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

Gilda Padalino[1], Nelly El-Sakkary[2], Lawrence J. Liu[2], Chenxi Liu[2], Dannielle S. G. Harte[3], Edward Sayers[4], Josephine Forde-Thomas[1], Helen Whiteland[1], George Johnson[2], Arwyn T. Jones[4], Marcella Bassetto[4], Salvatore Ferla[4], Conor R. Caffrey[2], Iain Chalmers[1], Andrea Brancale[4], Karl F. Hoffmann[1].

[1] Institute of Biological, Environmental and Rural Sciences (IBERS), Aberystwyth University, Aberystwyth, Wales, United Kingdom.

[2] Swansea University Medical School, Swansea SA2 8PP, UK.

[3] Center for Discovery and Innovation in Parasitic Diseases (CDIPD), Skaggs School of Pharmacy and Pharmaceutical Sciences, University of California, San Diego, La Jolla, CA 92093, USA.

[4] School of Pharmacy and Pharmaceutical Sciences, Cardiff University, Redwood Building, King Edward VII Avenue, Cardiff, CF10 3NB, UK.

[5] Department of Chemistry, College of Science and Engineering, Swansea University, Swansea SA2 8PP, UK.

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.

Keywords: Schistosomiasis, Quinoxaline, SAR, drug discovery