Prediction of the Physicochemical and ADMET Properties of Indeno[1,2-b]Indole Derivatives as Potent ABCG2 Inhibitors

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ABCG2 is an ATP-binding cassette sub-family G member 2 protein implicated in the transport of various molecules across extra- and intra-cellular membranes. This protein is known to be implicated in xenobiotic transporters. Since discovering its role in multidrug resistance, numerous studies have been made in order to inhibit its function (1),(2). A series of indeno[1,2-b]indoles previously synthetized as human casein kinase 2 (CK2) inhibitors were found to selectively inhibit ABCG2 (3). Compounds with N5-phenethyl derivatives showed the lowest IC50 values for ABCG2 in the submicromolar range. Our study was aimed at predicting in silico properties of the most promising candidates for an in vivo evaluation by using the Molinspiration software (v2013.09) for the physicochemical parameters, the ACD/Lab Percepta sofware (v14.0.0) for the ADMET properties, and the OECD QSAR Toolbox (v3.2) for the evaluation of toxicity risks, in order to select the best candidate(s). Results show that compounds with the lowest solubility are correlated with a low absorption rate. The distribution profile is similar for all molecules which have a high affinity to plasmatic proteins and could be active in the central nervous system. All compounds have a low to moderate risk of reprotoxicity, and could be mutagenic but with inconclusive risks of clastogenicity or carcinogenicity for mouse and rodents. The acute, sub chronic and chronic health effects are lower for SiA3 cetonic and BZA37 phenolic compounds of each category. The software predictions give a selection of the best profiles, so these results can be used for further in vitro chemosensibility test in order to select the best candidate for in vivo tests.

References:
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