

SCYX 7158 CHEMISTRY BACKGROUND AND NEW FINDINGS

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Human African trypanosomiasis (HAT) represents a significant public health problem in sub-Saharan Africa affecting hundreds of thousands of individuals. An urgent need exists for the discovery and development of new, safe, and effective drugs to treat HAT, as existing therapies have poor safety profiles, difficult treatment regimens, limited effectiveness, and a high cost of goods. From a collaborative effort between SCYNEXIS, Anacor Pharmaceuticals, Pace University, and DNDi, we summarize optimization of a novel class of small boron-containing compounds, the oxaboroles. We have identified SCYX-7158 as an effective, safe, and orally active treatment for HAT in a mouse model of stage 2 (CNS) disease. SCYX-7158 is active *in vitro* against relevant strains of *Trypanosoma brucei*, including *T. b. rhodesiense* and *T. b. gambiense* (IC₅₀ values 0.18-0.98 mM), and is efficacious in both stage 1 and stage 2 murine HAT models. Physicochemical and *in vitro* ADME properties of SCYX-7158 are consistent with the compound being orally available, metabolically stable, readily CNS permeable and with low risk for drug drug interactions. In the stage 2 mouse model, SCYX-7158 is effective orally at doses as low as 12.5 mg/kg (QD per 7 days). *In vivo* pharmacokinetic characterization of SCYX-7158 shows that the compound is highly bioavailable in rodents and non-human primates, has low intravenous plasma clearance, a 24-hr elimination half-life, and a volume of distribution that indicates good tissue distribution. Most importantly, in rodents brain exposure of SCYX-7158 is high, with C_{max} higher than 10 g/mL and AUC_{0-24hr} higher than 100 g*hr/mL following a 25 mg/kg oral dose. Furthermore, SCYX-7158 readily distributes into the CSF to achieve therapeutically relevant concentrations in this compartment. Based on these properties, which promise lower rates of recrudescence than with current standard of care, SCYX-7158 has been selected as a preclinical candidate for treatment of stage 2 HAT.