3D-QSAR based on Quantum-Chemical Molecular Fields: Towards an Improved Description of Halogen Interactions

Stefan Güssregen\textsuperscript{1)}, Hans Matter\textsuperscript{1)}, Gerhard Hessler\textsuperscript{1)}, Marco Müller\textsuperscript{1)}, Friedemann Schmidt\textsuperscript{1)}, Timothy Clark\textsuperscript{2)}

1) Sanofi-Aventis Deutschland GmbH, Industriepark Höchst, 65926 Frankfurt am Main, Germany
2) Computer-Chemie-Centrum, Universität Erlangen Nürnberg, Nägelsbachstr. 25, 91052 Erlangen, Germany

Current force field-based methods have limitations in the description of molecules. This is especially true for halogens and hypervalent elements such as sulphur. Here, the anisotropy of the electron density distribution (‘σ-hole’) is ignored. As a consequence, some important non-covalent interactions such as halogen-bonds or halogen-pi interactions, which are of high relevance in lead optimization [1,2], can not be accounted for.

Using tailored scoring functions or 3D-QSAR techniques employing molecular fields it is possible to compensate in part for such limitations. It is interesting to note that QM-based methods, which do not suffer from those limitations, have not been used widely in the context of 3D-QSAR in the past. Recently, the concept of calculating QM properties such as ionization potential, electron affinity or polarizability in a local context was introduced [3].

We have demonstrated the usefulness such local properties in molecular-field-based 3D-QSAR with a public data set of GABA\textsubscript{A}/Benzodiazapine receptor ligands and an internal data set for factorXa (fXa) inhibitors.

A ligand-based alignment of a set of 1,4-diazepine inhibitors [5] formed the starting point for 3D-QSAR models predicting the affinity against two receptor subtypes, GABA\textsubscript{A} and Benzodiazapine receptor. Here, models of higher predictive power were obtained for the QM-based properties based molecular fields than for those derived with the standard CoMFA method.

Furthermore, a structure-based alignment was created for a set of fXa inhibitors by docking into a representative crystal structure. This alignment was previously used to deduce 3D-QSAR models based on CoMFA and CoMSIA methods [4]. While predictive models have been obtained, important SAR-features have not been picked up, such as the interaction of chlorine and bromine atoms with a tyrosine side-chain that ultimately led to the development of orally active fXa drugs. Using QM-based molecular fields models of equal predictive power were obtained that were able to provide additional insights into the SAR.