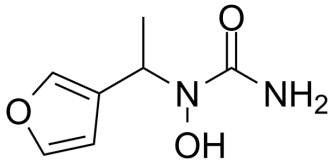
A-69412

Cat. No.:	HY-101945
CAS No.:	123606-23-5
Molecular Formula:	$C_7H_{10}N_2O_3$
Molecular Weight:	170.17
Target:	Lipoxygenase
Pathway:	Metabolic Enzyme/Protease
Storage:	Please store the product under the recommended conditions in the Certificate of Analysis.



BIOLOGICAL ACTIVITY

Description	A-69412 is a reversible, specific inhibitor of the 5-lipoxygenase (5-LO). A-69412 has the potential to treat asthma and ulcerative colitis, and possibly other inflammatory and allergic conditions.	
IC_{50} & Target	5-LO	LTB4 1 μM (IC_{50})
In Vitro	A-69412 inhibits the formation of 5-HETE by the 20000×g supernatant of RBL-I cells in a dose-dependent fashion. The shift to greater potency at lower substrate concentrations is consistent with A-69412 being a competitive inhibitor of the enzyme. A-69412 also inhibits the formation of LTB_4 in calcium ionophore A23187 stimulated human PMNL (IC_{50}=8.9 μM). A-69412 is more potent in inhibiting LTB_4 formation in ionophore-stimulated human whole blood. The potency of A-69412 in a number of assays using several donors consistently show activity in the low micromolar range (mean IC_{50}=1.4 μM, range 0.5-3 μM, 9 donors), several fold more potent than its activity in the other in vitro assays[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	
In Vivo	Oral doses of A-69412 are found to inhibit leukotriene production in a number of species. For example, A-69412 is found to be a potent long-acting inhibitor of leukotriene formation in vivo in the rat (oral ED_{50}=5 mg/kg). A-69412 is remarkably potent in the dog, giving nearly complete inhibition through 16 h after a single 5 mg/kg dose. Plasma concentrations in the dog studies are 38 μM at 0.5 h after dosing and 5 μM at 16 h. These data are consistent with the 100% inhibition seen ex vivo at 0.5 h post-dosing and the 90% inhibition seen at 16 h. As would be expected from the pharmacokinetic results, A-69412 is clearly superior to zileuton in the cynomolgus monkey. A-69412 gave >50% inhibition of ex vivo LTB_4 biosynthesis in the monkey for 8 h, while zileuton is effective only in the first 2 h after oral dosing. An anaphylactic reaction in the rat peritoneal cavity of passively sensitized animals produces large amounts of sulfidopeptide leukotrienes. Given as an oral solution, A-69412 dose-dependently inhibits leukotriene production in the peritoneal cavity of the rat. In one of the experiments, blood levels of A-69412 are measured. These values range from 4 to 100 μM with doses ranging from 2 to 50 mg/kg. A-69412 also significantly inhibits the reaction if dosed (10 mg/kg) at times up to 8 h before challenge. Plasma concentrations of A-69412 are measured in the time course studies and are found to range from 44 μM at 0.5 h to 10 μM at 8 h after dosing[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.	

PROTOCOL

Animal	Dogs, Rats and Monkeys[1]

Administration [1]	A-69412 is suspended in 0.2% methylcellulose with a Potter-Elvehjem homogenizer equipped with a Teflon-coated pestle and administered orally (20 mg/kg) to beagle dogs, cynomolgus monkeys and male Sprague-Dawley rats. Zileuton is used for comparison. All animals are fasted overnight before dosing but allowed water ad libitum. Heparinized blood samples are obtained before and at various times after compound administration in the dog and monkey studies. Groups of rats are dosed with vehicle or A-69412 and 1 h and 15 min later, the animals are sacrificed and blood collected by cardiac puncture into heparinized syringes. Aliquots of blood from all the three species are incubated at 37°C with 50 μM calcium ionophore, A23187. After 30min, the blood is placed in an ice bath and analyzed for LTB_4[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Bell RL, et al. The properties of A-69412: a small hydrophilic 5-lipoxygenase inhibitor. Agents Actions. 1993 Mar; 38(3-4):178-87.

Tel: 609-228-6898 Fax: 609-228-5909 E-mail: tech@MedChemExpress.com
Address: 1 Deer Park Dr, Suite Q, Monmouth Junction, NJ 08852, USA