

ALIGNMENT-FREE 4D-QSAR: APPLYING THE XMAP TECHNIQUE IN PROSPECTIVE ANALYSES

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The recently developed alignment-free 4D-QSAR technique xMaP¹ provides a very straightforward and convenient way of creating QSAR models with predictive power. For each molecule in the dataset under scrutiny a conformer ensemble is determined. Afterwards, molecular surface properties important for non-covalent interactions are calculated and subsequently transferred to an alignment-free descriptor. This descriptor is the basis for generating and validating the QSAR model with various sophisticated chemometric techniques. As a result, an easily interpretable model is obtained.

The xMaP technique has been applied to a dataset of 76 Dopamine D1-receptor antagonists^{2,3} and led to a QSAR model of satisfactory statistical quality ($R^2=0.78$, $R^2_{CV-1}=0.71$, $R^2_{CV-50\%}=0.64$). This model was interpreted to find important pharmacophoric patterns. A N-methyl-moiety as well as two distinct aromatic rings were identified as important. The result was used in two different ways. First, the activities of eight newly synthesized, not-yet-tested compounds were predicted and ranked. After the compounds have been tested, it turned out that this ranking was in good agreement with the actual measurements which underlines the validity of the xMaP model. Second, a compound was suggested that directly fits the proposed pharmacophore: N-Methyldiphenylamine. It was purchased and tested for its antagonistic activity, which was found to be at a K_i value of 1.7 μM .

- [1] J.Scheiber, N. Stiefl, K. Baumann, In: QSAR & Molecular Modelling in Rational Design of Bioactive Molecules, E. Aki-Sener, I. Yalcin (Eds.) *Proc. of the 15th EURO-QSAR*, Ankara, Turkey
- [2] Wittig TW, Decker M, Lehmann J., *J Med Chem.* 2004 Aug 12;47(17):4155-8.
- [3] Witt T, Hock FJ, Lehmann J., *J Med Chem.* 2000 May 18;43(10):2079-81.