Different Handling of a Hydrophobic Pocket and Consequences for Screening Results in Catalyst, Phase and MOE

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Three pharmacophore modeling programs Catalyst (Accelrys), Phase (Schrödinger), and MOE (Chemical Computing Group) are compared with respect to their virtual screening results relying on a structure based pharmacophore model. We have chosen Human Rhinovirus (HRV) coat protein because of the properties of its binding pocket: there is only one hydrogen bond acceptor at the entrance of the pocket, the remainder of the pocket is mainly hydrophobic and has the shape of a narrow tube. Hydrophobic regions cannot be localized clearly on the ligand in contrast to hydrogen bond acceptors and are therefore especially challenging in the field of pharmacophore modeling. They are suspected to contribute substantially to differences in the screening results. To investigate these differences we tried to find a model which could be translated into every software package and still represents all chemical information obtained by X-Ray structure alignment and thorough literature search. The problem was that descriptors with equivalent names sometimes got assigned to different functional groups. A similar hit list in the test set was considered a good criterion for model similarity.