Docking-based virtual screening identification of multi kinase-targeting inhibitors with *in vitro* phenotypic activity against *Schistosoma mansoni*

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ABSTRACT

Currently, praziquantel (PZQ) is the only available drug that is effective against all *Schistosoma* species, even considering its low efficacy against early stages of the worm. In the search for new drugs to tackle schistosomiasis, computer-aided drug design has proven a helpful tool to enhance the search and initial identification of schistosomicidal compounds, allowing fast and cost-efficient progress in drug discovery. The combination of *in silico* high-throughput screening followed by *in vitro* phenotypic assays allows the assessment of enormous libraries of compounds with the potential to inhibit biological targets. Besides, the drug discovery field has witnessed a shift from traditional approaches of finding potent selective inhibitors against individual targets, towards identifying promiscuous compounds with multi-target efficacy and less toxicity ("Multi-target drugs"). In order to explore this paradigm, we employed molecular docking for *in silico* screening of five predicted homology models of *Schistosoma mansoni* kinase proteins (SmJNK, Smp38, SmERK1, SmERK2, and SmFES) against approximately 85,000 molecules from the Managed Chemical Compounds Collection of the University of Nottingham (UK). Based on molecular docking scores, we selected 169 molecules, 78 of which were single kinase-targeting compounds and 91 predicted to target all MAP kinases. All compounds were screened *in vitro* against larval and adult stages of *S. mansoni*. In total, 88 (52%) molecules were considered active in at least one of the assays. This approach shows a much higher efficiency when compared to using only traditional high-throughput *in vitro* screening assays, where initial positive hits are retrieved from testing thousands of molecules. Additionally, when we focused on compound promiscuity over selectivity, we were able to efficiently detect 36 active compounds that are predicted to target four SmMAP kinases at the same time. This approach reinforces the concept of selecting multi-target inhibitors aiming for one 'drug-many targets'. Moreover, at least 49 active compounds presented satisfactory druggability score when compared to PZQ, allowing further optimisation to improve potency. In conclusion, our data support the hypothesis that compound prioritization against many targets is a helpful alternative for drug discovery against schistosomiasis.

Keywords: *Schistosoma mansoni* protein kinases, computer-aided drug design, phenotypic screening, multi-target drugs