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Case Study

Monoamines such as dopamine, serotonin and epinephrine play a variety of roles in brain chemistry. The development of tools to better understand how these small molecules act on the brain is an ongoing pursuit. The dopamine transporter (DAT) is of particular interest, but no crystallographic information about its structure is available. In the present study[1] the researchers probed the structure of the DAT using computational methods.

The objective of the study was to generate a pharmacophore for the DAT and verify its accuracy using a test set of ligands. To generate the pharmacophore, a multistep approach using a variety of computational methods was used. First, a training set of 36 piperidine-based analogues of cocaine was compared using the Genetic Algorithm Similarity Program (GASP). This program analyzed the structures of the compounds to identify common spatial arrangements of the functional groups. Using this, eight initial pharmacophores were generated.

To refine the dataset, the 36 ligands were superimposed on one representative compound using FlexS, a flexible superposition algorithm. Then a Computational Molecular Field Analysis (CoMFA) was performed. Of the eight initial pharmacophores, only two were deemed useful for further improvement. The two pharmacophores were further improved by varying the conformations of each ligand using FlexS and running the CoMFA again. Ultimately both models were able to predict the binding affinity of the training set with an r^2 greater than 0.99. Visualization of the pharmacophores shows that in both cases a H-bond donor, H-bond acceptor atom, and H-bond acceptor site are involved in ligand binding. The models, when tested on six additional ligands, gave very accurate predictions of binding affinity.

In conclusion, the work presented in this paper shows that a reasonable picture of the DAT can be elucidated based the binding affinities of a small set of compounds. This model of the DAT facilitates the study of novel therapeutics.

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[1] Yuan, H.; Kozikowski, A.; Petukhov, P. *J. Med. Chem.* **2002**, *47*, 6137-6143.