PHARMACOPHORE MODELLING FOR LIGANDS OF PROTEIN KINASE C

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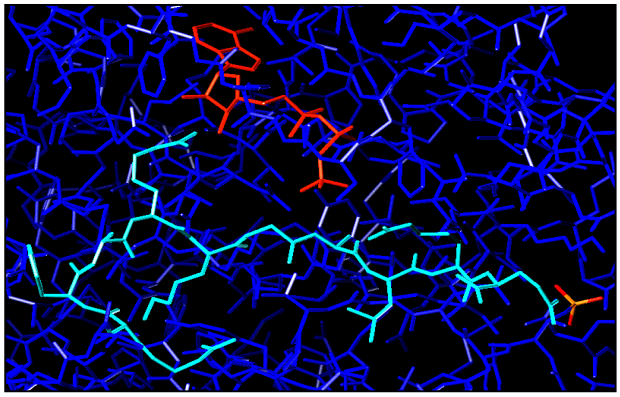
INRODUCTION

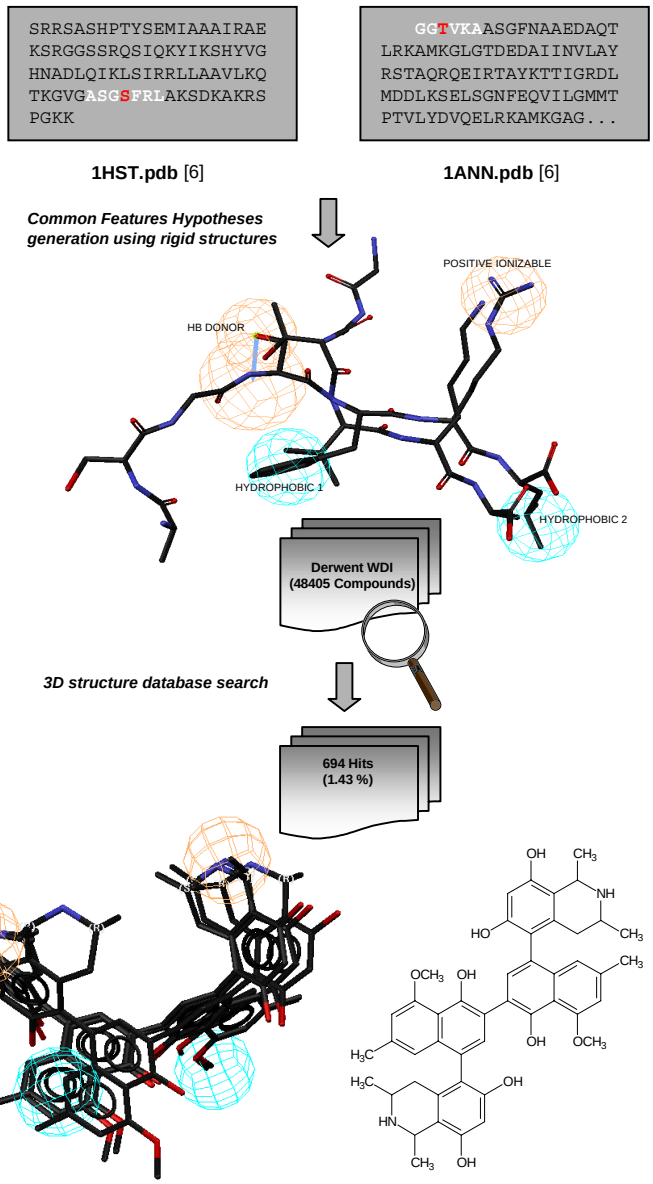
Protein kinase C is a phospholipid dependent serine/threonine kinase family consisting of at least eleven closely related isoenzymes that play key roles in the signal transduction pathways. The availability of nonpeptide isoenzyme specific PKC inhibitors could be of great advantage for explaining the exact functions of distinct PKC isoenzymes that still remain largely unclear [1]. Numerous potent PKC inhibitors have been described up to date, however, highly specific nonpeptide inhibitors are known only for few isoenzymes [2,3]. A number of relatively short peptides that resemble the pseudosubstrate sequence or mimic PKC substrates has been reported to inhibit PKC and their affinity to the different isoenzymes varies considerably. These facts suggest that the substrate binding region of the enzyme could be a promising target for the development of new PKC inhibitors [1].



Model of the protein kinase C βII catalytic subunit complexed with ATP (redorange) and the pseudosubstrate peptide (cyan) [4].

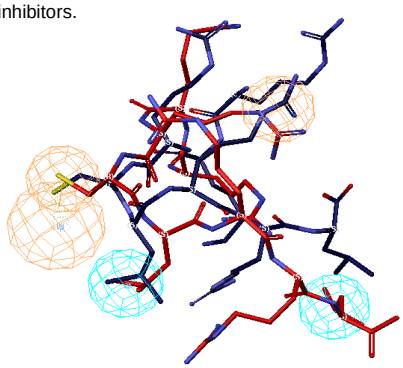
METHODS

***HipHop* algorithm** implemented in the Catalyst™ [5] software.
Training Set: 3D structure fragments containing a phosphorylation site of two natural PKC substrates from the RCSB Protein Data Bank™ [6]: Annexin IV (1ANN, amino acid sequence ^{6}GGTVKA^{11}) and Histone H5 (1HST, chain B, amino acid sequence ^{89}ASGSFRL^{96}).
Functions: *H-Bond Acceptor*, *H-Bond Donor*, *Hydrophobic* and *Positive Ionizable*. HB Acceptor, HB Donor and Positive Ionizable were customized to exclude peptide backbone elements.



RESULTS AND PERSPECTIVES

In this study a chemical function based pharmacophore model for protein kinase C ligands was generated starting from rigid structure fragments of natural PKC substrates. The highest rank *Common Features Hypothesis* obtained was used as a query for searching the Derwent World Drug Index database (WDI). The resulting hit list contained at least one substance class known to inhibit PKC [7]. Several flexible PKC substrate or substrate-like peptides fit the hypothesis. Moreover it showed to be enantioselective as well. Further optimization of this approach may lead to the discovery of new classes of nonpeptidic PKC inhibitors.



PKC substrate analogue peptides RKRCLRRL (red) and RKR(S-)CLRRL (blue) fitted to the hypothesis . The fit values = 3.3 and 2.33, respectively, indicate that the model remains selective with flexible and feature rich compounds .

Example for active compounds retrieved from the WDI: Michellamine alkaloids inhibit PKC by binding to the catalytic domain and apparently by blocking both the ATP and the substrate binding site [7]. The model is also able to distinguish between stereoisomers. The R-configured compound maps to all features of the hypothesis but in a different way with Fit = 0.16 vs. 1.99/2.33 (S-configuration).

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