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Drug Design And Development Using Pharmacophore Modeling And Virtual Screening

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A drug discovery cycle, to identify, to optimize and eventually take a compound to the market is generally along process (approx 12–15 years) and is very expensive (approx $500million R&D expense). The enormous pressure that pharmaceutical and biotech companies are facing, has created the need to apply all available techniques to decrease attrition rates, costs and the time to market. Pharmacophore identification is one such technique. As case study example of drug design against Cycloxygenase (COX) enzyme is being discussed here using Catalyst Software. COX enzyme catalyze the biosynthesis of prostaglandins and thromboxane from arachidonic acid (AA). In the present paper we summarize, the development of hypotheses of a dataset comprising six chemically diverse series of known inhibitors for COX-2, by using the Catalyst/ Hypogen module. The most predictive pharmacophore model, consisting of four features, namely, one hydrogen bond donors, one hydrogen bond acceptor, one hydrophobic aliphatic and one ring aromatic feature, had a correlation (r) of 0.954 and a root mean square deviation of 0.894. The model was validated on a test set consisting of six different series of structurally diverse 27 compounds and performed well in correctly classifying active and inactive molecules correctly. The resultant best hypothesis was used to screen databases viz. NCI and maybridge to produce hit compounds. 264 hits were obtained which were arranged according to their fit value in 8 categories and subjected to secondary screening using Lipnski's rule of five. The resultant compounds were then docked into the COX-2 binding site to study the ligand – protein interaction and binding energies were evaluated in terms of LUDI scores. Several new structural scaffolds have been obtained as a result of the virtual screening. The Compounds were screened in in-vitro assay and novel scaffolds were identified as lead compounds for development of COX-2 inhibitors.