FlexNovo: Structure-based searching in chemistry-spaces

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At the beginning of a drug discovery project, a possible strategy for lead identification would be the structure-based search in extremely large Chemistry-spaces. Since such spaces cannot be enumerated for efficiency reasons, new tools for exploiting the combinatorial structure of the spaces are needed. This was the reason for the development of the new molecular design software FlexNovo.

FlexNovo performs a structure-based search in large Chemistry-spaces following a sequential growth strategy. The Chemistry-spaces usually consist of several hundreds to thousands of chemical fragments and a corresponding set of rules, which primarily specifies how the fragments can be connected with each other. FlexNovo is based on the FlexX[1] docking software and makes use of its incremental construction algorithm.

FlexNovo has been used to design potential inhibitors for a couple of targets of pharmaceutical interest by using a large Chemistry-space. The determined structures were visually inspected and the proposed binding modes compared to binding modes of known inhibitors. The preliminary results show that FlexNovo is able to create a set of reasonable molecules which fulfill the chemical and steric constraints of the respective active site.

References

[1] Rarey M, Kramer B, Lengauer T, Klebe G, *J. Mol. Biol.*, 1996, **261**, 470.