

Product Data Sheet

Product Name: PF06650833

Cat. No.: GC19287

Chemical Properties

Cas. No. 1817626-54-2

SMILES NC(C1=C(OC)C=C2C(C=CN=C2OC[C@@H]3[C@H](CC)[C@H](F)C(N3)=O)=C1)=O

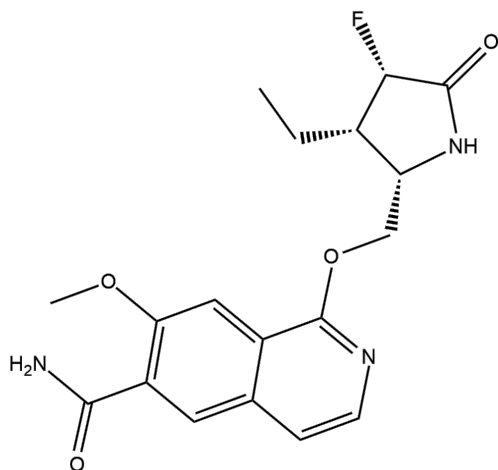
Formula $C_{18}H_{20}FN_3O_4$ M.Wt 361.37

Solubility DMSO : ≥ 33 mg/mL (91.32 mM) Storage Store at -20°C

General tips For obtaining a higher solubility, please warm the tube at 37°C and shake it in the ultrasonic bath for a while. Stock solution can be stored below -20°C for several months.

Shipping Condition Evaluation sample solution : ship with blue ice All other available size: ship with RT, or blue ice upon request.

Structure



Background

PF06650833 is a potent, selective and orally active inhibitor of interleukin-1 receptor associated kinase 4 (IRAK4) with IC_{50} s of 0.2 and 2.4 nM in the cell and PBMC assay, respectively.

PF06650833 is used to treat diseases such as rheumatoid arthritis, lupus, and lymphomas[1][2].

The kinome selectivity profile of PF06650833 (Compound 40) is assessed in a panel of 278 kinases (Invitrogen) at 200 nM inhibitor concentration using the ATP K_m for each kinase. Approximately 100% inhibition is observed for IRAK4[1]. Lactam PF06650833 (Compound 40) is assessed in a

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whole cell functional VEGF2R assay (PAE-KDR cell line). No activity is observed at concentrations up to and including 30 μ M. In a voltage clamp assay, PF06650833 inhibits hERG current by 25% at 100 μ M[1]. The ability of PF06650833 (Compound 40) to inhibit five major CYP450 enzymes is assessed using pooled human liver microsomes and probe substrates for the CYP450 enzymes. At a concentration of 3 μ M of PF06650833, less than 5% inhibition of CYPs 1A2, 2C8, 2C9, 2D6, and 3A4 is observed. Lactam PF06650833 is examined for time dependent inhibition effects on six major CYP450 enzymes (CYP1A2, 2B6, 2C8, 2C9, 2C19, and 2D6) using pooled human liver microsomes and probe substrates. At 100 μ M of PF06650833, no time dependent CYP inhibition is observed. The potential induction of CYP3A by PF06650833 is assessed using cryopreserved human hepatocytes and afforded a 4.4-fold increase in mRNA at 10 μ M[1].

PF06650833 (Compound 40; 0.3-30 mg/kg; oral administration; for 2.5 hours; male Sprague-Dawley rats) treatment significantly inhibits LPS-induced TNF- α in a dose dependent manner. Mean exposures of PF06650833 in plasma are 2.1 nM, 7.7 nM, 19 nM and 150 nM free, respectively, at 2.5 hours after oral administration of PF06650833 at 0.3, 1, 3, and 30 mg/kg. The fraction unbound in rat plasma of PF06650833 is 0.3[1].

References:

- [1]. Lee KL, et al. Discovery of Clinical Candidate 1-[(2S,3S,4S)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy}-7-methoxyisoquinoline-6-carboxamide (PF-06650833), a Potent, Selective Inhibitor of Interleukin-1 Receptor Associated Kinase 4 (IRAK4), by Fragment-Based Drug Design. J Med Chem. 2017 Jul 13;60(13):5521-5542.
- [2]. Seganish WM. Inhibitors of interleukin-1 receptor-associated kinase 4 (IRAK4): a patent review (2012-2015). Expert Opin Ther Pat. 2016 Aug;26(8):917-32.

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