ML375

Cat. No.: HY-12567

CAS No.: 1488362-55-5

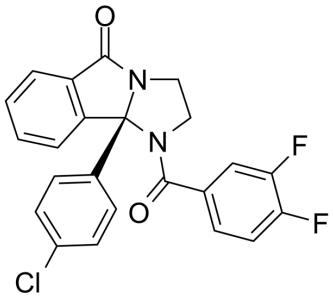
Molecular Formula: $C_{23}H_{15}ClF_2N_2O_2$

Molecular Weight: 424.83

Target: mAChR

Pathway: GPCR/G Protein; Neuronal Signaling

Storage: Please store the product under the recommended conditions in the Certificate of Analysis.



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].

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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 (ML375). J Med Chem. 2013 Nov 27;56(22):9351-5.

[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.

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

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