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The estimation and application of fragments' contributions to the ligand binding energy

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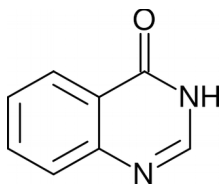
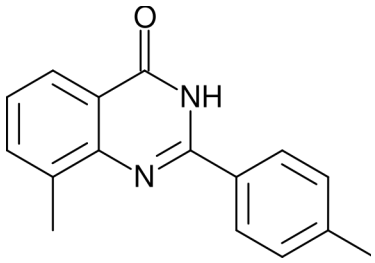
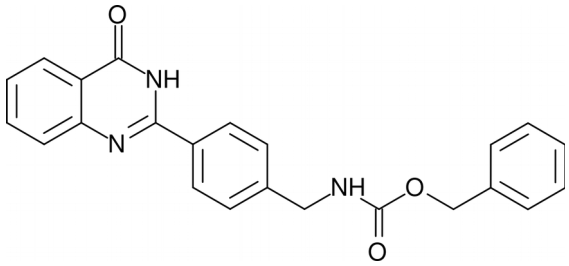
During lead-optimization there is often a need to maximize the use of a certain synthetic framework or the privileged fragment. In the early stages the focus tend to be moved from the use of that fragment to optimization of substituent groups, which form efficient interaction with pockets of a binding site. This direction of optimization of a structure, despite initially fast first results, often leads to deadlock. In this work we offer an approach which rationally guides on the use of fragments by estimating their utility metrics. The estimate of utility is produced by extracting a share of a fragment from the energy of interaction.



Fragment 0



Compound 1



Compound 2

The method was tested by retrospective analysis using tankyrase-2 as the target and its inhibitors as ligands (compound 1 and 2) [1,2]. Compound 1 and 2 were docked into the binding site of tankyrase-2 by AutoDock Vina. For each position found the positions of the constituent fragments were extracted. For each fragment the estimate of binding energy and its share were produced. On the basis of the share of the fragment 0 the position of the compound 1 was chosen for further optimization.

Compound 2 was used to validate the retrospective prediction of the best position of compound 1. The estimate of the fragment's share of compound 2 allowed to choose a few positions, one of which turned out to be close to native position of the ligand (rmsd[fragment] = 1.5 Å).

Thus, the estimate of the fragment's share allowed to choose the rational way of further optimization using only limited amount of experimental information at hand.

1. Nathubhai, Amit, et al. "Structure-activity relationships of 2-arylquinazolin-4-ones as highly selective and potent inhibitors of the tankyrases." European journal of medicinal chemistry118 (2016): 316-327.

2. Nathubhai, Amit, et al. "Design and discovery of 2-arylquinazolin-4-ones as potent and selective inhibitors of tankyrases." ACS medicinal chemistry letters 4.12 (2013): 1173-1177.