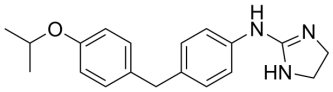
RO1138452

Cat. No.:	HY-108912
CAS No.:	221529-58-4
Molecular Formula:	$C_{19}H_{23}N_3O$
Molecular Weight:	309.41
Target:	Prostaglandin Receptor
Pathway:	GPCR/G Protein

Storage:

Powder	-20°C	3 years
	4°C	2 years
In solvent	-80°C	2 years
	-20°C	1 year



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (323.20 mM; Need ultrasonic)
Ethanol : 50 mg/mL (161.60 mM; Need ultrasonic)

Preparing Stock Solutions	Mass / Solvent / Concentration	1 mg	5 mg	10 mg
	1 mM	3.2320 mL	16.1598 mL	32.3196 mL
	5 mM	0.6464 mL	3.2320 mL	6.4639 mL
	10 mM	0.3232 mL	1.6160 mL	3.2320 mL

Please refer to the solubility information to select the appropriate solvent.

In Vivo

1. Add each solvent one by one: 50% PEG300 >> 50% saline
   Solubility: 10 mg/mL (32.32 mM); Clear solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: ≥ 2.5 mg/mL (8.08 mM); Clear solution
3. Add each solvent one by one: 10% DMSO >> 90% (20% SBE-β-CD in saline)
   Solubility: 2.5 mg/mL (8.08 mM); Suspended solution; Need ultrasonic

BIOLOGICAL ACTIVITY

Description

RO1138452 is a potent and selective IP (prostacyclin) receptor antagonist. RO1138452 displays high affinity for IP receptors. In human platelets, pK_i is 9.3±0.1; in a recombinant IP receptor system, pK_i is 8.7±0.06.

IC_{50} & Target

Rat I_2 Receptor 7 nM (IC_{50})	Rat I_2 Receptor 8.33 (pKi)	Rabbit PAF Receptor 52.9 nM (IC_{50})	Human α_{2A} adrenoceptor 724 nM (IC_{50})
Rat α_{1B} adrenoceptor	Human Muscarinic M_4	Human muscarinic M_2	Human muscarinic M_1

	3280 nM (IC_{50})	Receptor 1450 nM (IC_{50})	Receptor 2220 nM (IC_{50})	Receptor 2570 nM (IC_{50})
	Human muscarinic M_5 Receptor 3110 nM (IC_{50})	Rat 5-HT_{1B} Receptor 1130 nM (IC_{50})	pig 5-HT_{2C} Receptor 1190 nM (IC_{50})	Rat 5-HT_{2A} Receptor 3040 nM (IC_{50})
	Human 5-HT_{1A} Receptor 8580 nM (IC_{50})	Guinea-pig 5-HT_4 Receptor 8910 nM (IC_{50})	Rat α_{1B} adrenoceptor 5.87 (pKi)	Human α_{2A} adrenoceptor 6.49 (pKi)
	Human muscarinic M_1 Receptor 5.66 (pKi)	Human muscarinic M_5 Receptor 5.81 (pKi)	Human muscarinic M_2 Receptor 5.88 (pKi)	Human muscarinic M_4 Receptor 6.14 (pKi)
	Rabbit PAF Receptor 7.9 (pKi)	Guinea-pig 5-HT_4 Receptor 5.35 (pKi)	Human 5-HT_{1A} Receptor 5.37 (pKi)	Rat 5-HT_{2A} Receptor 5.71 (pKi)
	Rat 5-HT_{1B} Receptor 6.11 (pKi)	Pig 5-HT_{2C} Receptor 6.11 (pKi)		

In Vitro

RO1138452 is IP receptor antagonist. The pIC_{50} values of RO1138452 in attenuating cAMP accumulation is 7.0±0.07. Functional antagonism of RO1138452 is studied by measuring inhibition of carbaprostacyclin-induced cAMP accumulation in CHO-K1 cells stably expressing the human IP receptor. The antagonist affinity (pK_i) of RO1138452 is 9.0±0.06. Selectivity profiles for RO1138452 are determined via a panel of receptor binding and enzyme assays. RO1138452 displays affinity at imidazoline$_2$ (I_2) (8.3) and platelet activating factor (PAF) (7.9) receptors[1]. RO1138452 (10 pM-10 μM) added to cells concurrently with a fixed concentration of Taprostene (1 μM) prevents, in a concentration-dependent manner, the inhibition of CXCL9 and CXCL10 release, with $p[A]_{50}$ (molar) values of -8.73±0.11 and -8.47±0.16 (p>0.05), respectively[2].

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

In Vivo

RO1138452 is a potent and selective antagonist for both human and rat IP receptors and that is possesses analgesic and anti-inflammatory potential. RO1138452 (1-10 mg/kg, i.v.) significantly reduces acetic acid-induced abdominal constrictions. RO1138452 (3-100 mg/kg, p.o.) significantly reduces carrageenan-induced mechanical hyperalgesia and edema formation. One hour after administration of RO1138452 (5 mg/kg, i.v.) to rats, the total plasma concentration is 0.189 μg/mL, whereas the free plasma concentrations is calculated to be 0.009 μg/mL (28 nM)[1].

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PROTOCOL

Kinase Assay [1]

Selectivity is determined by the ability of RO1138452 (10 μM) to displace specific binding of standard radioligands at 51 receptors. When significant displacement of radioligand is observed (>70% for RO1138452), complete concentration-dependent displacement curves (in triplicate) are constructed to generate IC_{50} values. Displacement binding at the EP_3 receptor is performed. Enzyme inhibition assays are also conducted. RO1138452 is evaluated at 10 μM in triplicate for inhibition of COX isoforms: COX-1 (ram seminal vesicle), COX-2 (sheep placenta and human umbilical vein). Arachidonic acid is used as a substrate and PGE_2 accumulation is detected[1].

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Cell Assay [2]

BEAS-2B cells are incubated for 30 min at 37°C in supplement-free keratinocyte serum-free medium (KSFM) in the absence and presence of 100 nM RO1138452. Cells are washed with supplement-free KSFM, incubated in the same medium for defined periods, and exposed to 1 μM Taprostene. Four hours later, cells are harvested in reporter lysis buffer, and luciferase activity is measured. The viability HAECs and BEAS-2B cells is determined colorimetrically by measuring the reduction of the tetrazolium salt MTT to formazan, by mitochondrial dehydrogenases[2].

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

Animal Administration [1]	Rats[1] Male Sprague-Dawley rats (n=3) are administered RO1138452 (5 mg/kg, i.v.). At various times after dose administration, the rats are anesthetized by halothane (5%), blood is collected by orbital bleed into a heparinized syringe and a plasma fraction is obtained by centrifugation of the blood at 2600× g for 5 min in a clinical centrifuge. The level of RO1138452 in each sample is determined by high-performance liquid chromatography with detection by mass spectrometry[1]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Bley KR, et al. RO1138452 and RO3244794: characterization of structurally distinct, potent and selective IP (prostacyclin) receptor antagonists. Br J Pharmacol. 2006 Feb;147(3):335-45.

[2]. Ayer LM, et al. 4,5-Dihydro-1H-imidazol-2-yl)-[4-(4-isopropoxy-benzyl)-phenyl]-amine (RO1138452) is a selective, pseudo-irreversible orthosteric antagonist at the prostacyclin (IP)-receptor expressed by human airway epithelial cells: IP-receptor-mediated

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