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**ABSTRACT TEMPLATE**

**Inhibition of cytochrome P450 3A4 and P-glycoprotein transporter by *2*-hydroxytriazolo[4,*5*-b]pyridine**

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 (The main text, Times New Roman font, 12 points) The analgesic effects of opioids are mediated through four known receptors: mu-(MOR), kappa-(KOR), delta-(DOR), and the opioid receptor-like 1 (ORL-1). Of the opioid analgesics, mu-opioid agonists (MOAs) are the most commonly used. *2*-hydroxytriazolo [4,*5*-b]pyridine was synthesized as a potentialMOA. Pyridines are potent inhibitors of P-glycoprotein and are compounds that reverse the multidrug resistance phenomenon in cancer cells. Besides, pyridines are known to inhibit rodent Cyp3a enzymes (Black et al.: J. Biol. Chem. 269 (1964) 1238).

We examined if *2*-hydroxytriazolo[4,*5*-b]pyridine inhibits cytochrome P450 3A4 (CYP3A4) enzyme and P-glycoprotein transporter.

For this purpose, we use human liver microsomes and MDCKII cells with artificial expression of human P-glycoprotein transporter (ABCB1 gene). Midazolam was used as a CYP3A4 substrate. Digoxin was used as a P-glycoprotein substrate in transport assays.

We found efficient inhibition of P-glycoprotein transporter but not CYP3A4 by 2-hydroxytriazolo[4,*5*-b]pyridine with IC50 0.03 and 25.2 μM, respectively. Despite this fact, CYP3A4 inhibition by the compound appeared as a mechanism-based (irreversible) interaction.

We can conclude that the novel pyridine compound is a potent P-glycoprotein inhibitor. Since CYP3A4 is responsible for the metabolism of more than 50% of medicines, we propose/hypothesize that *2*-hydroxytriazolo[4,*5*-b]pyridine may also inhibit CYP3A4 after high doses with significant consequences for drug-drug interactions.

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