

## **Aurones as modulators of the ABC transport activity: Potential to overcome multidrug resistance in cancer chemotherapy**

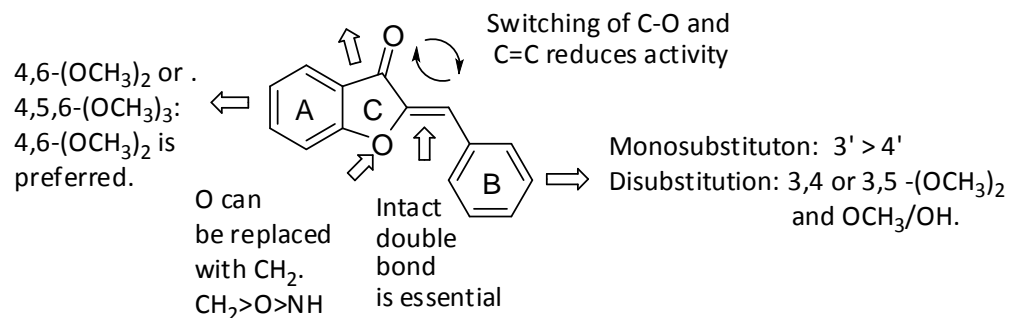
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Multidrug resistance (MDR) is a phenomenon associated with the resistance of tumor cells to the cytotoxic actions of structurally dissimilar drugs commonly used in cancer chemotherapy. The most common mechanism by which cancer cells acquire resistance is through the increased expression of ATP-binding cassette (ABC) transport proteins. These transporters utilize the energy of cellular ATP to actively efflux anti-cancer drugs out of cells, hence limiting the intracellular accumulation of these agents to levels that are inadequate for therapeutic effect. ABC transporters that play key roles in MDR are ABCB1 (P-glycoprotein), ABCC1 (multidrug resistant protein 1) and ABCG2 (breast cancer resistant protein BCRP). Of these, ABCG2 is the most recent to be described and less is known of compounds that are capable of modulating ABCG2 efflux activity. We have identified aurones (2-benzylidenebenzofuran-3(2H)-ones) as potent inhibitors of ABCG2 efflux activity.<sup>1,2</sup> Detailed analysis of structure-activity identified key features necessary for interaction (Figure 1). A pharmacophore model was proposed based on the 112 aurone analogs, the features of which compared favorably with a previously reported model.<sup>3</sup> Our study has shown that aurones are promising compounds associated with low toxicities and potent modulatory effects on the ABCG2 efflux protein. Thus, they warrant further scrutiny as lead templates for potential MDR reversal agents.

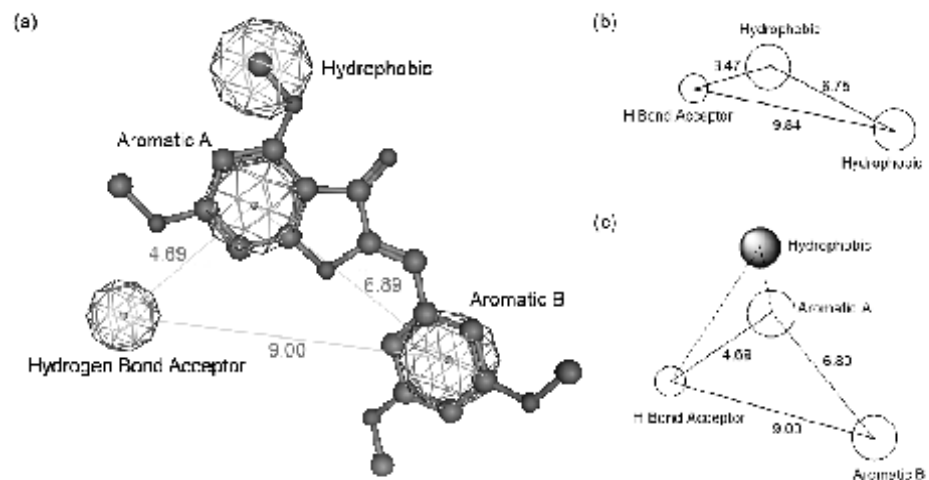
### **References**

1. Sim HM et al. *Eur J Pharm Sci* 35, 293 (2008)
2. Sim HM et al *ChemMedChem*, 6: 713 (2011)
3. Matsson P et al., *J Pharmacol. Exp Ther.* 323, 19 (2007)

Intact Ring C. Ring expansion to flavones allowed but not ring cleavage to chalcones



### Summary of structural features of the aurone template that are essential for interaction with ABCG2



a) Pharmacophore model of ABCG2 modulators derived by Sim et al. <sup>2</sup> It comprises 2 aromatic features, one hydrophobic group and a hydrogen bond acceptor projection point. (b) Pharmacophore model of ABCG2 modulators derived by Matsson et al. <sup>3</sup> Distances Å between features are indicated. (c) Distances between features of the pharmacophore model depicted in (a).