

## **[L8] Covalent ligands: challenges and approaches for docking and design**

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Covalent ligands have recently regained considerable attention in drug discovery. The rational design of such ligands, however, is still faced with particular challenges, mostly related to the fact that covalent bond formation is a quantum mechanical phenomenon which cannot adequately be handled by the force fields or empirical approaches typically used for non-covalent protein-ligand interactions. Although the necessity for quantum chemical approaches is clear, they cannot yet routinely be applied to large data sets for screening or for a broad exploration of binding modes in docking calculations. On the other hand, technical solutions for performing docking calculations with covalent ligands are available, but their scope is normally quite limited. Scoring functions typically neglect the contribution from covalent bond formation completely. In this situation, the question arises how to approach covalent ligands and which methods to choose for their docking and design. The options currently available for different scenarios will be presented and discussed.