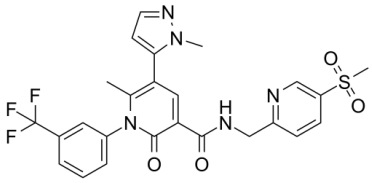
Data Sheet

Product Name:	Alvelestat
Cat. No.:	CS-1684
CAS No.:	848141-11-7
Molecular Formula:	C25H22F3N5O4S
Molecular Weight:	545.53
Target:	Elastase
Pathway:	Metabolic Enzyme/Protease
Solubility:	DMSO : ≥ 33 mg/mL (60.49 mM)



BIOLOGICAL ACTIVITY:

Alvelestat (AZD9668) is an orally bioavailable, affinity and selective inhibitor of **neutrophil elastase (NE)** with a **pIC_{50}** value of 7.9 nM, a **K_i** value of 9.4 nM and a **K_d** value of 9.5 nM[1]. IC50 & Target: pIC: 7.9 nM; Ki: 9.4 nM; Kd: 9.5 nM (neutrophil elastas)[1] **In Vitro:** Alvelestat (20 μg/mL; 16 hours; HBE and A549 cells) treatment decreases cells death and decreases the levels of IL-1β, IL-6, and TNF-α in vitro[2]. **In Vivo:** Alvelestat (1-10 mg/kg; oral administration; twice daily; for 4 days; Female BALB/cJBomTac mice) treatment reduces the inflammatory response to cigarette smoke as indicated by a reduction in BAL neutrophils and interleukin-1β[1].

PROTOCOL (Extracted from published papers and Only for reference)

Kinase assay [1] The binding kinetics between AZD9668 and human NE are analyzed using a BIAcore T100 instrument and a direct binding assay. NE (100 μg/ml in 10 mM acetate buffer, pH 4.5), preincubated for 10 min with AZD9668 (1 μM) to maintain active site availability, is immobilized to a CM5 sensor chip surface by amine coupling. An activated and deactivated CM5 chip surface using amine coupling is used as a control surface. After equilibration with running buffer (0.1 M Tris-HCl, pH 7.4, containing 0.5 M NaCl buffer, pH 7.4, with 1% DMSO, AZD9668 is injected over the immobilized enzyme at a flow rate of 50 μl/min, and the association rate is determined. After 1 min, running buffer is applied to the surface, and the dissociation rate is determined over 5 min. The rate of complex (AB) formation between AZD9668 (A) and the immobilized NE (B) during the sample injection is given by: d[AB]/dt = kon[A][B] - koff[AB]. Cell Assay [1] In the whole-blood assay, citrate anti-coagulated human whole blood is incubated with AZD9668 for 15 min before the addition of opsonized zymosan (final concentration 0.75 mg/ml). NE activity is measured in cell-free plasma after the addition of NE substrate (71 μM final concentration in 0.1 M Tris-HCl, pH 7.4 containing 0.5 M NaCl) and incubation for 60 min at room temperature. Animal administration [1] Human NE (250 U/ml and 1 ml/kg body weight), dissolved in 9 mg/ml NaCl, is given to female C57BL/6JBomTac mice intratracheally 1 h after oral administration of AZD9668 in drug vehicle (0.5% hydroxypropyl methylcellulose in citrate buffer). Nondrug-treated control and NE-treated animals are administered either 9 mg/ml NaCl or human NE as appropriate 1 h after administration of drug vehicle. Four hours later, the mice are sacrificed by an overdose of pentobarbital and subjected to BAL. The BAL fluid is then centrifuged and the cell pellet is resuspended in 1 ml of deionized water to lyse the red blood cells. Hemorrhage is defined as the concentration of hemoglobin in BAL cell lysate and calculated by determining the absorbance at 412 nm and extrapolating the values from a hemoglobin reference curve.

References:

[1]. Stevens T, et al. AZD9668: pharmacological characterization of a novel oral inhibitor of neutrophil elastase. J Pharmacol Exp Ther. 2011 Oct;339(1):313-20.

[2]. Li H, et al. Neutrophil extracellular traps contribute to the pathogenesis of acid-aspiration-induced ALI/ARDS. Oncotarget. 2017 Nov 28;9(2):1772-1784.

CAIndexNames:

3-Pyridinecarboxamide, 1,2-dihydro-6-methyl-5-(1-methyl-1H-pyrazol-5-yl)-N-[[5-(methylsulfonyl)-2-pyridinyl]methyl]-2-oxo-1-[3-(trifluoromethyl)phenyl]-

SMILES:

O=C(C1=CC(C2=CC=NN2C)=C(C)N(C3=CC=CC(C(F)(F)F)=C3)C1=O)NCC4=NC=C(S(=O)(C)=O)C=C4

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