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Flavonoids as Inhibitors of MRP1-like Efflux Activity in Human Erythrocytes. A Structure-Activity Relationship Study

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The potency of flavonoids (isoflavones, flavones, and flavanones) to inhibit efflux of 2',7'-bis-(carboxypropyl)-5(6)-carboxyfluorescein (BCPCF) from human erythrocytes was investigated. Structure-activity relationship analysis showed that the strongest inhibitors were found among flavanones bearing a hydrophobic prenyl, geranyl, or lavandulyl group at position 8 (and hydroxyl groups at 5 and 7) in ring A. A prenyl group at position 5' or stilbene at positions 4'-5' in ring B further seemed to increase inhibitor potency. The most efficient flavanones, euchrestaflavanone A and sophoraflavanone H, were approximately 20 times more efficient than genistein, and induced 50% inhibition of BCPCF efflux (IC_{50}) at 3 microM (60 min, 37 degrees C). This is comparable to IC_{50} of benzbromarone (4 microM) and lower than IC_{50} of indomethacin (10 microM), both known MRP1 (ABCC1) inhibitors. It is suggested that BCPCF efflux is mainly due to MRP1 activity. Our results indicate that flavonoid molecular structure provides a promising base for development of potent MRP1 inhibitors.