TEACHING AN OLD DOG NEW TRICKS – OPTIMIZED FINGERPRINT AS A BASIS FOR NEW COMPOUNDS FORMATION

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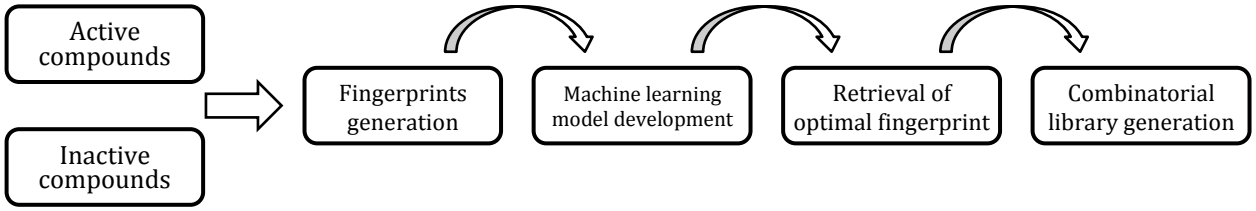
Great popularity of virtual screening approaches has triggered not only the search for new tools for active compounds identification, but also caused the development of methodologies for generation of virtual libraries of potentially active molecules. The most popular ways for making new structures from the already existing ligands are bioisosteric replacement,[1] core hopping,[2] and hybridization of ligands.[3]

In the present study, the new concept for such libraries generation was developed. In contrast to the already used combinatorial approaches, the optimization is performed on different level, without the explicit use of the chemical structure. It uses the string substructural representation of molecules [4] and generates new compounds from the optimal fingerprint provided by machine learning algorithms. In order to reduce the size of the output library (the irreversible nature of fingerprints imposes the necessity of enumerating all possible connections between substructures indicated as important for particular activity profile), the system of constraints for the substructural connections was developed. The library post-processing with the use of hashed fingerprints [4] leads to reasonable database narrowing, and the resulting final outcome provides interesting connections between particular substructures, discovering the structurally new potential ligands. The poster presents the case study of serotonin receptor 5-HT_6, and the resulting compounds are evaluated in terms of their activity potency towards 5-HT_6R.



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