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Mechanism of Human Cytochrome P450 1B1 Inhibition by A Stilbene Analog

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Tetramethoxystilbene, a trans-stilbene analog, has demonstrated potential as a specific inhibitor of human P450 1B1. To find more hydrophilic and potent inhibitor, a series of synthetic tetramethoxystilbene derivatives were prepared and their inhibitory potentials were evaluated with the bacterial membrane of human P450 1A1, 1A2 and 1B1 co-expressed with human NADPH-P450 reductase. Of the compounds tested, an imidazole stilbenoid compound exhibited a potent inhibition of human P450 1B1 with an IC50value of 3 nM. It also showed the inhibition of P450 1A1 with IC50 value of 48 nM and P450 1A2 with IC50 value of 117 nM. Imidazole stilbenoid was considered as a mixed-type inhibitor for all three P450 1 enzymes. The Ki values for P450 1A1, 1A2, and 1B1 inhibition were 15, 30, and 1.4 nM, respectively. Preincubation of P450 1B1 with NADPH showed that imidazole stilbenoid may be an irreversible mechanism-based inactivator. Treatment with antioxidants such as glutathione, N-acetylcysteine or dithiothreitol could not recover P450 1B1 inhibition by imidazole stilbenoid. Taken together, these results indicated that imidazole stilbenoid is a new potent inhibitor of P450 1B1 and will be helpful to elucidate the mechanisms of P450 1B1 action in cells.

Keyword : P450, imidazole stilbenoid, inhibitor