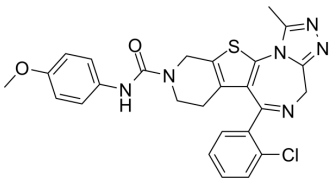
Setipafant

Cat. No.:	HY-101675
CAS No.:	132418-35-0
Molecular Formula:	$C_{26}H_{23}ClN_6O_2S$
Molecular Weight:	519.02
Target:	Platelet-activating Factor Receptor (PAFR)
Pathway:	GPCR/G Protein
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	Setipafant is a platelet-activating factor (PAF) antagonist.
IC_{50} & Target	PAF[1]
In Vivo	Animals are separated into six groups: U_4, controls; S, sham operated animals undergoing laparotomy; I_4 and I_9, ligation of the mesenteric vessels in the last ileal loop; IT_4 and IT_9, same procedure together with treatment with Setipafant (50 mg/kg) orally before and after surgery and intraperitoneally during surgery. Animals are killed at day 4 in groups U_4, S, I_4 and IT_4 and at day 9 in groups I_9 and IT_9, with histological studies and mediator measurements taken. Macroscopic and histological lesions of intestinal wall in groups I_4, I_9, IT_4 and IT_9 are similar to those of human neonatal necrotizing enterocolitis and do not vary according to the absence or the presence of Setipafant (BN 50727) treatment. Peritoneal bands are significantly reduced in treated groups IT_4 and IT_9 as compared with untreated ones I_4 and I_9. Mucosal PAF levels in the terminal ileum are higher in group I_4 than in groups U_4 or I_9. In the upper loop, mucosal PAF levels are comparable in all groups. An increase in stool PAF levels is observed only in group I_9, whereas values comparable to those observed in controls are detected in other groups[1]. Pretreatment of the animals with one or other of the structurally unrelated PAF receptor antagonists, BN 52021 (10 mg/kg, i.p.) or BN 50727 (1 mg/kg, i.p.) significantly reduces Dexamethasone-induced gastric damage. In these animals neither petechiae nor erosions are observed[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Animal Administration [1][2]	Piglets[1] Male and female newborn piglets weighing 1550±31 g are used in all experiments. Six groups are studied. Group U_4 is the nonsurgical control group (n=15). No anesthesia is given. Animals are entrusted to their mother and killed at D_4. Group S is the sham control group (n=15). At D2 animals undergo laparotomy, intestinal exteriorization, and manipulation for 10 minutes before reintroduction to the abdominal cavity. They are killed at D4. Group I_4 consist of animals (n=15) in which ischemia surgery is performed at D2, and animals are killed at D4. Group IT_4 consist of animals (n=15) treated as in I_4 together with treatment with Setipafant (BN 50727), a PAF receptor antagonist, orally (50 mg/kg of body weight) the day before and daily after surgery until death, and intraperitoneally (50 mg/kg) during surgery. Group I_9 consisted of animals (n=15) in which ischemia surgery is performed at D2, and animals are killed at D9. Group IT_9 consist of animals (n=15) undergoing the same procedure as in Is together with treatment with Setipafant as in IT_4. Another group, U_9, is made up of control animals (n=15) that are used only for weight and blood sample studies at D9.

Rats[2]

Male, Wistar rats weighing 160-205 g are used. Between 09 h 00 min and 10 h 00 min each day the animals are given an intraperitoneal injection of the PAF receptor antagonists, BN 52021 (10 mg/kg) or BN 50727(1 mg/kg), or their vehicle, and 30 min later they receive a subcutaneous injection of Dexamethasone sodium phosphate or vehicle. The effectiveness of BN 52021 and BN 50727 treatments is tested in preliminary experiments in anaesthetized (Inactin, 100 mg/kg, i.p.) male rats by injecting 25 and 50 ng/kg PAF into the right femoral vein 30 min before and 30 min after administration of either BN 52021, 10 mg/kg, i.p., or BN 50727, 1 mg/kg, i.p. Mean arterial blood pressure is monitored through a catheter inserted into the right femoral artery by an electromanometer using a Statham P23 dB pressure transducer.

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

REFERENCES

[1]. de Boissieu D, et al. Effect of BN 50727 on pathological findings and tissue platelet activating factor levels during ileal ischemia in newborn piglets. J Pediatr Surg. 1996 Dec;31(12):1675-9.

[2]. Filep JG, et al. Dexamethasone-induced gastric mucosal damage in the rat: possible role of platelet-activating factor. Br J Pharmacol. 1992 Apr;105(4):912-8.

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