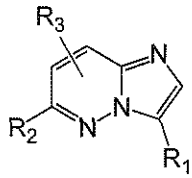
inhibition of AAK1 activity may have utility in the treatment of schizophrenia, cognitive deficits in schizophrenia, Parkinson's disease, bipolar disorder, and Alzheimer's disease.

3. SUMMARY

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

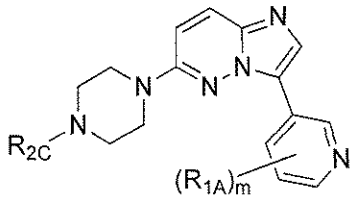


and pharmaceutically acceptable salt thereof, wherein: R_1 is R_{1A} or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more R_{1A}; each R_{1A} is independently $-OR_{1C}$, $-N(R_{1C})_2$, $-C(O)R_{1C}$, $-C(O)OR_{1C}$, $-C(O)N(R_{1C})_2$, $-N(R_{1C})C(O)OR_{1C}$, 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 disclosure encompasses pharmaceutical compositions and dosage forms comprising a compound disclosed herein (*i.e.*, a compound of the disclosure).

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

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



or a pharmaceutically acceptable salt thereof, wherein:

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;

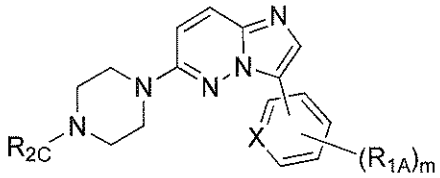
each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl;

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 another 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;

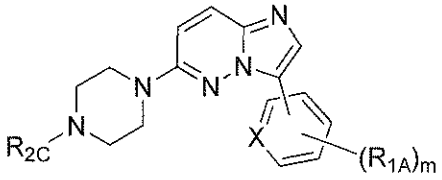
each R_{2C} is independently -$C(O)OR_{2D}$, -$C(O)N(R_{2D})_2$, or -$N(R_{2D})C(O)OR_{2D}$, which optional substitution is with one or more with one or more amino, cyano, halo, hydroxyl, or R_{2D};

R_{2D} is 2-12-membered heterocarbyl comprising at least one nitrogen atom; and

m is 0-3;

with the proviso that when X is CH, m is 1 and R_{1A} is chloro, R_{2D} is not t-butyl.

In yet another 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 -$C(O)R_{2D}$;

each R_{2D} is 2-12-membered heterocarbyl comprising at least one nitrogen atom; and

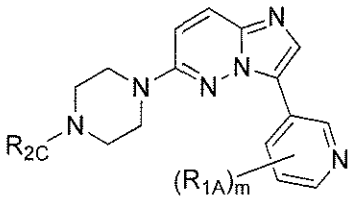
m is 0-3;

with the proviso that when X is CH, m is 1 and R_{1A} is chloro, R_{2D} is not t-butyl.

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

1. A compound of the formula:



or a pharmaceutically acceptable salt thereof, wherein:

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;

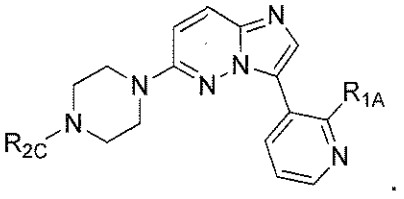
each R_{1C} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of cyano, halo or hydroxyl;

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};

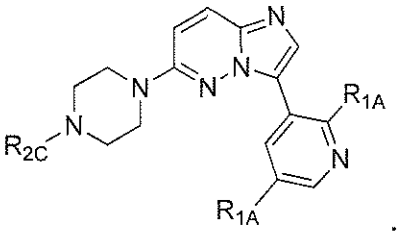
each R_{2D} is independently hydrogen or optionally substituted C_{1-12} hydrocarbyl or 2-12-membered heterocarbyl, which optional substitution is with one or more of amino, cyano, halo, hydroxyl; and

m is 0-3.

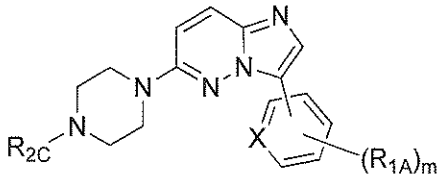
2. The compound of claim 1, which is of the formula:



3. The compound of claim 1, which is of the formula:



4. 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;

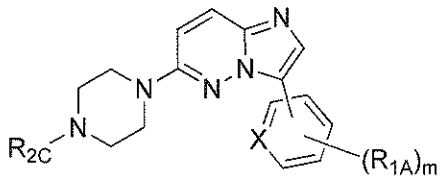
each R_{2C} is independently $-C(O)OR_{2D}$, $-C(O)N(R_{2D})_2$, or $-N(R_{2D})C(O)OR_{2D}$, which optional substitution is with one or more with one or more amino, cyano, halo, hydroxyl, or R_{2D};

R_{2D} is 2-12-membered heterocarbyl comprising at least one nitrogen atom; and

m is 0-3;

with the proviso that when X is CH, m is 1 and R_{1A} is chloro, R_{2D} is not t-butyl.

5. 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 $-C(O)R_{2D}$;

each R_{2D} is 2-12-membered heterocarbyl comprising at least one nitrogen atom; and

m is 0-3;

with the proviso that when X is CH, m is 1 and R_{1A} is chloro, R_{2D} is not t-butyl.