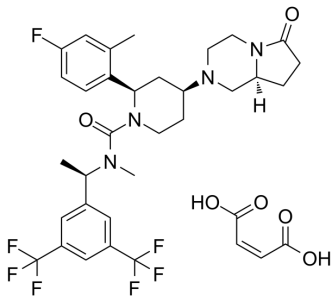
Orvepitant maleate

Cat. No.:	HY-122347A
CAS No.:	579475-24-4
Molecular Formula:	$C_{35}H_{39}F_7N_4O_6$
Molecular Weight:	744.7
Target:	Neurokinin Receptor
Pathway:	GPCR/G Protein; Neuronal Signaling
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	Orvepitant maleate (GW823296 maleate) is potent, selective, orally active and well-tolerated neurokinin-1 receptor (NK-1) antagonist with a pK_i of 10.2 for human neurokinin-1 receptor. Orvepitant maleate can across the blood-brain barrier. Orvepitant maleate has the potential for depressive disorder and chronic refractory cough (CRC) treatment[1][2].
IC_{50} & Target	NK1 10.2 (pKi)
In Vitro	Orvepitant (Compound 3a) is further characterized in terms of the ability to functionally inhibit substance P (SP)-induced release of cytosolic Ca^{2+} in human neurokinin-1 receptor (hNK1)-CHO cells. Orvepitant (0.3-10 nM), pre-incubated for 1 h at 37□ before adding the agonist SP, produces a non-surmountable antagonism of agonist concentration-response curve. For Orvepitant apparents pK_B value of 10.30[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	Orvepitant (Compound 3a; 0.3-10 mg/kg; Oral administration; marmoset) treatment shows a dose dependant reduction of the number of postures was observed at 1 mg/kg (34.9% reduction), 3 mg/kg (36.6% reduction) and 10 mg/kg (46.4% reduction), suggesting a potential anxiolytic-like effect of the compound[1]. Orvepitant (compound 3a) shows an oral bioavailability (F) of 17% in rat and 55% in dog, plasma clearance (Clp) of 29 mL/min/kg in rat and 6 mL/min/kg in dog and a half-life of 2.3 h in rat and 6.1 h in dog. As far as the brain penetration in rats is concerned, a B/P ratio of 1.2 is observed 5 min after the i.v. administration of a 1 mg/kg dose of Orvepitant[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Human threat test in the marmoset (HTT)[1]
Dosage:	0.3 mg/kg, 1 mg/kg, 3 mg/kg and 10 mg/kg
Administration:	Oral administration
Result:	A dose dependant reduction of the number of postures was observed at 1 mg/kg (34.9% reduction), 3 mg/kg (36.6% reduction) and 10 mg/kg (46.4% reduction).

REFERENCES

[1]. Di Fabio R, et al. Identification, biological characterization and pharmacophoric analysis of a new potent and selective NK1 receptor antagonist clinical candidate. Bioorg Med Chem. 2013 Nov 1;21(21):6264-73.

[2]. Smith J, et al. The Neurokinin-1 Receptor Antagonist Orvepitant Is a Novel Antitussive Therapy for Chronic Refractory Cough: Results From a Phase 2 Pilot Study (VOLCANO-1). Chest. 2020 Jan;157(1):111-118.

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