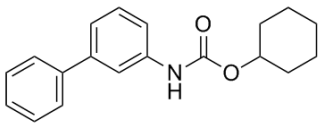
URB602

Cat. No.:	HY-100792		
CAS No.:	565460-15-3		
Molecular Formula:	$C_{19}H_{21}NO_2$		
Molecular Weight:	295.38		
Target:	Others		
Pathway:	Others		
Storage:	Powder	-20°C	3 years
		4°C	2 years
	In solvent	-80°C	6 months
		-20°C	1 month



SOLVENT & SOLUBILITY

In Vitro

DMSO : 100 mg/mL (338.55 mM; Need ultrasonic)

Preparing Stock Solutions	Solvent / Mass / Concentration	1 mg	5 mg	10 mg
	1 mM	3.3855 mL	16.9273 mL	33.8547 mL
	5 mM	0.6771 mL	3.3855 mL	6.7709 mL
	10 mM	0.3385 mL	1.6927 mL	3.3855 mL

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

In Vivo

1. Add each solvent one by one: 10% DMSO >> 40% PEG300 >> 5% Tween-80 >> 45% saline
   Solubility: 2.5 mg/mL (8.46 mM); Suspended solution; Need ultrasonic
2. Add each solvent one by one: 10% DMSO >> 90% corn oil
   Solubility: ≥ 2.5 mg/mL (8.46 mM); Clear solution

BIOLOGICAL ACTIVITY

Description

URB602 is a selective monoacylglycerol lipase (MGL) inhibitor, which inhibits rat brain MGL with IC_{50} of 28±4 μM through a noncompetitive mechanism.

IC_{50} & Target

IC50: 28±4 μM (rat brain MGL)[1]

In Vitro

Without URB602, the apparent Michaelis constant (K_m) of MGL for 2-AG is 24±1.7 μM and the maximum velocity (V_{max}) is 1814±51 nmol min per mg protein; with URB602, the K_m is 20±0.4 μM and the V_{max} is 541±20 nmol min per mg protein (n=4). When organotypic slice cultures of rat forebrain are incubated with URB602 (100 μM), both baseline and Ca^{2+}-ionophore-stimulated 2-arachidonoylglycerol (2-AG) concentrations are increased[1]. URB602 is an inhibitor of monoacylglycerol lipase (MGL), a serine hydrolase involved in the biological deactivation of the endocannabinoid 2-arachidonoyl-sn-glycerol (2-AG).

	URB602 weakly inhibits recombinant MGL (IC_{50}=223±63 μM) through a rapid and noncompetitive mechanism[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	URB602 at doses of 20 and 40 mg/kg tends to reduce upper GI transit and slow colonic propulsion. When taken together as whole gut transit, URB602 dose dependently inhibits transit (P<0.05) compared with the vehicle control group. The inhibitory action of 40 mg/kg URB602 on whole gut transit is absent in these mice, indicating CB_1 receptor involvement in the inhibitory action[3]. URB602 decreases the AUC of pain behaviour during the early phase of the formalin test with an ED_{50} of 0.06±0.028 μg for JZL184 and 120±51.3 μg for URB602 in adult male Sprague-Dawley rats. Both MGL inhibitors also suppresses pain behaviour during the late phase of formalin pain, with an ED_{50} of 0.03±0.011 μg for JZL184 and 66±23.9 μg for URB602[4]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Kinase Assay [2]	Samples containing either URB602 (300 μM), MGL (1.4 pM), or both URB602 and MGL are incubated at 37°C for 30 min in assay buffer. At various time points, the reaction is stopped with an equal volume of ice-cold methanol and directly analyzed in positive ionization mode by LC/MS. A SB-CN column (150×2.1 mm i.d., 5 μm) eluted is used with a linear gradient of methanol in water containing 0.25% acetic acid and 5 mM ammonium acetate (from 60% to 100% of methanol in 8 min) at a flow rate of 0.5 mL/min with column temperature at 50°C. Capillary voltage is set at 4 kV and fragmentor voltage is 100V. Nebulizer pressure is set at 60 psi. N_2 is used as drying gas at a flow rate of 13 liters/min and a temperature of 350°C. ESI is in the positive mode and a full scan spectrum is acquired from m/z 100 to 600. Extracted ion chromatograms are used to quantify URB602 ($[M+H]^+$, m/z 296)[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3][4]	Mice[3] Male C57BL/6 mice (5-6 wk; 20-26 g) or female $CB1^{-/-}$ mice (8 wk; 18-22 g) on a C57BL/6 background are used. After an overnight fasting period (water ad libitum), a marker is administered orally to assess upper GI transit, as described in detail by others. At 30 min after intraperitoneal (ip) administration of URB602 (20 or 40 mg/kg) or vehicle (10% DMSO/Tween 80 in saline), an oral gavage of 200 μL of an Evans blue marker (5% Evans blue, 5% gum arabic) is administered. After 15 min animals are killed by cervical dislocation and the intestine from the region of the pyloric sphincter to the ileocecal junction is immediately removed. The distance traveled by the marker is measured in centimeters and expressed as a percentage of the total length of the small intestine. Rats[4] Three hundred and seven adult male Sprague-Dawley rats weighing 275-350 g, at the time of testing, are used. In a first study, the dose-response curves for JZL184 and URB602 are determined using the AUC of Phase 1 or Phase 2 pain behaviour. In a second study, the antinociceptive effects of JZL184 (300 μg) and URB602 (600 μg) are evaluated following injection in the paw, ipsilateral or contralateral to formalin, to exclude the possibility that systemic leakage contributed to the pattern of results obtained. In a third study, antinociceptive effects of ED_{50} doses of JZL184 (0.03 μg i.paw) or URB602 (66 μg i.paw), in combination with 2-AG (ED_{50} dose of 1 μg i.paw), are quantified to evaluate the presence of additive or synergic effects of these drugs. In a fourth study, antinociceptive effects of JZL184 (at 10 μg i.paw, an analgesic dose) are studied in the presence or absence of either AM251 or AM630 to determine whether these effects are mediated through CB_1 and/or CB_2 receptors. The CB_1 receptor antagonist AM251 exhibits 306-fold selectivity for CB_1 over CB_2 receptors, whereas the CB_2 receptor antagonist AM630 exhibits 70-165-fold selectivity for CB_2 over CB_1 receptors. The doses employed (AM251 at 80 μg i.paw and AM630 at 25 μg i.paw) are those which block peripheral antinociceptive effects of URB602 in Wistar rats. For the first study (n=4-6 per group for URB602 and n=6-8 per group for JZL184) and for all the other behavioural studies (n=6 per group), drugs, administered either alone or in combination, are dissolved in the same total volume (50 μL) and injected into the right hind paw. Preliminary experiments (n=8 per group; data not shown) confirmed that formalin-induced pain behaviour did not change following intra-paw administration of either vehicle (PEG 300: Tween 80 in a 4:1 ratio or DMSO: ethanol: cremophor: 0.9% saline in a 1:1:1:17 ratio]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Hohmann AG, et al. An endocannabinoid mechanism for stress-induced analgesia. Nature. 2005 Jun 23;435(7045):1108-12.

[2]. King AR, et al. URB602 inhibits monoacylglycerol lipase and selectively blocks 2-arachidonoylglycerol degradation in intact brain slices. Chem Biol. 2007 Dec;14(12):1357-65.

[3]. Duncan M, et al. Distribution and function of monoacylglycerol lipase in the gastrointestinal tract. Am J Physiol Gastrointest Liver Physiol. 2008 Dec;295(6):G1255-65.

[4]. Guindon J, et al. Peripheral antinociceptive effects of inhibitors of monoacylglycerol lipase in a rat model of inflammatory pain. Br J Pharmacol. 2011 Aug;163(7):1464-78.

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