Lead Optimization of Novel Boron-Containing Drug Candidates for the Treatment of Human African Trypanosomiasis

Robert Jacobs1, Charles Ding2, Yvonne Freund3, Kurt Jamaragni2, Jacob Plattner2, Cyrus Bacchi3, Nigel Yarlet3, Matthew Orr1, Bakela Nare1, Cindy Rewerts1, Daitao Chen1, Andy Noe1, Jessica Sligar1, Matthew Jenks1, Stephen Wring1, Robert Don4.

1SCYNEXIS, Inc., Research Triangle Park, NC, United States, 2Anacor Pharmaceuticals, Inc., Palo Alto, CA, United States, 3Pace University, New York, NY, United States, 4Drugs for Neglected Disease initiative, Geneva, Switzerland.

Abstract

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 suffer from 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 report ongoing lead optimization efforts on a novel class of small molecule boron-containing compounds, exemplified by SCYX-6759. These compounds inhibit in vitro growth of T. b. brucei with IC50 > 100 nM, are not cytoxic to mammalian cells, and exhibit good physiochemical and pharmacokinetic properties. In a murine model of CNS-stage disease utilizing the TREU667 strain of T. b. brucei, treatment with 50 mg/kg of SCYX-6759 BID for 14 days has demonstrated 100% efficacy, resulting in absence of blood parasites for >180 days. Development of a structure-activity relationship (SAR) profile for this chemical series and efforts to improve biological and pharmacokinetic profiles in the CNS-disease model through chemical modifications are reported herein.

Results

Oxaborole 6-N-Benzamides

- Active against T. b. brucei in vitro, with good PK and physiochemical properties.
- Efficacious in vivo against both acute (Stage I) and CNS (Stage II) infection in mouse model.
- Exemplified by SCYX-6759.

Acute In Vivo Efficacy (Stage I)

- Any group necessary for good activity.
- 2-Cl or 2-CF3 increase potency.
- 5'-OCH3, 7-OCH3, and 7-CH3 well tolerated.
- 5-F well tolerated.
- Oxaboroles have been identified as a promising lead series for the treatment of HAT; demonstrating high in vitro potency vs. T. b. brucei and good PK and physicochemical properties.

In Vivo Pharmacokinetics

- SCYX-7158 demonstrates robust in vivo activity in mouse model.
- ** Also fully efficacious at 5 mg/kg, p.o., b.i.d. (3/3 cured).

CNS (Stage II) Efficacy

- SCYX-7158 sustains >80% in CNS for over 24 hours.
- Excellent PK and CNS disposition at small cost to potency.

Summary

- Oxaboroles have been identified as a promising lead series for the treatment of HAT; demonstrating high in vitro potency vs. T. b. brucei and good PK and physicochemical properties.
- Lead optimization of the 6-N benzamide region has afforded compounds that are orally active in murine models of both acute (stage I) and chronic (stage II) trypanosomiasis.
- Functionalization of the C-3 position on the oxaborole ring has significantly improved overall PK properties, particularly by increasing CNS disposition and retention.
- The optimized lead compound (SCYX-7158) is currently demonstrating robust in vivo activity against stage II trypanosomiasis at clinically relevant dosing levels in ongoing studies.
- Further biological, toxicological and pharmacokinetic profiling of SCYX-7158 is also in progress.