

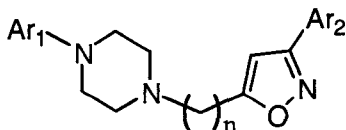
[S7-2] [10/18/2002(Fri) 14:00-14:30/Hall A]

## Three-dimensional Pharmacophore Mapping of a Series of Isoxazolyloxy-piperazine Inhibitors Selectively acting on the Dopamine D<sub>4</sub> Receptor

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The discovery of new ligands with affinity and selectivity for the dopamine D<sub>4</sub> receptor subtypes is an important area in medicinal chemistry. The distribution of the D<sub>4</sub> receptors in the limbic areas of brain suggests that these receptors may be particularly an attractive target for the design of potential selective antipsychotic drugs without causing extrapyramidal side effects. Since no structure information is available about the inhibitors in complex with D<sub>4</sub> receptor, a ligand-based approach was implemented in an attempt to understand the important interactions necessary for ligand binding. The pharmacophores classically determine the fundamental characteristics, in terms of nature and disposition of chemical groups required for a biological affinity. In this work, we used isoxazolyloxy-piperazine analogues as ligands, which covers a 4 log unit range to develop pharmacophore hypotheses, with various substituents and alkyl chain lengths through combinatorial method.



Scheme 1. Basic skeleton of all compounds used in pharmacophore analysis

To reach our research objectives modeling techniques (HypoGen and HipHop) have been used, including the pharmacophore modeling procedure implemented in the CATALYST package. HypoGen generates 3D pharmacophore models from a collection of molecules

possessing a range of diversity in both structures and activities. These hypotheses could be used as queries to search 3D databases to retrieve structures that fit the hypothesis, or as models to predict the activities of novel compounds. HipHop provides feature-based alignment of a collection of compounds without considering activity. Common features hypothesis generation is designed specifically for finding the chemical features shared by a set of compounds and for providing the compounds' relative alignments with a hypothesis these expressing common features. It can also be useful for stimulating ideas about structure-activity when one has only a few molecules that have similar activity but dissimilar and/or flexible structures.

From the calculated 10 results from HypoGen analysis, it is found that the best hypothesis (hypothesis 1) has good correlation and the lowest root-mean-square deviation with four features which include Hydrogen Bond Acceptor lipid (HBA1-1, HBA1-2), Hydrophobic Aromatic (HpAr), Ring Aromatic (RA). The best model showed high correlation (regression=0.950 in HypoGen analysis) and predictive power (mean value of residual values between measured and estimated activities in test set = 0.320). It also rationalized the relationships between structure and biological activity of these inhibitors of dopamine D4 receptor. This successful prediction was further validated on several structurally diverse compounds active against dopamine D4 receptor using HipHop method. Using the training set of five inhibitors with the multiconformation, the pharmacophore model was generated as three feature model containing hydrogen bond acceptor (HBA), hydrogen bond acceptor lipid (HBA1) and hydrophobic aromatic (HpAr) features.

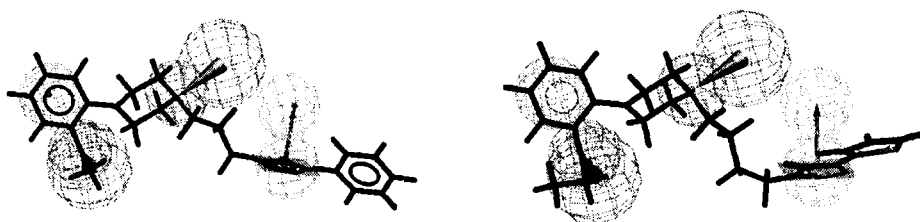


Figure 1. Superposition of the most active compound from the training and test set on the best pharmacophore model from Catalyst/HypoGen.

The superposition of two pharmacophore models from HypoGen and HipHop analysis.

Three features (two HBAs, one HpAr) were overlapped except for one HBAI feature of HypoGen are crucial to ligand binding. This validation study provides additional confidence for the pharmacophore model obtained from HypoGen and HipHop.

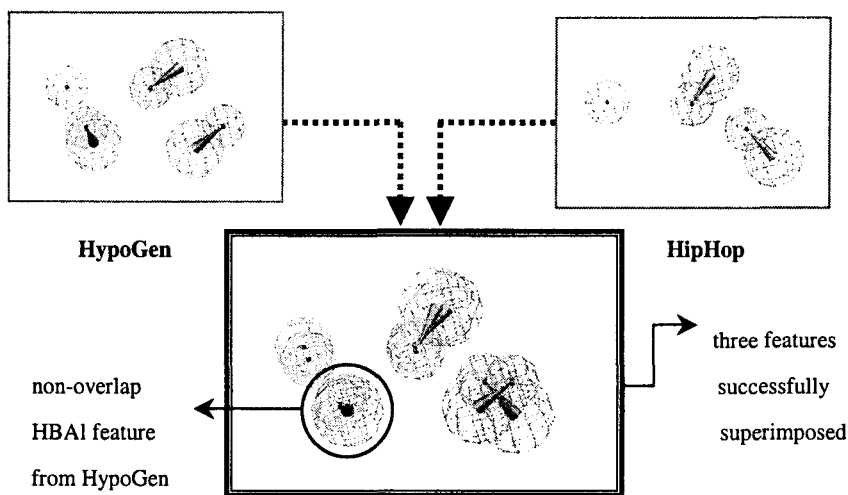


Figure 2. Overlapping of pharmacophore hypothesis obtained by HypoGen and HipHop analysis

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