cognitive deficits in schizophrenia, Parkinson's disease, neuropathic pain, bipolar disorder, and Alzheimer's disease.

In addition, studies using Huh-7.5 cells indicate a potential utility for AAK1 kinase inhibitors in the treatment of hepatitis C (HCV) infection. Reduction of AAK1 protein using RNA interference mediated gene silencing, treatment with the kinase inhibitor sunitinib (a potent AAK1 inhibitor), and overexpression of Mu2 (AAK1 substrate) phosphorylation site mutant all result in reduced HCV virion assembly. Furthermore, the same treatments were shown to inhibit HCV entry, suggesting AAK1 inhibitors can disrupt two host dependent stages of the virus life cycle (Neveu *et al.*, PLoS Pathog. 2012, 8, 1-16; Neveu *et al.*, J. Virol. 2015, posted online 4 February). AAK1 inhibitors may also be useful against HIV and HBV (*See, e.g.,* Boge *et al.*, J. Biol. Chem. 1998, 273, 15773-15778).

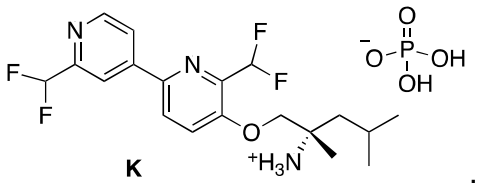
A number of AAK1 inhibitors have disclosed in the literature. *See, e.g.,* Hartz, R.A., *et al.*, J. Med. Chem., 2021 Aug 12;64(15):11090-11128. One example is the specific AAK1 inhibitor (*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine, which has been prepared on a small, laboratory scale. *See, e.g.,* U.S. patent no. 9,902,722. Unfortunately, synthetic approaches useful in the laboratory setting are rarely suitable for large-scale manufacture of pharmaceutically acceptable material. For example, the creation of potentially harmful reaction byproducts needs to be minimized, and the use of toxic solvents and reagents are preferably avoided. Moreover, reaction conditions that may work on a gram scale are often inefficient or even dangerous when scaled up.

Similarly, solid forms of a compound that may be sufficient for pre-clinical testing (*e.g.*, amorphous forms), are not necessarily suitable for large scale manufacture and storage. Some forms may be more stable than others. For example, some forms may decompose more readily when exposed to heat or moisture; others may change to forms having different pharmacological properties (*e.g.*, bioavailability) than the original. Some may have solubility profiles that render formulation difficult; others may be more difficult to obtain without impurities that could affect their safety when administered to patients. Consequently, a need exists for solid forms of (*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine, or pharmaceutically acceptable salts thereof, that can be prepared in commercially useful quantities, are stable, and are readily formulated into safe and effective dosage forms.

3 SUMMARY

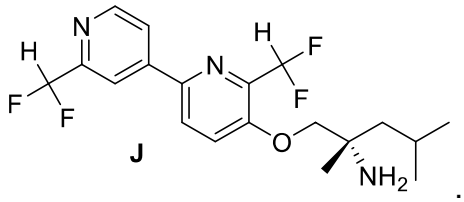
This application is directed to solid forms of the adaptor associated kinase 1 (AAK1) inhibitor (*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J) and salts thereof.

A particular aspect of this invention encompasses solid forms of ((*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-aminium dihydrogen phosphate (Compound K):



K

In another aspect, there is provided a composition comprising an active pharmaceutical ingredient (API), an excipient, and a lubricant, wherein the API is a crystalline compound, which compound is a pharmaceutically acceptable salt of (*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



J

In another aspect, there is provided a tablet comprising the composition as defined above.

In another aspect, there is provided the use of a compound as defined above in the manufacture of a medicament for treating or managing pain.

In another aspect, there is provided the use of a formulation as defined above in the manufacture of a medicament for treating or managing pain.

In another aspect, there is provided a compound as defined above or a formulation as defined above in therapy.

Other embodiments of the disclosure encompass methods of preparing Compound K and pharmaceutical compositions comprising it. This disclosure also encompasses methods of its use to treat or manage diseases and disorders, including pain (*e.g.*, neuropathic pain) and viral infections.

4 BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 provides a representative X-ray powder diffraction (XRPD) pattern of crystalline solid form I of ((*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-aminium dihydrogen phosphate (Compound K). The spectrum was obtained using a Bruker X-ray diffractometer with a LYNXEYE detector (copper Kα radiation).

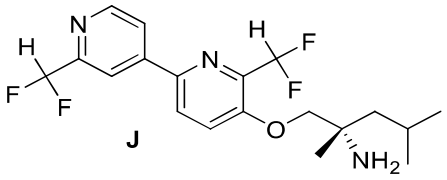
FIG. 2 provides a representative differential scanning calorimetry (DSC) thermogram of a crystalline solid form of Compound K. The thermogram was obtained using a TA Instruments DSC

Q2000 instrument and a hermetically sealed gold crucible filled under ambient conditions. Two scans were performed. After the melting was completed in the first scan, the sample was rapidly cooled at approximately -40 K per minute to -50 °C, and a second scan was recorded. The heating rate was 10 K per minute in both scans.

FIG. 3 provides a flowchart of the process used to prepare tablets comprising 50 mg of Compound K.

DETAILED DESCRIPTION

This invention is directed to (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



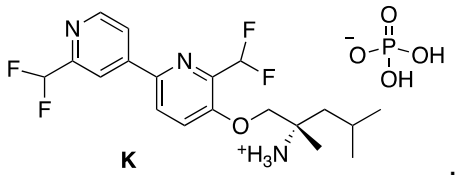
J

and pharmaceutically acceptable salts thereof. Particular salts include hydrochloride and phosphate salts.

CLAIMS

What is claimed is:

1. A crystalline compound, which compound is ((*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4- dimethylpentan-2-aminium dihydrogen phosphate (Compound K):



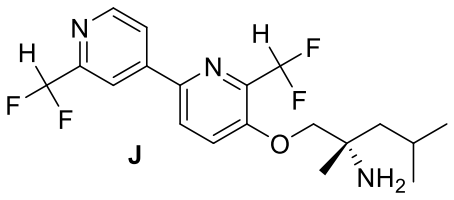
K

.

2. The crystalline compound of claim 1, which has an XPRD pattern comprising peaks at one or more of about 4.81, 5.99, 7.44, 7.89, 11.66, 14.85, 15.77, 19.19, 20.86, 21.65, 23.96, 24.48, or 24.73 degrees 2-theta.

3. The crystalline compound of claim 1, which has a melting point of about 184 °C.

4. A composition comprising an active pharmaceutical ingredient (API), an excipient, and a lubricant, wherein the API is a crystalline compound, which compound is a pharmaceutically acceptable salt of (*S*)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine (Compound J):



J

.

5. The composition of claim 4, which comprises less than 0.05 (*e.g.*, less than 0.01, 0.005, or 0.001) weight percent of at least one of the compounds listed in Table 2.

6. A tablet comprising the composition of claim 4.

7. The table of claim 6, which is coated.

8. The tablet of claim 6, which comprises 10, 20, or 50 mg of a pharmaceutically acceptable salt of Compound J.

9. The composition of claim 4 or the tablet of claim 6, wherein the pharmaceutically acceptable salt of Compound J is Compound K.

10. Use of a compound of claim 1 in the manufacture of a medicament for treating or managing pain.

11. Use of a formulation of claim 4 in the manufacture of a medicament for treating or managing pain.

12. The method of claim 10 or 11, wherein the pain is neuropathic pain.

13. The compound of claim 1 or the formulation of claim 4 for use in therapy.