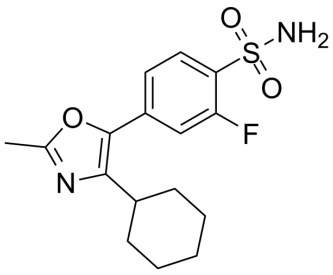
Tilmacoxib

Cat. No.:	HY-U00197
CAS No.:	180200-68-4
Molecular Formula:	$C_{16}H_{19}FN_2O_3S$
Molecular Weight:	338.4
Target:	COX
Pathway:	Immunology/Inflammation
Storage:	Powder -20°C 3 years 4°C 2 years In solvent -80°C 6 months -20°C 1 month



BIOLOGICAL ACTIVITY

Description	Tilmacoxib (JTE522) is a highly selective, time-dependent and irreversible human COX-2 inhibitor with an IC_{50} of 85 nM in an enzyme assay.
IC_{50} & Target	Human COX-2 85 nM (IC_{50})
In Vitro	Inhibitory activity and the mechanism of action of Tilmacoxib (JTE-522), a novel selective cyclooxygenase (COX)-2 inhibitor, on human COX-1 and COX-2 are investigated and compared with those of reference compounds. In an enzyme assay, Tilmacoxib inhibits yeast-expressed human recombinant COX-2 with an IC_{50} of 0.085 μM. In contrast, Tilmacoxib does not inhibit human COX-1 prepared from human platelets at concentrations up to 100 μM. In a cell-based assay, Tilmacoxib diminishes lipopolysaccharide-induced prostaglandin E2 production in human peripheral blood mononuclear cells (COX-2) (IC_{50}=15.1 nM). On the other hand, Tilmacoxib is less potent at inhibiting calcium ionophore-induced thromboxane B2 production in washed human platelets (COX-1) (IC_{50}=6.21 μM). Tilmacoxib shows highly selective inhibition of human COX-2, and its activity is more selective than that of other COX-2 inhibitors (NS-398 and SC-58635). Human recombinant COX-2 activity is attenuated by Tilmacoxib in a dose-dependent and time-dependent manner[1]. Inhibition of proliferation of gastric epithelial cells by a cyclooxygenase 2 inhibitor, Tilmacoxib (JTE522), is also mediated by a PGE_2-independent pathway Combination of Tilmacoxib and Arachidonic acid results in a marked retardation of wound healing compared to the control, but Tilmacoxib does not completely suppress the increase in cellular PGE_2 content following the addition of arachidonate[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
In Vivo	The present experiment is designed to assess the potential chemopreventive properties of Tilmacoxib (JTE-522), a new selective cyclooxygenase-2 inhibitor, on the induction of 1,2-dimethylhydrazine (DMH)-induced colonic aberrant crypt foci (ACF), a marker of rat colon carcinogenesis. A total of 80 male F344 rats are treated with 3 or 10 mg/kg of body weight Tilmacoxib or vehicle by oral gavage five times weekly from the start of the experiment. One week later, rats receive s.c. injections of saline or 20 mg/kg of body weight DMH once weekly for four successive weeks. At the end of 12 weeks after the start of experiment, all rats are sacrificed and colons are evaluated for ACF. 10 mg/kg Tilmacoxib significantly suppresses the total ACF/colon. No inhibitory effect is observed in the 3 mg/kg Tilmacoxib treatment group. Administration of 10 mg/kg Tilmacoxib significantly suppresses ACF formation with a 30% reduction in total ACF/colon ($p<0.01$). Furthermore, the data on crypt multiplicity show that 10 mg/kg Tilmacoxib significantly reduces the formation of foci containing 1-3 crypts but not foci containing four crypts or more. Administration of the low dose of Tilmacoxib (3 mg/kg) has no inhibitory effects on

	either the total ACF or crypt multiplicity[3]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

PROTOCOL

Cell Assay [2]	Tilmacoxib is resolved with DMSO prior to the experiment and concentrations of 1-100 μM are assessed. Effects of Arachidonic acid are assessed at concentrations of 0, 5 and 20 μg/mL. Further, the combination of Tilmacoxib (100 μM) with Arachidonic acid (20 μg/mL) is assessed in additional experiments. Circular artificial wounds are created after formation of complete monolayer cell sheets. Tilmacoxib and Arachidonic acid are added just after wound formation. The process of epithelial restoration is monitored by measuring the cell-free area using an inverted phase-contrast microscope every 24 h. Changes in the cell-free area during restoration are analyzed quantitatively with an image analyser[2]. MCE has not independently confirmed the accuracy of these methods. They are for reference only.
Animal Administration [3]	Rats[3] A total of 80 male F344 rats, 5 weeks old, are used. Rats at 6 weeks of age after 1 week of acclimatization are divided randomly into five groups. The rats in groups 1-3 (20 rats each) are injected s.c. with DMH (20 mg/kg body wt) from 1 week after the start of the experiment, once weekly for four successive weeks. Those in groups 4 and 5 (10 rats each) are injected s.c. with 0.9% saline at the same time. Group 2 is treated with Tilmacoxib at a dose of 3 mg/kg body wt by oral gavage, five times weekly from the start of the experiment to the end of the experiment. Groups 3 and 5 are treated with Tilmacoxib at the dose of 10 mg/kg body wt in the same manner as group 2. Groups 1 and 4 are treated with 0.5% CMC alone, without Tilmacoxib. Body weight, water and food consumption are measured weekly during the experiment. MCE has not independently confirmed the accuracy of these methods. They are for reference only.

REFERENCES

[1]. Wakitani K, et al. Profile of JTE-522 as a human cyclooxygenase-2 inhibitor. Jpn J Pharmacol. 1998 Nov;78(3):365-71.

[2]. Hirose M, et al. Inhibition of proliferation of gastric epithelial cells by a cyclooxygenase 2 inhibitor, JTE522, is also mediated by a PGE2-independent pathway. Aliment Pharmacol Ther. 2002 Apr;16 Suppl 2:83-9.

[3]. Wei M, et al. Chemopreventive effect of JTE-522, a selective cyclooxygenase-2 inhibitor, on 1, 2-dimethylhydrazine-induced rat colon carcinogenesis. Cancer Lett. 2003 Dec 8;202(1):11-6.

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