NOVEL COMPOUNDS FOR THE TREATMENT OF CHAGAS' DISEASE

M. Keenan[1], M. Abbott[1], T. Akama[5], P. Alexander[1], T. Armstrong[2], W. M. Best[1], B. Berven[1], A. Botero[2], J. Chaplin[1], S. Charman[3], E. Chatelain[4], H. Diao[1], E. Easom[5], T. Von Geldern[4], M. Kerfoot[2], A. Khong[2], J. McManus[1], I. Scandale[4], A. R. Thompson[3], Z. Wang[1], K. White[3]

[1]Epichem, Murdoch, WA, Australia
[2]Veterinary and Biomedical Sciences, Murdoch University, Murdoch, WA, Australia
[3]Centre for Drug Candidate Optimisation, Monash University, Parkville, VIC, Australia
[4]Drugs for Neglected Diseases initiative, Geneva, Switzerland
[5]Anacor Pharmaceuticals, Inc, Palo Alto, CA, United States

Chagas' disease causes suffering for an estimated 8 million people worldwide with 100 million at risk, costs 667,000 DALYs per year and is endemic in 21 Latin American countries causing social and economic hardship for some of the world's poorest populations. Current drug therapies, benznidazole (Rochagan®) and nifurtimox (Lampit®), are only effective during the acute stage of infection and are met with low compliance due to undesirable side-effects and extended treatment times. The causative agent of Chagas' disease, *Trypanosma cruzi*, is an intracellular parasite with a complex life cycle in the mammalian host, and the ultimate challenge for new treatments is to achieve parasitological cure of the chronic form of the disease. The Chagas' disease Drug Discovery Consortium has several compound series in development, one of which is derived from the fungicide fenarimol. These compounds have high potency (in the low nM range) against *T. cruzi in vitro* with no associated cytotoxicity, are easy to synthesise, have good metabolic stability and oral bioavailability, are non-toxic *in vivo* and demonstrate efficacy in a murine model of *T. cruzi* infection. A new series of compounds to the discovery effort containing an oxaborole motif are less potent *in vitro*, but lead compound AN4169 exhibits excellent activity in the murine *in vivo T. cruzi* infection model. Chemical and biological studies undertaken in the development of these series towards the goal of delivering new drug candidates for Chagas' disease will be presented.