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 mechanismbased 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-methoxyifflaiamine (**2**), lunamarine (**3**), and lunine (**12**) increased their inhibitory activity with increasing preincubation time. Then, we further examined the possibility of mechanismbased 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.

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