

Tram-34 inhibits rat CYP450 2B1, 2C6 and 3A2

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Tram-34 (1-[(2-Chlorophenyl)diphenylmethyl]-1H-pyrazole) is an analogue of the antifungal agent clotrimazole. It blocks the intermediate conductance calcium-activated potassium current (IKCa, $K_d \cong 25$ nM) but unlike clotrimazole, has no effect on human CYP3A4 (Wulff et al, 2000). However, unlike in humans, clotrimazole is a non-selective inhibitor of rat CYP450s (Eagling et al, 1998). Therefore, we tested the hypothesis that Tram-34 is also an inhibitor of rat CYP450s. The abilities of Tram-34 and clotrimazole to inhibit the biotransformation of fluorogenic substrates by rat CYP450 1A2, 2A2, 2B1, 2C6, 2D2, 3A1 and 3A2 expressed in baculovirus-infected insect cells was examined by methods reported previously (Makaji et al, 2009). Clotrimazole inhibited all isoforms but Tram-34 was inactive against rat CYP450 1A2, 2A2, 2D2 and 3A1 at concentrations up to 10 μ M. However, Tram-34 did inhibit CYP450 2B1, 2C6 and 3A2 with potencies as shown in Table 1.

	Tram-34		Clotrimazole	
	Ki (μ M)	pKi \pm sem	Ki (μ M)	pKi \pm sem
CYP2B1	1.6	5.8 \pm 0.2	0.005	8.3 \pm 0.1
CYP2C6	0.3	6.5 \pm 0.1	0.09	7.03 \pm 0.05
CYP3A2	1.6	5.8 \pm 0.1	0.16	6.8 \pm 0.1

Values are means of 3 to 4 experiments

Tram-34 inhibits rat CYP450 2B1, 2C6 and 3A2 with potencies that are lower than those of its analogue clotrimazole. Its effects on CYP450s are considerably less potent than its effects on IKCa. Nevertheless, if excessive concentrations of Tram-34 are used to block IKCa in rats, the results may be complicated by effects on signalling through CYP2C6.

Wulff H et al (2005) J Med Chem 48:287-291.

Eagling VA et al (1998) Br J Clin Pharmacol 45:107-114.

Makaji E et al (2009) Toxicol Sci in press.

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