Anti-schistosomal activities of quinoxaline-containing compounds: from hit identification to lead optimisation

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Schistosomiasis is a neglected disease of poverty that is caused by infection with blood fluke species contained within the genus Schistosoma. For the last 40 years, control of schistosomiasis in endemic regions has been predominantly facilitated by administration of a single drug, praziquantel. Due to limitations in this mono-chemotherapeutic approach for sustaining schistosomiasis control into the future, alternative anti-schistosomal compounds are increasingly being sought by the drug discovery community. Herein, we describe a multi-pronged, integrated strategy that led to the identification and further exploration of the quinoxaline core as a promising anti-schistosomal scaffold.
Firstly, phenotypic screening of commercially available small molecules resulted in the identification of a moderately active hit compound against *Schistosoma mansoni* (1, EC$_{50}$ = 4.59 µM on schistosomula). Secondary exploration of the chemical space around compound 1 led to the identification of a quinoxaline-core containing, non-genotoxic lead (compound 22). Compound 22 demonstrated substantially improved activities on both intra-mammalian (EC$_{50}$ = 0.44 µM and 84.7 nM, on schistosomula and adult worm, respectively) and intra-molluscan (sporocyst) *S. mansoni* lifecycle stages. Further medicinal chemistry optimisation of compound 22, resulting in the generation of 20 additional analogues, improved our understanding of the structure-activity relationship and resulted in considerable improvements in both anti-schistosome potency and selectivity (e.g. compound 30; EC$_{50}$ = 2.59 nM on adult worms; selectivity index compared to the HepG2 cell line = 348). Some compound 22 derivatives (e.g. compounds 31 and 33) also demonstrated significant activity against the two other medically important species, *Schistosoma haematobium* and *Schistosoma japonicum*. Further optimization of this class of anti-schistosomal is ongoing and could lead to the development of an urgently-needed alternative to praziquantel for assisting in schistosomiasis elimination strategies.

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