

Conference abstract PO-02

QSAR, HQSAR and GRIND Studies on a Set of Heterocyclic Propafenone-Type Inhibitors of P-Glycoprotein

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P-Glycoprotein (P-gp) is a member of the ABC (ATP binding cassette) super-family of transport proteins, which in addition to their physiological role in tissue protection, actively extrude a large variety of therapeutically administered drugs from the malignant cells and thus are responsible for multiple drug resistance (MDR) in cancer patients [1]. Since the discovery of P-gp more than 30 years ago many studies have shown that MDR can be reversed by the use of inhibitors, often denoted as MDR modulators.

A series of Benzophenone, Phenylpyrazolon and Benzopyridine derivatives structurally related to propafenone were synthesised and tested for their ability to inhibit P-gp mediated daunomycin efflux in multidrug resistant CCRF-CEM vcr 1000 cells [2, 3]. SAR studies were performed by 2D QSAR, HQSAR and GRIND descriptors. 2D QSAR studies showed a good correlation of activity with lipophilicity. The inclusion of partial charge and number of H-bond donor atoms as descriptors led to a QSAR equation of high predictive power ($q^2=0.72$). The model was utilized to predict the activity of a test set giving an r^2 value of 0.74. HQSAR models indicate that the ether oxygen linker group between the hetero aromatic ring and the propanolamine side chain is pharmacologically important. Different substitution pattern at the central aromatic ring also influence the activity. Results from GRIND-studies show that two H-bond acceptors in the ligands at a distance of 11.20–11.60Å are beneficial for high activity. Shape of the molecules also affects the activity. Two H-bond donor groups at a distance of 6.40–6.80Å contribute negatively to the activity of the propafenone-type compounds.

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- [1] Labeed FH, Coley HM, Thomas H, Hughes MP. Assessment of Multidrug Resistance Reversal Using Dielectrophoresis and Flow Cytometry. *Biophys J.* 2003, 85: 2028–2034. doi:10.1016/S0006-3495(03)74630-X
- [2] Chiba P, Holzer W, Landau M, Bechmann G, Lorenz K, Plagens B, Hitzler M, Richter E, Ecker G. Substituted 4-Acylpyrazoles and 4-Acylprazolones: Synthesis and Multidrug Resistance-Modulating Activity. *J Med Chem.* 1998; 41: 4001–4011. doi:10.1021/jm980121y