R_3 is hydrogen or C_{1-6} alkyl optionally substituted with one or more cyano, halo or hydroxyl.

2. ~~A method of treating or managing a disease or disorder mediated by AAK1 activity, which comprises administering to a patient in need thereof~~Use of a therapeutically effective amount of a compound of the formula:



or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or managing a disease or disorder mediated by AAK1 activity, wherein:

R_1 is R_{1A} or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1A};

each R_{1A} is independently -OR_{1C}, -$N(R_{1C})_2$, -$C(O)R_{1C}$, -$C(O)OR_{1C}$, -$C(O)N(R_{1C})_2$, -$N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B};

each R_{1B} is independently -OR_{1C}, -$N(R_{1C})_2$, -$C(O)R_{1C}$, -$C(O)OR_{1C}$, -$C(O)N(R_{1C})_2$, -$N(R_{1C})C(O)OR_{1C}$, cyano or halo;

each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more cyano, halo or hydroxyl;

R_2 is -$NR_{2A}R_{2B}$, wherein R_{2A} is hydrogen and R_{2B} is optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{2C};

or R_{2A} and R_{2B} are taken together to form a 4-7-membered heterocycle optionally substituted with one or more R_{2C};

each R_{2C} is independently -OR_{2D}, -$N(R_{2D})_2$, -$C(O)R_{2D}$, -$C(O)OR_{2D}$, -$C(O)N(R_{2D})_2$, -$N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more amino, cyano, halo, hydroxyl, or R_{2D};

each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more amino, cyano, halo, or hydroxyl; and

R_3 is hydrogen or C_{1-6} alkyl optionally substituted with one or more of cyano, halo or hydroxyl.

3. The ~~method~~ use of claim 2, wherein the disease or disorder is Alzheimer's disease, bipolar disorder, pain, Parkinson's disease, or schizophrenia.

4. The ~~method~~ use of claim 3, wherein the pain is neuropathic pain.

5. The ~~method~~ use of claim 4, wherein the neuropathic pain is fibromyalgia or peripheral neuropathy (*e.g.*, diabetic neuropathy).

6. The method of claim 1 or use of any of ~~the preceding~~ claims 2-5, wherein R_1 is R_{1A}.

7. The method of claim 1 or use of any of ~~the preceding~~ claims 2-5 or method or use of claim 6, wherein R_1 is optionally substituted C_{1-12} hydrocarbyl.

8. The method or use of claim 7, wherein R_1 is optionally substituted phenyl.

9. The method of claim 1 or use of any of ~~the preceding~~ claims 2-5 or method or use of any of claims 6-8, wherein R_1 is optionally substituted 2-12-membered heterocarbyl (*e.g.*, 2-8 membered heterocarbyl, 2-6 membered heterocarbyl, 2-6 membered heterocarbyl).

10. The method or use of claim 9, wherein R_1 is optionally substituted pyridinyl, thiophen, or imidazol.

11. The method of claim 1 or use of any of claims 2-5 or method or use of any of ~~the preceding~~ claims 6-10, wherein R_{1A} is halo.

12. The method of claim 1 or use of any of claims 2-5 or method or use of any of ~~the preceding~~ claims 6-11, wherein R_{1A} is $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, or $-C(O)N(R_{1C})_2$.

13. The method of claim 1 or use of any of claims 2-5 or method or use of any of ~~the preceding~~ claims 6-12, wherein R_{1A} is $-OR_{1C}$.

14. The method of claim 1 or use of any of claims 2-5 or method or use of any of ~~the preceding~~ claims 6-13, wherein R_{1B} is $-N(R_{1C})_2$, $-OR_{1C}$, halo.

15. The method of claim 1 or use of claim 2, wherein or R_{2A} and R_{2B} are taken together to form a 4-7-membered heterocycle optionally substituted with one or more R_{2C}.

16. The method of claim 1 or use of any of claims 2-5 or method or use of any of ~~the preceding~~ claims 6-15, wherein R_{1C} is hydrogen.

17. The method of claim 1 or use of any of claims 2-5 or method or use of any of ~~the preceding~~ claims 6-16, wherein R_{1C} is C_{1-12} hydrocarbyl (*e.g.*, C_{1-6} hydrocarbyl, C_{1-4} hydrocarbyl such as methyl, ethyl, propyl).

18. The method of claim 1 or use of any of claims 2-5 or method or use of any of ~~the preceding~~ claims 6-17, wherein R_{2C} is $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, or $-N(R_{2D})C(O)OR_{2D}$.

19. The method of claim 1 or use of any of claims 2-5 or method or use of any of ~~the preceding~~ claims 6-18, wherein R_{2C} is $-C(O)R_{2D}$.

20. The method of claim 1 or use of any of claims 2-5 or method or use of any of ~~the preceding~~ claims 6-19, wherein R_{2D} is hydrogen.

21. The method of claim 1 or use of any of claims 2-5 or method or use of any of ~~the preceding~~ claims 6-20, wherein R_{2D} is C_{1-12} hydrocarbyl (*e.g.*, C_{1-6} hydrocarbyl, C_{1-4} hydrocarbyl such as methyl, ethyl, propyl).

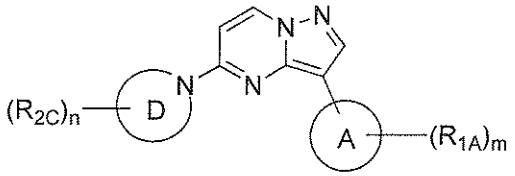
22. The method of claim 1 or use of any of claims 2-5 or method or use of any of ~~the preceding~~ claims 6-21, wherein R_{2D} is 2-12-membered heterocarbyl comprising at least one nitrogen atom.

23. The method of claim 1 or use of any of claims 2-5 or method or use of any of ~~the preceding~~ claims 6-22, wherein at least one R_{2D} is optionally substituted C_{1-12} hydrocarbyl, which optional substitution is with one or more of amino, cyano, halo, hydroxyl.

24. The method of claim 1 or use of any of claims 2-5 or method or use of any of ~~the preceding~~ claims 6-23, wherein R_{2D} is 2-12-membered heterocarbyl comprising at least one nitrogen atom.

25. The method of claim 1 or use of any of claims 2-5 or method or use of any of ~~the preceding~~ claims 6-24, wherein R_3 is hydrogen.

26. The method of claim 1 or use of claim 2, wherein the compound is of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

A is cyclic C_{1-12} hydrocarbyl or 4-7-membered heterocycle;

D is 4-7-membered heterocycle;

each R_{1A} is independently -OR_{1C}, -$N(R_{1C})_2$, -$C(O)R_{1C}$, -$C(O)OR_{1C}$, -$C(O)N(R_{1C})_2$, -$N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B};

each R_{1B} is independently -OR_{1C}, -$N(R_{1C})_2$, -$C(O)R_{1C}$, -$C(O)OR_{1C}$, -$C(O)N(R_{1C})_2$, -$N(R_{1C})C(O)OR_{1C}$, cyano or halo;

each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl;

each R_{2C} is independently -OR_{2D}, -$N(R_{2D})_2$, -$C(O)R_{2D}$, -$C(O)OR_{2D}$, -$C(O)N(R_{2D})_2$, -$N(R_{2D})C(O)OR_{2D}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more with one or more amino, cyano, halo, hydroxyl, or R_{2D};

each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of amino, cyano, halo, or hydroxyl;

n is 1-3; and

m is 0-3.

27. The method or use of claim 26, with the provision that D is not piperidinyl.

28. The method or use of claim 26, with the provision that R_{2C} is not -$N(R_{2D})_2$.

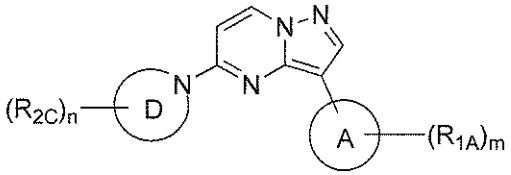
29. The method or use of claim 26, with the provision that A is not phenyl.

30. The method or use of claim 26, with the provision that m is 1.

31. The method or use of claim 26, with the provision that m is 2.

32. The method or use of claim 26, with the provision that R_{2D} is not ethyl.

33. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

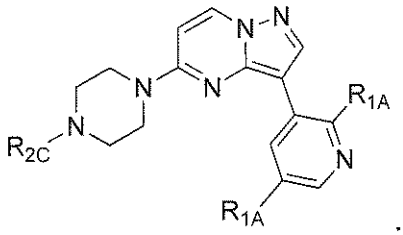
A is cyclic C_{1-12} hydrocarbyl or 4-7-membered heterocycle;

D is 4-7-membered heterocycle;

each R_{1A} is independently -OR_{1C}, -$N(R_{1C})_2$, -$C(O)R_{1C}$, -$C(O)OR_{1C}$, -$C(O)N(R_{1C})_2$, -$N(R_{1C})C(O)OR_{1C}$, cyano, halo, or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1B};

each R_{1B} is independently -OR_{1C}, -$N(R_{1C})_2$, -$C(O)R_{1C}$, -$C(O)OR_{1C}$, -$C(O)N(R_{1C})_2$, -$N(R_{1C})C(O)OR_{1C}$, cyano or halo;

49. The compound of claim 47, which is of the formula:



50. The compound of any of claims 33-49, wherein at least one R_{1A} is halo.

51. The compound of any of claims 33-49, wherein at least one R_{1A} is $-OR_{1C}$.

52. The compound of claim 51, wherein R_{1C} is optionally substituted C_{1-12} hydrocarbyl (*e.g.*, C_{1-6} hydrocarbyl, C_{1-4} hydrocarbyl).

53. The compound of any of claims 33-49, wherein R_{2C} is $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, or $-N(R_{2D})C(O)OR_{2D}$.

54. The compound of any of claims 33-49, wherein R_{2C} is $-C(O)R_{2D}$.

55. The compound of claim 53 or 54, wherein each R_{2D} is independently hydrogen or C_{1-12} hydrocarbyl (*e.g.*, C_{1-6} hydrocarbyl, C_{1-4} hydrocarbyl).

56. The compound of claim 53 or 54, wherein at least one R_{2D} is optionally substituted C_{1-12} hydrocarbyl, which optional substitution is with one or more of amino, cyano, halo, hydroxyl.

57. The compound of claim 53 or 54, wherein R_{2D} is 2-12-membered heterocarbyl comprising at least one nitrogen atom.

58. A pharmaceutical composition comprising a compound of any of claims 33-57 and a pharmaceutically acceptable excipient or diluent.

59. A method of inhibiting AAK1 activity, which comprises contacting AAK1 with a compound of any of claims 33-57.

60. ~~A method of treating or managing a disease or disorder mediated by AAK1 activity, which comprises administering to a patient in need thereof a~~ Use of a therapeutically effective amount of a compound of any of claims 33-57, or a pharmaceutical composition of claim 58 in the manufacture of a medicament for treating or managing a disease or disorder mediated by AAK1 activity.

61. The ~~method~~ use of claim 60, wherein the disease or disorder is Alzheimer's disease, bipolar disorder, pain, Parkinson's disease, or schizophrenia.

62. The ~~method~~ use of claim 61, wherein the pain is neuropathic pain.

63. The ~~method~~ use of claim 62, wherein the neuropathic pain is fibromyalgia or peripheral neuropathy (*e.g.*, diabetic neuropathy).