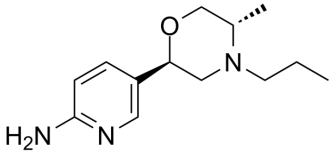
PF-592379

Cat. No.:	HY-U00400
CAS No.:	710655-15-5
Molecular Formula:	$C_{13}H_{21}N_3O$
Molecular Weight:	235.33
Target:	Dopamine Receptor
Pathway:	GPCR/G Protein; Neuronal Signaling
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	PF-592379 is a potent dopamine D_3 receptor agonist with an EC_{50} of 21 nM.
IC_{50} & Target	EC50: 21 nM (D_3 receptor)[1][2][3] Ki: 322 nM (D_3 receptor)[2] Ki: 215 nM (hD_3 receptor), 4165 nM (hD_4 receptor)[3] EC50: 3.9 μM (hD_4 receptor)[3]
In Vitro	PF-592379 appears to be a full agonist (E_{max}=95%) when compared with the standard Pramipexole, a D_2/D_3 receptor agonist for the treatment of Parkinson's disease[1]. PF-592379 is a potent and selective dopamine 3 agonist with EC_{50} and K_i of 21 nM and 322 nM, respectively[2]. In vitro binding assays show that PF-592379 (PF-592,379) selectively binds human D_3 receptors with a high affinity (K_i=215 nM). Although PF-592379 also binds to human D_4 receptors (K_i=4165 nM), it displays a 19-fold binding selectivity for human D_3 over D_4 receptors. PF-592379 fails to bind human D_2 (K_i≥10 μM), D_1 (K_i≥10 μM), or D_5 (K_i≥10 μM) receptors at concentrations of up to 10 μM, and thus is at least 46-fold selective for D_3 over D_2, D_1, and D_5 receptors[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	PF-592379 is an oral dopamine 3 agonist in rat, and dog. PF-592379 has low-moderate clearance relative to liver blood flow of 6.3 and 8.5 mL/min/kg in dog and 44.8 and 58.2 mL/min/kg in rat. It has high permeability in Caco-2 cells and is completely absorbed in rat and dog pharmacokinetic studies with an oral bioavailability of 28% in both rats and 61 and 87% in the dogs[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [3]	The binding affinities of PF-592379 (PF-592,379) and 7-OH-DPAT are characterized at each the five dopamine receptor subtypes using the following radioligands: [^{3}H]SCH23390 (D_1 and D_5, 70 Ci mmol, 1 nM), [^{3}H]U-86170 (D_2, 62 Ci/mmol, 2 nM), and [^{3}H]spiperone (D_3 and D_4, 96 Ci/mmol, 0.2 nM). CHO cells expressing recombinant human D_1, D_2, D_3, D_4, and D_5 receptors are rinsed with, and harvested in, ice-cold Ca^{2+}/Mg^{2+}-free phosphate-buffered saline prior to pelleting (500g, 5 min), resuspension in 25 mM Tris, 5 mM EDTA, and 5 mM EGTA, pH 7.5, and freezing the cells in liquid nitrogen. Upon thawing, the cells are homogenized and centrifuged at 1,000g to remove nuclei and unbroken cells, with the supernatant subsequently centrifuged at 47,000g. The membrane pellet is then washed with Tris, EGTA, EDTA, resuspended in 20 mM

	HEPES, pH 7.5, 150 mM NaCl, 10 mM $MgCl_2$, and 1 mM EDTA, and frozen in liquid nitrogen prior to storage of membrane aliquots at -70°C. Membranes are then thawed and diluted into 20 mM HEPES, pH 7.4, 150 mM NaCl, 10 mM $MgCl_2$, or 1 mM EDTA, 10 mM $MgSO_4$, with binding reactions carried out in a total volume of 0.9 ml for 1 h at room temperature, and stopped by vacuum filtration. Nonspecific binding is assessed with 3 μM SCH23390 (D_1-like antagonist) or 3 μM haloperidol (D_2-like antagonist). Competition binding experiments employ 11 concentrations of PF-592379 or 7-OH-DPAT run in duplicate. IC_{50} values are determined by fitting the data to a one-site model by nonlinear least-squares minimization, and K_i values are calculated with the Cheng-Prusoff equation[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [1]	Rats[1] Male Sprague-Dawley rats (~8-10 weeks and 250 g) are surgically prepared with an indwelling jugular vein cannula at least 2 days before administration of dose. Rats had free access to food (rat diet pellets) and water throughout the duration of the study. Four rats receive PF-592379 either by IV dosing via the caudal vein (n=2) or via oral dosing (n=2) (both routes 2 mg/kg, 1 mL/kg). Blood samples (175 μL) are collected into heparinised tubes before dosing and at time points over a 24 h period from the jugular vein cannula, which is flushed with heparinised saline (100 μL, 10 units/mL), and plasma is prepared by centrifugation and stored at -20°C until analysis[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Attkins N, et al. Pharmacokinetics and elucidation of the rates and routes of N-glucuronidation of PF-592379, an oral dopamine 3 agonist in rat, dog, and human. Xenobiotica. 2010 Nov;40(11):730-42.

[2]. Wager TT, et al. Dopamine D3/D2 Receptor Antagonist PF-4363467 Attenuates Opioid Drug-Seeking Behavior without Concomitant D2 Side Effects. ACS Chem Neurosci. 2017 Jan 18;8(1):165-177.

[3]. Collins GT, et al. Lack of abuse potential in a highly selective dopamine D3 agonist, PF-592,379, in drug self-administration and drug discrimination in rats. Behav Pharmacol. 2012 Jun;23(3):280-91.

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