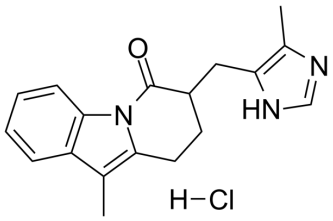
(±)-Fabesetron hydrochloride

Cat. No.:	HY-101638
CAS No.:	129299-81-6
Molecular Formula:	$C_{18}H_{20}ClN_3O$
Molecular Weight:	329.82
Target:	5-HT Receptor
Pathway:	GPCR/G Protein; Neuronal Signaling
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	(±)-Fabesetron hydrochloride ((±)-FK1052) is the racemate of Fabesetron hydrochloride, which is a potent 5-HT3 and 5-HT4 receptor dual antagonist[1].	
IC_{50} & Target	5-HT_3 Receptor	5-HT_4 Receptor
In Vivo	In conscious rats, both 5-HT and 5-methoxytryptamine significantly increase fecal pellet output and accelerate colonic transit. In contrast, the effect of 2-methyl-5-HT is slight. Although Ondansetron and Granisetron slightly reduce 5-HT (1 mg/kg s.c.) stimulated colonic transit, (±)-Fabesetron, at 0.1 mg/kg p.o., inhibits completely the increases in the colonic transit. Furthermore, (±)-Fabesetron, Ondansetron and Granisetron significantly depress the increase in fecal pellet output caused by wrap-restraint stress, with ED_{50} values of 0.21, 3.0 and 1.1 mg/kg p.o., respectively. Intraperitoneal administration of 5-HT and 5-methoxytryptamine, but not 2-methyl-5-HT, produces a dose-related increase in the incidence of diarrhea in fasted mice. 5-HT (0.32 mg/kg i.p.)-induced diarrhea is also inhibited by (±)-Fabesetron, Ondansetron and Granisetron, with ED_{50} values of 0.09, 2.3 and 0.88 mg/kg p.o., respectively[1]. (±)-Fabesetron (1 mg/kg i.v. ×4) apparently reduces delayed emesis caused by Methotrexate (MTX) and increases, but not significantly, the time for onset of emesis. Furthermore, increasing the dose to 3.2 mg/kg of (±)-Fabesetron also significantly inhibits the number of the emetic episodes induced by MTX, of which the action is more effective than the treatment with (±)-Fabesetron at 1 mg/kg[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	

PROTOCOL

Animal Administration [1]

Mice and Rats[1]

Male Sprague-Dawley rats weighing 220 to 330 g and male ddy mice weighing 25 to 35 g are used. (±)-Fabesetron, Ondansetron, Granisetron, Methysergide, Ketanserin and Atropine are dissolved in distilled water. 5-HT, 2-methyl-5-HT, 1-phenylbiguanide and 5-MeOT are dissolved in physiological saline. Diazepam is suspended with 0.5% methylcellulose solution. The drugs are administered to rats at a volume of 2 mL/ kg and to mice at a volume of 5 mL/kg.

Dogs[2]

Beagle dogs of either sex weighting 8.0 to18.5 kg are used in the study. Dogs are injected i.v. with MTX (2.5 mg/kg/mL) at 7:30 AM. The animal behavior is recorded using a video camera with an automatic night photographing system for up to 72 h and analyzed at the end of the experiment. (±)-Fabesetron (1 and 3.2 mg/kg), Ondansetron (1 mg/kg), Tropisetron (1 mg/kg), CP-122,721 (0.1 mg/kg), or vehicle (0.5 mL/kg) is administered i.v. at 24, 36, 48, and 60 h after MTX treatment. Episodes of emesis occurring within a few minutes are defined as a single emetic episode. A 12 h artificial light cycle (lights on between

7:30 AM and 7:30 PM) is used throughout the study. Dogs are given a standard laboratory dog chow (300 g/day) and water ad libitum. The animals are retested with MTX at least 6 weeks later.

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

REFERENCES

[1]. Kadowaki M, et al. Effect of FK1052, a potent 5-hydroxytryptamine3 and 5-hydroxytryptamine4 receptor dual antagonist, on colonic function in vivo. J Pharmacol Exp Ther. 1993 Jul;266(1):74-80.

[2]. Yamakuni H, et al. Probable involvement of the 5-hydroxytryptamine(4) receptor in methotrexate-induced delayed emesis in dogs. J Pharmacol Exp Ther. 2000 Mar;292(3):1002-7.

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