Product Data Sheet

Product Name: PF-592379
Cat. No.: GC31225

Chemical Properties

Cas. No.	710655-15-5		
SMILES	NC1=NC=C([C@@H]2CN(CCC)[C@@H](C)CO2)C=C1		
Formula	$C_{13}H_{21}N_3O$	M.Wt	235.33
Solubility	Soluble in DMSO	Storage	Store at -20°C
General tips	For obtaining a higher solubility , please warm the tube at 37 ℃ and shake it in the ultrasonic bath for a while.Stock solution can be stored below -20℃ 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	PF-592379		

Protocol

Caution: Product has not been fully validated for medical applications. For research use only.
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Kinase experiment:

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: [3H]SCH23390 (D1 and D5, 70 Ci mmol, 1 nM), [3H]U-86170 (D2, 62 Ci/mmol, 2 nM), and [3H]spiperone (D3 and D4, 96 Ci/mmol, 0.2 nM). CHO cells expressing recombinant human D1, D2, D3, D4, and D5 receptors are rinsed with, and harvested in, ice-cold Ca2+/Mg2+-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 MgCl2, 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 MgCl2, or 1 mM EDTA, 10 mM MgSO4, 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 (D1-like antagonist) or 3 μM haloperidol (D2-like antagonist). Competition binding experiments employ 11 concentrations of PF-592379 or 7-OH-DPAT run in duplicate. IC50 values are determined by fitting the data to a one-site model by nonlinear least-squares minimization, and Ki values are calculated with the Cheng-Prusoff equation[3].

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Animal experiment:

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].

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

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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.

Background

PF-592379 is a potent dopamine D3 receptor agonist with an EC50 of 21 nM.

PF-592379 appears to be a full agonist (Emax=95%) when compared with the standard Pramipexole, a D2/D3 receptor agonist for the treatment of Parkinson's disease[1]. PF-592379 is a potent and selective dopamine 3 agonist with EC50 and Ki of 21 nM and 322 nM, respectively[2]. In vitro binding assays show that PF-592379 (PF-592,379) selectively binds human D3 receptors with a high affinity (Ki=215 nM). Although PF-592379 also binds to human D4 receptors (Ki=4165 nM), it displays a 19-fold binding selectivity for human D3 over D4 receptors. PF-592379 fails to bind human D2 (Ki≥10 μM), D1 (Ki≥10 μM), or D5 (Ki≥10 μM) receptors at concentrations of up to 10 μM, and

thus is at least 46-fold selective for D3 over D2, D1, and D5 receptors[3].

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].

[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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