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Abstract

The implementation of a novel sequential computational approach that can be used effectively for virtual screening and identification of prospective ligands that bind to trypanothione reductase (TryR) is reported. The multistep strategy combines a ligand-based virtual screening for building an enriched library of small molecules with a docking protocol (AutoDock, X-Score) for screening against the TryR target. Compounds were ranked by an exhaustive conformational consensus scoring approach that employs a rank-by-rank strategy by combining both scoring functions. Analysis of the predicted ligand–protein interactions highlights the role of bulky quaternary amine moieties for binding affinity. The scaffold hopping (SHOP) process derived from this computational approach allowed the identification of several chemotypes, not previously reported as antiprotozoal agents, which includes dibenzothiepine, dibenzooxathiepine, dibenzodithiepine, and polycyclic cationic structures like thiaazatetracyclo-nonadeca-hexaen-3-ium. Assays measuring the inhibiting effect of these compounds on T. cruzi and T. brucei TryR confirm their potential for further rational optimization.