Lesogaberan napadisylate

Cat. No.: HY-10061A

CAS No.: 477956-38-0

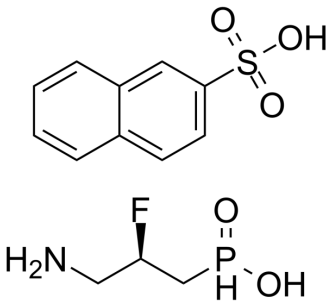
Molecular Formula: $C_{13}H_{17}FNO_5PS$

Molecular Weight: 349.31

Target: GABA Receptor

Pathway: Membrane Transporter/Ion Channel; Neuronal Signaling

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



BIOLOGICAL ACTIVITY

Description

Lesogaberan (AZD-3355) napadisylate is a potent and selective $GABA_B$ receptor agonist with an EC_{50} of 8.6 nM for human recombinant $GABA_B$ receptors. The affinity (K_is) of Lesogaberan napadisylate for rat $GABA_B$ and $GABA_A$ receptors, as measured by displacement of [^{3}H]GABA binding in brain membranes: 5.1 nM and 1.4 μM, respectively. Lesogaberan napadisylate inhibits transient lower esophageal sphincter relaxation through a peripheral mode of action[1].

IC_{50} & Target

Ki: 5.1±1.2 nM (rat $GABA_B$), 1.4±0.3 μM (rat $GABA_A$)[1]
EC50: 8.6±0.77 nM (human $GABA_B$ receptor)[1]

In Vitro

Lesogaberan (3-30 nM) enhances human islet cell proliferation in vitro[2].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Cell Proliferation Assay[2]

Cell Line:	Human islet cells
Concentration:	3, 10, and 30 nM
Incubation Time:	4 days
Result:	Had a small but nonsignificant promitotic effect at 3 nM, while treatment at higher dosages (10 and 30 nM) led to a 2-3-fold increase in proliferation relative to that of islets cultured in medium alone.

In Vivo

Lesogaberan (AZD3355) potently stimulates recombinant human $GABA_B$ receptors and inhibits transient lower esophageal sphincter relaxation (TLESR) in dogs, with a biphasic dose-response curve[1].
Oral Lesogaberan (0.08 mg/mL; 48 hours) protects human islet β-cells from apoptosis in islet grafts in mice[2].
Lesogaberan (7 μmol/kg) shows high oral availability (88% in the dog and 100% in the rat) and relatively low systemic clearance in female SpragueDawley rats[1].
MCE has not independently confirmed the accuracy of these methods. They are for reference only.

Animal Model:	Diabetic NOD/scid mice were implanted with human islets[2]
Dosage:	0.08 mg/mL

Administration:	Oral feeding; 48 hours
Result:	Significantly reduced the percentages of apoptotic islet cells and increased the frequency of insulin^{+} β-cells in human islet grafts.

Animal Model:	Female Sprague Dawley rats[1]
Dosage:	7 μmol/kg (Pharmacokinetic Analysis)
Administration:	Oral
Result:	High oral availability (88% in the dog and 100% in the rat) and relatively low systemic clearance. Plasma protein binding was 1% in rat and human plasma.

REFERENCES

[1]. Lehmann A, et al. (R)-(3-amino-2-fluoropropyl) phosphinic acid (AZD3355), a novel GABAB receptor agonist, inhibits transient lower esophageal sphincter relaxation through a peripheral mode of action. J Pharmacol Exp Ther. 2009 Nov;331(2):504-12.

[2]. Tian J, et al. Repurposing Lesogaberan to Promote Human Islet Cell Survival and β-Cell Replication. J Diabetes Res. 2017;2017:6403539.

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