

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

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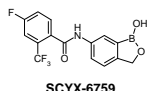
Abstract

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. brucei* with IC₅₀'s ~100 nM, are not cytotoxic to mammalian cells, and exhibit good physicochemical and pharmacokinetic properties. In a murine model of CNS-stage disease utilizing the TREU667 strain of *T. brucei*, treatment with 50 mg/kg of SCYX-6759 BID for 14 days has demonstrated >180 days 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 6N-Benzamides

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



T. brucei IC₅₀ = 180 nM

Cytotoxicity (L929) > 25 μM

LogD = 2.57

Solubility (pH 7.4) > 200 μM

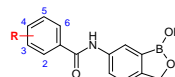
S₉ t_{1/2} > 350 min (mouse, rat, human)

P_{app} = 379 nm/s (AQ = 0.02)

Oral Bioavailability (mouse) = 63%

- Series limited by poor brain disposition and rapid clearance from CNS
- Progressed to lead optimization in mid-2008

Acute *In Vivo* Efficacy (Stage I)



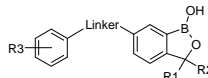
SCYX Id	R	<i>T. brucei</i> IC ₅₀ (nM)	L929 Cytotoxicity IC ₅₀ (μM)	Animals cured* (10 mg/kg, p.o., b.i.d.)
4424	H	160	> 39.5	NT
7582	2-F	130	> 36.9	1 / 3
5896	2,6-F ₂	159	> 34.5	1 / 3
4461	2-CF ₃	125	11.8	3 / 3
7620	2-Cl	70	> 34.8	3 / 3
6835	2-Cl, 4-F	147	> 32.7	3 / 3
6752	2-CF ₃ , 5-F	139	15.5	3 / 3
6759	2-CF ₃ , 4-F	180	> 29.5	3 / 3**

- Series demonstrates robust *in vivo* activity in mouse model
- *Cure = No parasitemia detectable for >30 days
- ** Also fully efficacious at 5 mg/kg, p.o., b.i.d. (3/3 cured)

SAR Development

- Aryl group necessary for good activity
 - 2-CF₃ or 2-Cl increase potency
 - 4-F improves metabolic stability
 - 5-F well tolerated
 - 5-OCH₃, 7-OCH₃, and 7-CH₃ lead to loss of activity
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- Sulfonamides show cytotoxicity and poor PK profiles.
 - Ureas demonstrate limited permeability
 - Amines and carbamates poorly tolerated
 - Boron required for activity
 - Reduced activity with increasing bulk at 3-position
 - 3-Substitution improves PK with slight loss in potency

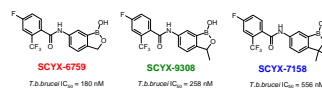
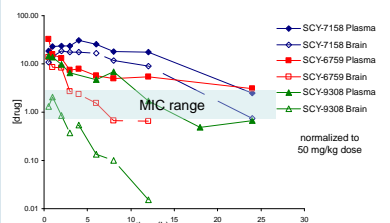
Addressing Pharmacokinetic Liabilities



SCYX Id	R ₁	R ₂	R ₃	Linker	<i>T. brucei</i> IC ₅₀ (nM)	Cytotox (μM)	MDR1-MDCK Permeability	
							P _{app} (nm/sec)	AQ
6759	H	H	2-CF ₃ , 4-F	-CONH-	180	> 25	380	0.02
9308	H	CH ₃	2-CF ₃ , 4-F	-CONH-	258	3.4	683	0.03
8258	H	isobutyl	2-CF ₃ , 4-F	-CONH-	6099	> 25	NT	NT
8240	H	cyclopentyl	2-CF ₃ , 4-F	-CONH-	7810	> 25	NT	NT
7158	CH ₃	CH ₃	2-CF ₃ , 4-F	-CONH-	556	> 25	415	0.03
2977	Spirocyclopropyl		2-CF ₃ , 4-F	-CONH-	523	> 25	632	0.08
7285	Spirocyclobutyl		2-CF ₃ , 4-F	-CONH-	892	> 25	NT	NT
1124	Spirocyclopentyl		2-CF ₃ , 4-F	-CONH-	13940	> 25	377	-0.02
4435	H	H	4-OCH ₃	-SO ₂ NH-	94	6.6	334	0.28
0278	CH ₃	CH ₃	4-OCH ₃	-SO ₂ NH-	6480	>25	NT	NT
6412	H	H	4-Cl	-NHCONH-	238	>25	234	NT
3569	CH ₃	CH ₃	4-Cl	-NHCONH-	>15000	>25	NT	NT

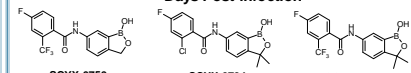
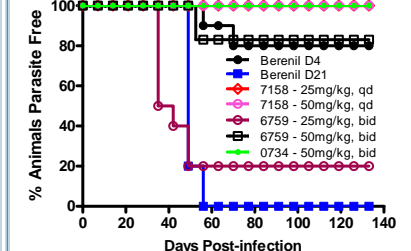
- SCYX-7158 found to possess the best combination of activity, pharmacokinetics, and physicochemical properties

In Vivo Pharmacokinetics



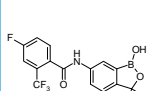
- SCYX-7158 sustains >MIC in CNS for over 24 hours
- Excellent PK and CNS disposition at small cost to potency

CNS (Stage II) Efficacy



- 3,3-Disubstituted oxaboroles show improved efficacy in a murine model for Stage II Trypanosomiasis.

SCYX-7158 – Optimized Lead Profile



T. brucei IC₅₀ = 556 nM

Cytotoxicity (L929) > 25 μM

LogD = 3.51

Solubility (pH 7.4) = 25 μM

S₉ t_{1/2} > 350 min (mouse, rat, human)

P_{app} = 414.8 nm/s (AQ = 0.03)

Oral Bioavailability (mouse) = 57%

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.