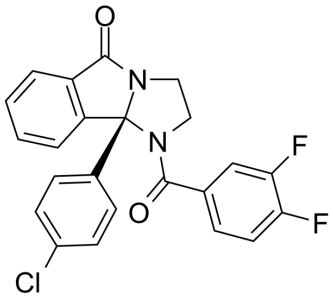
ML375

Cat. No.:	HY-12567
CAS No.:	1488362-55-5
Molecular Formula:	$C_{23}H_{15}ClF_2N_2O_2$
Molecular Weight:	424.83
Target:	mAChR
Pathway:	GPCR/G Protein; Neuronal Signaling
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 40 mg/mL (94.16 mM; Need ultrasonic and warming)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	2.3539 mL	11.7694 mL	23.5388 mL
	5 mM	0.4708 mL	2.3539 mL	4.7078 mL
	10 mM	0.2354 mL	1.1769 mL	2.3539 mL

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

BIOLOGICAL ACTIVITY

Description

ML375 (VU0483253) is a potent, highly selective, brain-penetrant and orally active M5 mAChR negative allosteric modulator (NAM) with IC_{50}s of 300 nM and 790 nM for human and rat M5, respectively. ML375 is inactive at human and rat M1-M4[1].

In Vitro

ML375 possesses high metabolic stability with low hepatic microsomal intrinsic clearance (CL_{int}; human 2.6 mL/min/kg, cynomolgus monkey (cyno), 20 mL/min/kg, rat, 24 mL/min/kg) and a corresponding low predicted hepatic clearance in multiple species (CL_{hep}; human, 2.3 mL/min/kg, cyno, 14 mL/min/kg rat, 18 mL/min/kg)[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

In Vivo

ML375 (10-30 mg/kg; i.p.; once) attenuates both the reinforcing effects and the relative strength of cocaine[2].

ML375 exhibits low clearance (CL_p, 2.5 mL/min/kg) and a long elimination half-life ($T_{1/2}$, 80 hr) in rodents (male, Sprague-Dawley rat, 1 mg/kg IV,) and nonhuman primates (male, cynomolgus monkey, 1 mg/kg, CL_p, 3.0 mL/min/kg, $T_{1/2}$, 10 hr)[1].

ML375 also demonstrates high oral bioavailability (%F, 80) following administration of a suspension-dose to male SD rats with a maximal plasma concentration (C_{max}) of 1.4 μM and a corresponding time to reach C_{max} (T_{max}) of 7 hours[1].

MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Male Sprague-Dawley rats (70 days old; 260-300 g) injected with cocaine[2]
Dosage:	10 mg/kg, 30 mg/kg
Administration:	i.p.; once
Result:	Produced dose-related reductions in cocaine self-administration.

REFERENCES

[1]. Patrick R Gentry, et al. Discovery of the first M5-selective and CNS penetrant negative allosteric modulator (NAM) of a muscarinic acetylcholine receptor: (S)-9b-(4-chlorophenyl)-1-(3,4-difluorobenzoyl)-2,3-dihydro-1H-imidazo[2,1-a]isoindol-5(9bH)-one (ML

[2]. Barak W Gunter, et al. Selective inhibition of M 5 muscarinic acetylcholine receptors attenuates cocaine self-administration in rats. Addict Biol. 2018 Sep;23(5):1106-1116.

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