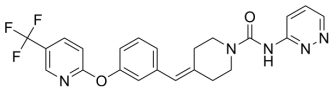
Redafamdastat

Cat. No.:	HY-14376
CAS No.:	1020315-31-4
Molecular Formula:	$C_{23}H_{20}F_3N_5O_2$
Molecular Weight:	455.43
Target:	FAAH; Autophagy
Pathway:	Metabolic Enzyme/Protease; Neuronal Signaling; Autophagy
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 2 years -20°C 1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : ≥ 100 mg/mL (219.57 mM)

* "≥" means soluble, but saturation unknown.

Preparing Stock Solutions

Solvent / Mass / Concentration	1 mg	5 mg	10 mg
1 mM	2.1957 mL	10.9786 mL	21.9573 mL
5 mM	0.4391 mL	2.1957 mL	4.3915 mL
10 mM	0.2196 mL	1.0979 mL	2.1957 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.75 mg/mL (6.04 mM); Clear solution
2. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: ≥ 2.75 mg/mL (6.04 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.75 mg/mL (6.04 mM); Clear solution

BIOLOGICAL ACTIVITY

Description	Redafamdastat (PF-04457845) is a highly efficacious and selective FAAH inhibitor with IC_{50} values is 7.2±0.63 nM and 7.4±0.62 nM for hFAAH and rFAAH, respectively.
IC_{50} & Target	IC50: 7.2±0.63 nM (hFAAH), 7.4±0.62 nM (rFAAH)[1]
In Vitro	Redafamdastat inhibits FAAH by a covalent, irreversible mechanism involving carbamylation of the active-site serine

	nucleophile of FAAH with high in vitro potency (k_{inact}/K_i and IC_{50} values of 40300 $M^{-1}s^{-1}$ and 7.2 nM, respectively, for human FAAH). Redafamdastat has exquisite selectivity for FAAH relative to other members of the serine hydrolase superfamily as demonstrated by competitive activity-based protein profiling. Redafamdastat completely inhibits FAAH in human and mouse membrane proteomes at both 10 and 100 μM with no off targets[1]. Redafamdastat is completely selective for FAAH, and none of the other FP-reactive serine hydrolases in the tested tissues are inhibited by Redafamdastat even at 100 μM[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Oral administration of Redafamdastat at 0.1 mg/kg results in efficacy comparable to that of naproxen at 10 mg/kg in a rat model of inflammatory pain. Oral administration of Redafamdastat causes a significant inhibition of mechanical allodynia measured after 4 h with a minimum effective dose (MED) of 0.1 mg/kg. Furthermore, at 0.1 mg/kg (p.o.), Redafamdastat inhibits the pain response to a comparable degree as the nonsteroidal anti-inflammatory drug naproxen at 10 mg/kg[1]. FAAH is confirmed to be completely inhibited in mice treated with Redafamdastat at 1 and 10 mg/kg p.o. by competitive activity-based protein profiling (ABPP) study[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [1]	The IC_{50} values for the inhibition of hFAAH and rFAAH by PF-04457845 is determined. PF-04457845 is preincubated with FAAH for 60 min before initiating the reaction by the addition of the substrate oleamide. Mouse and human tissues are prepared and inhibitor selectivity is assessed by competitive activity-based protein profiling[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1][2]	Rats[1] PF-04457845 is administered orally to male Sprague-Dawley rats (200g-250g) at the indicated dose (mg/kg) as a nanocrystalline suspension in 2% polyvinylpyrrolidone and 0.15% sodium dodecyl sulfate in H_2O. The dose volume is 10 mL/kg. The Paw Withdrawal Threshold (PWT) is evaluated at 4 h post dose. PWT measurements are averaged and statistical comparisons between groups are made using analysis of variance and unpaired T-tests. Mice[2] Male C57BL6/J mice (7 weeks old; n=8) are treated with PF-04457845 (1 or 10 mg/kg in polyethyleneglycol 300 vehicle by oral administration in a volume of 4 mL/kg), the synthetic cannabinoid agonist WIN 55,212-2 (1 or 10 mg/kg in 18:1:1 saline/Emulphor/ethanol vehicle by intraperitoneal administration in a volume of 10 mL/kg), or the corresponding vehicle. Mice are evaluated for hypomotility, hypothermia, antinociceptive, and cataleptic effects at 4 h or 30 min after PF-04457845 or WIN 55,212-2 administration, respectively, using the tetrad tests except that catalepsy is assessed for 60 s instead of 10 s. Statistical analysis is performed using the Student's t test comparing each treatment group with vehicle. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

CUSTOMER VALIDATION

- Cell Death Differ. 2022 Sep 14.
- Neurotoxicology. 2021 May 28.
- Neurotoxicology. 2020 Mar;77:127-136.
- Int J Toxicol. 2017 Sep/Oct;36(5):395-402.
- Médecine vétérinaire, Ecole Nationale. Université de Toulouse. 12 Jan 2018.

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REFERENCES

[1]. Johnson DS, et al. Discovery of PF-04457845: A Highly Potent, Orally Bioavailable, and Selective Urea FAAH Inhibitor. ACS Med Chem Lett. 2011 Feb 10;2(2):91-96.

[2]. Ahn K, et al. Mechanistic and pharmacological characterization of PF-04457845: a highly potent and selective fatty acid amide hydrolase inhibitor that reduces inflammatory and noninflammatory pain. J Pharmacol Exp Ther. 2011 Jul;338(1):114-24.

[3]. Buntyn RW, et al. Inhibition of Endocannabinoid-Metabolizing Enzymes in Peripheral Tissues Following Developmental Chlorpyrifos Exposure in Rats. Int J Toxicol. 2017 Jan 1:1091581817725272.

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