Mechanism-based CYP2D6 inactivation by acridone alkaloids of Indonesian medicinal plant *Lunasia amara*

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Fourteen acridone alkaloids isolated from Lunasia amara Blanco were tested for their mechanism-based inhibition on human liver microsomal dextromethorphan O-demethylation activity, a prototype marker for cytochrome P450 2D6 (CYP2D6). Among the 14 compounds, 5-hydroxygraveroline (1), 8-methoxyiffiaimine (2), lunamarine (3), and lunine (12) increased their inhibitory activity with increasing preincubation time. Then, we further examined the possibility of mechanism-based inhibition on 5-hydroxygraveroline (1) and lunamarine (3), which showed the potent inhibition. Further investigations on 1 and 3 showed that the characteristic time- and concentration-dependent inhibition, which required a catalytic step with NADPH, was not protected by nucleophiles, and was decreased by the presence of a competitive inhibitor. Thus, 1 and 3 were concluded as mechanism-based inactivators of CYP2D6.

*Fitoterapia* 83 (2012) 774–779