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Virtual screening by high-throughput docking using hydrogen bonding constraints for targeting a protein-protein interface in *M. tuberculosis*

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The resurgence of Tuberculosis, caused primarily by *Mycobacterium tuberculosis*, and the appearance of drug resistant tuberculosis strains encourage the need for new drugs with alternative mode of actions [1]. An interesting drug-target is the Thioredoxin-Reductase (TrxR)/Thioredoxin (Trx) System of *M. tuberculosis*, which is responsible for providing reducing equivalents for many cellular processes including bacterial antioxidant defence [2].

We performed a virtual screening approach for identifying novel drugs for the treatment of Tuberculosis that used the hydrogen bonding constraint functionality of GOLD for pre-processing instead of using pharmacophore filtering. Two important hydrogen bonding interactions could be identified at the protein-protein interface of the TrxR-Trx complex. A high-throughput docking was applied to filter the Intervet in-house compound library (~6.5 million compounds) for possible hits that interact with these two hydrogen bonding acceptors. This reduced the number of interesting compounds to 151768 that were redocked without any constraints and more accurate docking settings. Finally, the ranking of the reduced compound set was obtained using a normalisation based on molecular weight [3] and a consensus scoring in a restrictive way using Chemscore and ASPscore.

So far, six out of the first 25 of the ranked compound list showed an activity with an IC_{50} value upto µM range. Especially three compounds with different scaffolds and a low molecular weight are promising candidates for further developments.

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