Inhibition of Cytochrome P450 Enzymes by Quinones and Anthraquinones.


Abstract

In-silico docking studies and QSAR analysis of a number of in-house cytochrome P450 inhibitors have revealed important structural characteristics that are required for a molecule to function as a good inhibitor of P450 enzymes 1A1, 1A2, 2B1 and/or 2A6. These insights were incorporated into the design of pharmacophores used for a 2D-search of the Chinese medicine database. Emodin, a natural anthraquinone isolated from Rheum emodi and known to be metabolized by cytochrome P450 enzymes, was one of the hits and was used as the lead compound. Emodin was found to inhibit P450s 1A1, 1A2 and 2B1 with IC50 values of 12.25 μM, 3.73 μM and 14.89 μM respectively. Based on the emodin molecular structure, further similarity searches of the PubChem and ZINC chemical databases were conducted resulting in the identification of 12 emodin analogs for testing against P450s 1A1, 1A2, 2B1 and 2A6 dependent activities. 1-amino-4-chloro-2-methylantracene-9,10-dione (compound 1) showed the best inhibition potency for P450 1A1 with an IC50 value of 0.40 μM. 1-amino-4-chloro-2-methylantracene-9,10-dione (compound 1) and 1-amino-4-hydroxyanthracene-9,10-dione (compound 2) both inhibited P450 1A2 with the same IC50 value of 0.53 μM. In addition, compound 1 acted as a mechanism-based inhibitor of cytochrome P450s 1A1 and 1A2 with KI and Kinactivation values of 5.38 μM and 1.57 min⁻¹ for P450 1A1, and 0.50 μM and 0.08 min⁻¹ for P450 1A2. 2,6-di-tert-butyl-5-hydroxynaphthalene-1,4-dione (compound 8) directly inhibited P450 2B1 with good selectivity and inhibition potency (IC50 = 5.66 μM). Docking studies using the 3D-structures of the enzymes were carried out on all of the compounds. The binding modes of these compounds revealed the structural characteristics responsible for their potency and selectivity. Compound 1 which is structurally similar to compound 2 in the presence of an amino group at position 1, showed a difference in the mechanism of inhibition towards P450s 1A1 and 1A2. The mechanism-based inhibition seen for compound 1 may be attributed to the presence of the methyl group at the 2 position, in close proximity to the amino group. Compound 2 which is otherwise similar, lacks that methyl moiety and did not show mechanism-based inhibition.

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