METHODS AND COMPOUNDS USEFUL IN THE SYNTHESIS OF AN AAK1 INHIBITOR

1 FIELD OF THE INVENTION

This application relates to methods of making (S)-1-((2',6-bis(difluoromethyl)-[2,4'-bipyridin]-5-yl)oxy)-2,4-dimethylpentan-2-amine and salt forms thereof, and to synthetic intermediates useful therein.

2 BACKGROUND OF THE INVENTION

Adaptor associated kinase 1 (AAK1) is a member of the Ark1/Prk1 family of serine/threonine kinases. AAK1 mRNA exists in two splice forms termed short and long. The long form predominates and is highly expressed in brain and heart (Henderson and Conner, Mol. Biol. Cell. 2007, 18, 2698-2706). AAK1 is enriched in synaptosomal preparations and is co-localized with endocytic structures in cultured cells. AAK1 modulates clathrin coated endocytosis, a process that is important in synaptic vesicle recycling and receptor-mediated endocytosis. AAK1 associates with the AP2 complex, which links receptor cargo to the clathrin coat. The binding of clathrin to AAK1 stimulates AAK1 kinase activity (Conner *et al.*, *Traffic* 2003, 4, 885-890; Jackson *et al.*, J. Cell. Biol. 2003, 163, 231-236). AAK1 phosphorylates the mu-2 subunit of AP-2, which promotes the binding of mu-2 to tyrosine containing sorting motifs on cargo receptors (Ricotta *et al.*, J. Cell Bio. 2002, 156, 791-795; Conner and Schmid, J. Cell Bio. 2002, 156, 921-929). Mu2 phosphorylation is not required for receptor uptake, but phosphorylation enhances the efficiency of internalization (Motely *et al.*, Mol. Biol. Cell. 2006, 17, 5298-5308).

AAK1 has been identified as an inhibitor of Neuregulin-1/ErbB4 signaling in PC12 cells. Loss of AAK1 expression through RNA interference mediated gene silencing or treatment with the kinase inhibitor K252a (which inhibits AAK1 kinase activity) results in the potentiation of Neuregulin-1 induced neurite outgrowth. These treatments result in increased expression of ErbB4 and accumulation of ErbB4 in or near the plasma membrane (Kuai *et al.*, *Chemistry and Biology* 2011, 18, 891-906). NRG1 and ErbB4 are putative schizophrenia susceptibility genes (Buonanno, Brain Res. Bull. 2010, 83, 122-131). SNPs in both genes have been associated with multiple schizophrenia endophenotypes (Greenwood *et al.*, Am. J. Psychiatry 2011, 168, 930-946). Neuregulin 1 and ErbB4 KO mouse models have shown schizophrenia relevant morphological changes and behavioral phenotypes (Jaaro-Peled *et al.*, Schizophrenia Bulletin 2010, 36, 301-313; Wen et al., Proc. Natl. Acad. Sci. USA. 2010, 107, 1211-1216). In addition, a single nucleotide polymorphism in an intron of the AAK1 gene has been associated with the age of onset of Parkinson's disease (Latourelle *et al.*, BMC Med. Genet. 2009, 10, 98). These results suggest that inhibition of AAK1 activity may have utility in the treatment of schizophrenia,