Pharmacophore Modeling of Cyclooxygenase-2 in LigandScout and Discovery Studio – A comparison

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In structure-based pharmacophore modeling, interaction patterns between a small active molecule and a target protein are translated into a three dimensional array of chemical features (e. g. hydrogen bond (HB) donor, HB acceptor, lipophilic, ionic, aromatic). This pharmacophore can then be used to select other molecules from virtual compound libraries that could show similar activity (virtual screening). Several software packages for this kind of modeling are available. DiscoveryStudio (DS), formerly Catalyst, is one of the longest established software packages for pharmacophore-based virtual screening, while LigandScout (LS), where a screening function became newly available in the 3.0 version, is one of the more recently developed programs. Both programs use different screening algorithms, so it is interesting to compare their performance in terms of predictive power. In this case study the two software packages are evaluated on the target cyclooxygenase (COX) 2, including the biological testing of predicted virtual hits from both programs.

COX 1 and 2 are important and very well examined targets in inflammation. A wide variety of active compounds and crystal structures are available. In this study pharmacophore modeling for COX 2 from a previous study [1] with the software DS [2] was compared to newly generated pharmacophore models generated with the software package LigandScout 3.0 [3].

Two models (one from each program) based on the protein databank entry 6COX were employed to screen commercially available substance libraries in the respective programs. The 10 top ranked hits (by geometrical fit value) for each model, respectively, were biologically tested in a cell-free enzymatic assay [4]. Both models retrieved five biologically active hits, respectively, of which two found by LS were highly active, one in the nanomolar range.

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