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Tautomerism in structure-based 3D pharmacophore modeling

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Tautomeric rearrangements on molecules lead to distinct equilibrated structural states of the same chemical compound, and evidently, have an impact on nearly all aspects of computer-aided chemical data processing [1] where the knowledge of the exact chemical structure is required (e.g. the calculation of chemical properties or interpretation of ligand-protein interactions). Although tautomerism is a well-known and well-documented phenomenon, it has long been disregarded in the field of drug design, which, as a consequence, leads to a possible misinterpretation of ligand binding interactions. Especially heuristic approaches, like structure-based pharmacophore modeling, are techniques that allow for consideration of several tautomeric forms, although this has not been done systematically by now. Recent approaches in the area of drug design mainly focus on virtual screening and tautomer enrichment of existing compound databases [2]. However, the effect of tautomerism in deriving interaction patterns within the protein-ligand complex (structure-based 3D pharmacophore modeling) has not yet been sufficiently addressed and thus leaves a wide and interesting field for future investigations. In the presented work various protein-ligand complexes have been studied where the tautomeric states of the ligand have a significant impact on derived 3D pharmacophores and the perception of binding modes, and also, tautomer-invariant pharmacophore patterns are introduced. Furthermore, an algorithm will be presented which enumerates all possible tautomers on both the receptor and ligand side under the constraints of a fixed active ligand conformation.

References

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