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POTENT INHIBITION OF HUMAN CYTOCHROME P450 1 ENZYMES BY DIMETHOXYPHENYL VINYL THIOPHENE.

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Recently we have reported that various hydroxystilbenes show strong inhibition of human P450 1 activity. A series of synthetic trans-stilbene derivatives were prepared and their inhibitory potentials were evaluated with the bacterial membrane of recombinant human P450 1A1, 1A2 or 1B1 coexpressed with human P450/NADPH-450 reductase to find new candidates for cancer chemoprevention. Of the compounds tested, SY-021 (3,5-dimethoxyphenyl vinyl thiophene) exhibited a potent inhibition of human P450 1B1 with an IC50 value of 2 nM. SY-021 also showed the inhibition of P450 1A1 with IC50 value of 61 nM and P450 1A2 with IC50 value of 11 nM. SY-021 showed 31-fold selectivity for P450 1B1 over P450 1A1 and 6-fold selectivity for P450 1B1 over 1A2. We have further investigated the inhibition kinetics of P450 1A1, 1A2 and 1B1 by SY-021. The mode of inhibition by SY-021 was non-competitive for all three P450 1 enzymes. Effect of preincubation with NADPH on inhibition of P450 1B1 by SY-021 was determined. These results suggest that SY-021 is one of the most potent inhibitor of human P450 1 enzymes and may be considered as a good candidate for a cancer chemopreventive agent in human.

keyword : Cytochrome P450, Chemoprevention, Dimethoxyphenyl vinly thiophene, EROD, non-competitive inhibitor