



AN2920, A Novel Oxaborole, Shows
In Vitro and *In Vivo* Activity Against
Trypanosoma brucei



Collaboration to Develop Novel Oxaboroles for Treatment of Human African Trypanosomiasis

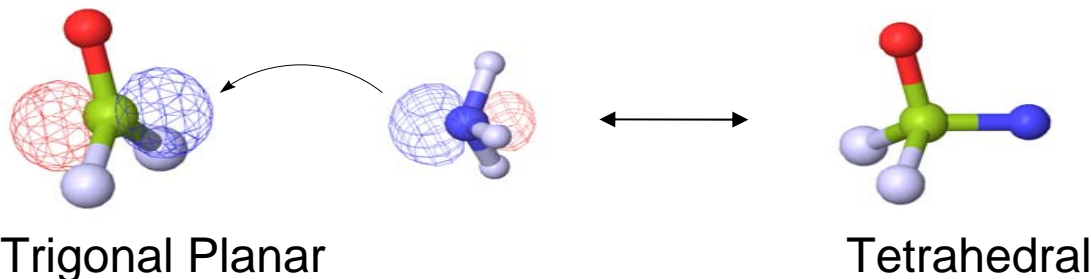


- Collaborators:

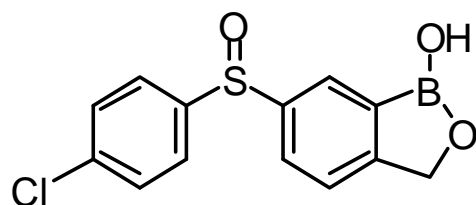
- DNDi
- Scynexis, Inc
- Sandler Center
- Haskins Laboratory, Pace University
- Antwerp University
- Swiss Tropical Institute
- Shanghai Jiao Tong University
- Anacor Pharmaceuticals, Inc.

- Why boron?

- Boron is a trivalent and trigonally planar molecule with a reactive P-orbital which, under certain conditions, can form a tetrahedral structure.
- Exploiting the P-orbital reactivity allows rational drug design and creation of compounds with unique properties beyond traditional small molecule drugs



HTS Screening Led to the Discovery of the Benzoxaborole, AN2920



AN2920

MW = 292.0
Log D = 2.51

<i>In vitro</i> Efficacy	AN2920 IC ₅₀ (μM)*
<i>T.b.brucei</i> (SBRI 427) ¹	0.411
<i>T.b.brucei</i> (EATRO 110) ^{1,2}	0.376
<i>T.b.brucei</i> (Squib 427) ³	0.284
<i>T. b. rhodes.</i> (STIB900) ³	0.535
<i>T. b. rhodes.</i> (STIB900) ⁴	0.473
Cytotoxicity (L929 cells) ¹	30.3
Cytotoxicity (MRC-5 cells) ³	42.9
Cytotoxicity (L6 cells) ⁴	253
Selectivity Index (SI)	>70

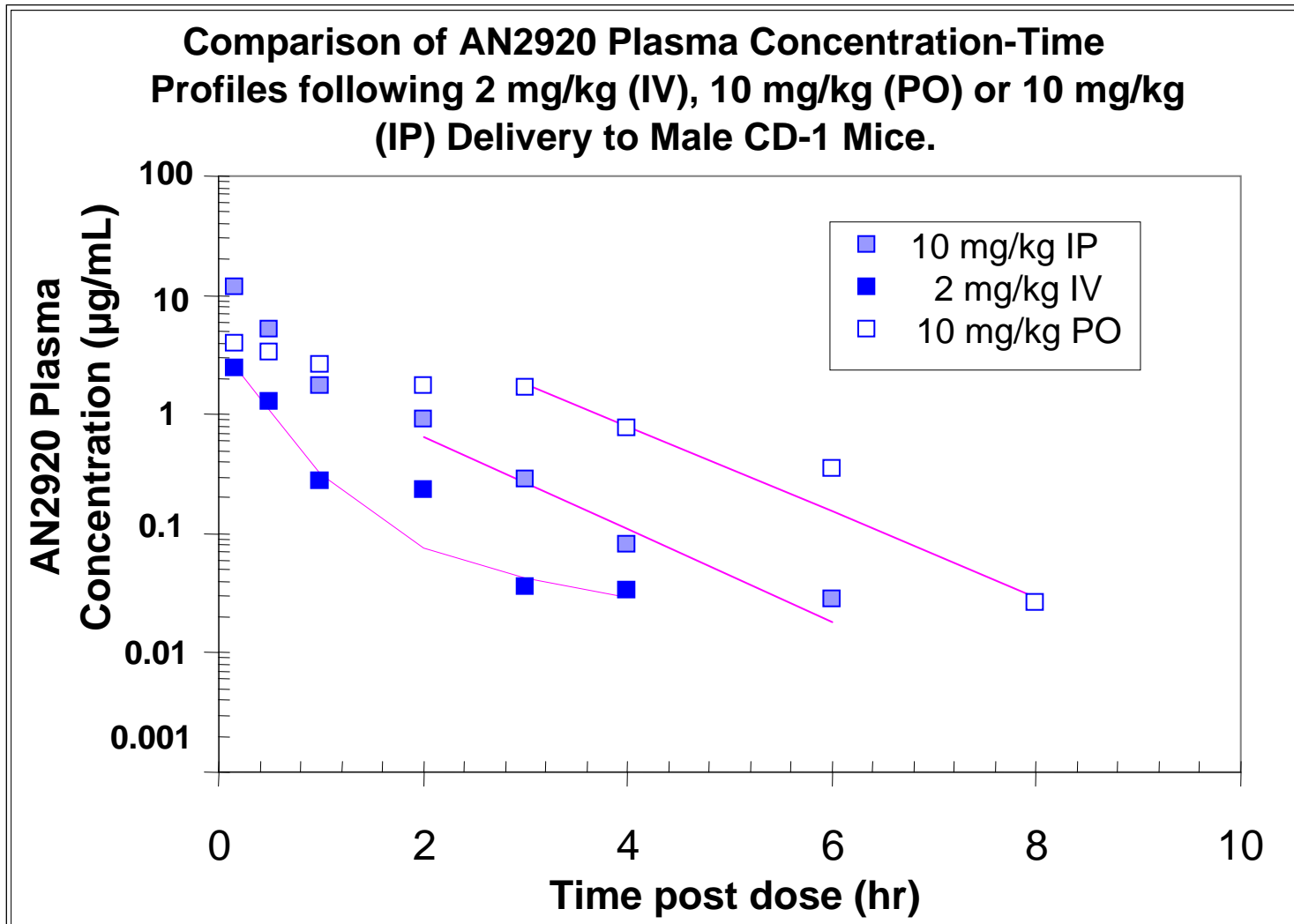
*Green colored values: acceptable for further development
¹SCYNEXIS; ²Sandler Center ³Antwerp; ⁴Swiss Tropical Institute

AN2920 Demonstrates Minimal *In Vitro* Metabolism or Inhibition of Cytochrome P450s



<i>In vitro</i> parameters	AN2920
T _{1/2} ' (Mouse Liver Microsomes, min)	> 350
T _{1/2} (Mouse S9, min)	146
% inhibition of Cytochrome P450s: CP1A2, 2C9, 2D6, 3A4 @ 10 μM	< 10
% inhibition of CYP2C19 @ 10 μM	50

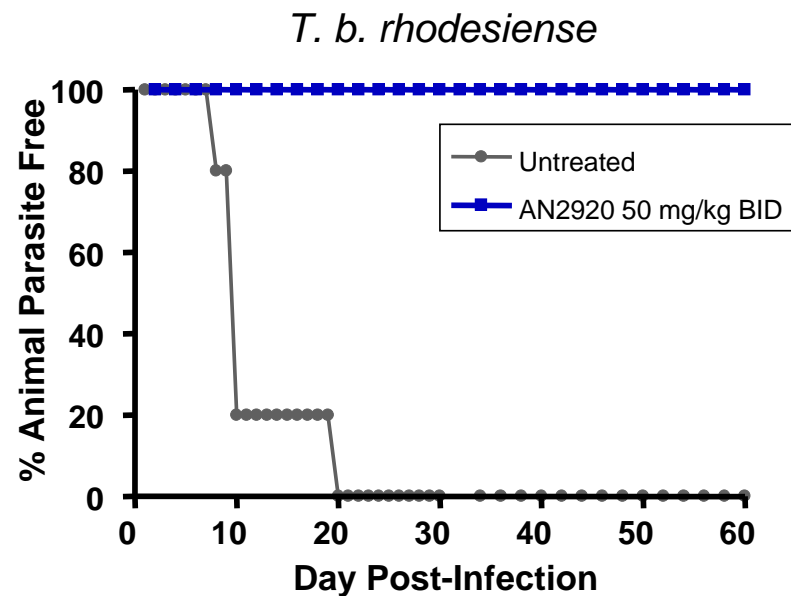
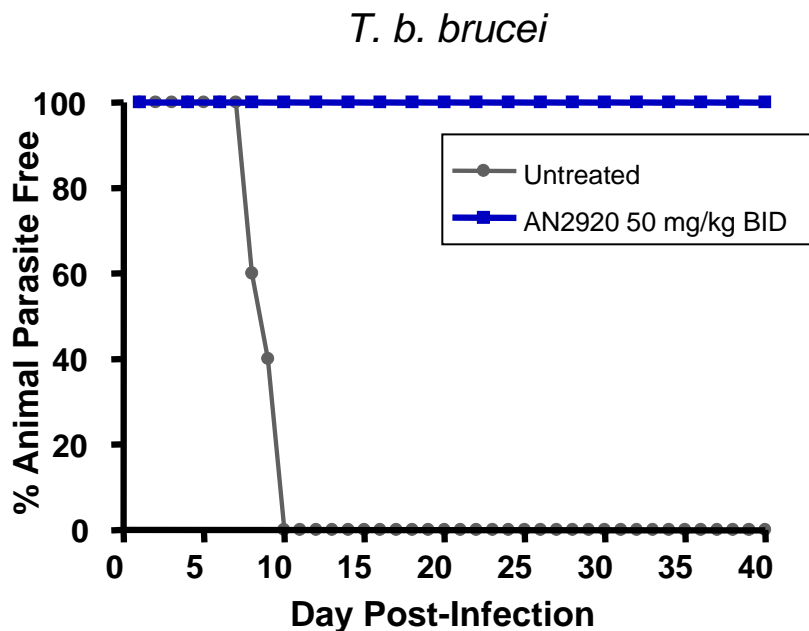
AN2920 Shows Good Plasma Exposure After IP, IV and PO Dosing in Mice.



AN2920 Protects Mice Against Infection With *T. b. brucei* or *T. b. rhodesiense*

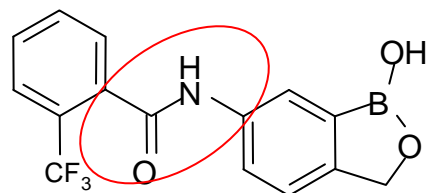


Acute infection models

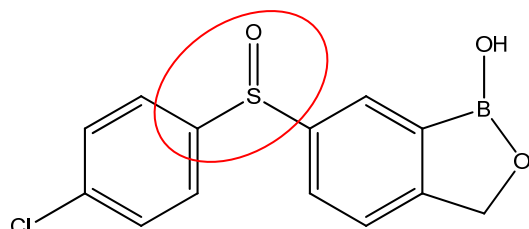


Female BALB/C mice inoculated IP with 600 *T. b. brucei* parasites or 10^4 *T. b. rhodesiense*. Treatment started 24 h post-infection for 5 days with 50 mg/kg BID, IP dosing. Survival monitored 40 or 60 days.

A Follow-on Oxaborole, AN3520, Protects *In vivo* at Lower Concentrations than AN2920



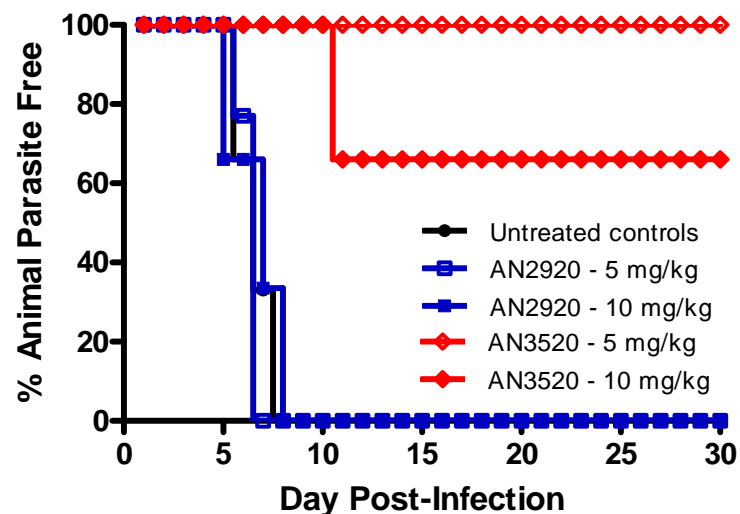
AN3520



AN2920

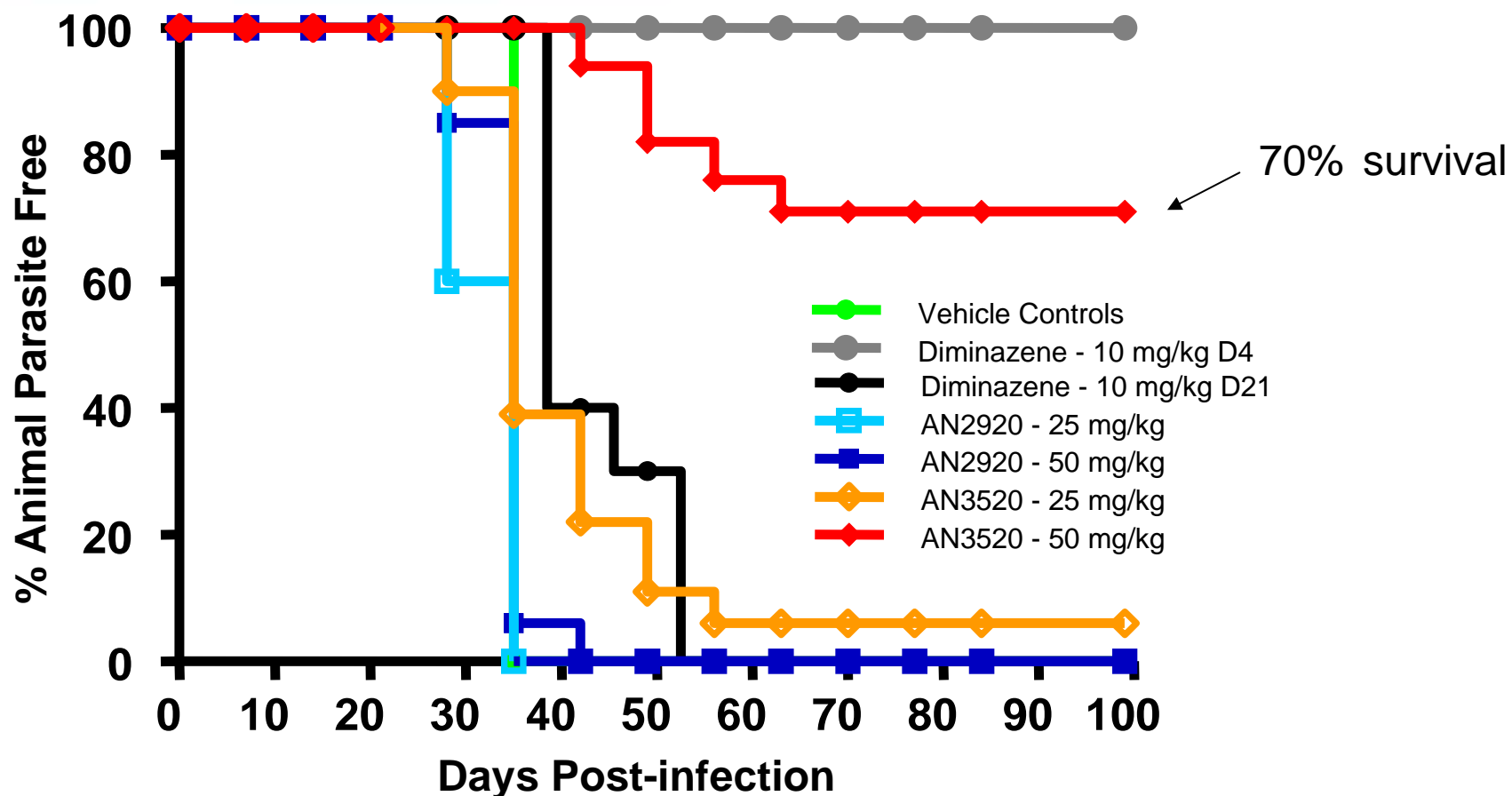
Compounds have similar *in vitro* efficacy, PK and *in vitro* metabolic profiles

Acute infection. *T. b. brucei*



Female Swiss Webster mice inoculated IP with 250,000 parasites of *T. b. brucei*. Treatment started 24 h post-infection, PO for 4 days, BID.

Activity of AN3520 and AN2920 Against a *T. brucei* CNS Infection in Mice



Female Swiss Webster mice infected with 10,000 TREU 667 *T. b. brucei*. Treatment started 21 days post-infection for 7 days with IP dosing, BID.

Summary



- Identified a novel series of benzoxaboroles with efficacy *in vitro* and *in vivo* against acute *T. b. brucei* and *T. b. rhodesiense* infection
- AN2920 and AN3520 both show good oral bioavailability, acceptable PK, and no pre-clinical safety flags.
- AN3520 allowed 70% survival of mice 99 days after infection with a CNS-tropic strain of *T. b. brucei*.
- Advancement of AN3520, and other class members, to IND-enabling toxicity and pharmacology studies is planned.

Information Sharing is Facilitated Through SCYNEXIS' HEOS[®]



SCYNEXIS - HEOS[®] - [project: ANACOR - compound: SCYX0001034420 - batch: PCANA00-0011] - Windows Internet Explorer

Compound ID: SCYX0001034420
 Compound Name:
 Trivial Name:
 Exact Mass: 292.546
 Molecular Weight: 292.013211
 Molecular Formula: C13H10BClO3S
 Stereo Designation:
 Status:

Batch Number	Salt	External ID	Project ID	Library Name	Chemist Name	Registered Date	Registered By
PCANA00-0011	NONE	AN2920	ANACOR	PURECOMPOUNDS	Matt Orr	25-MAR-2008	Matt Orr
PCANA00-0113	NONE	AN2920	ANACOR	PURECOMPOUNDS	Joe Perales	18-JUN-2008	Joe Perales
PCANA00-0208	NONE	AN2920	ANACOR	PURECOMPOUNDS	Jessica Sliger	28-JUL-2008	Jessica Sliger

Sample	Assay Type	Organism	Test Parameter	Dose	Test Value	Test Date	Tester
3068260	HAT in vitro IN VITRO	T. b. rhodesiense STB 900	SI		= 79.2	04-JUN-2008	LMPVTHATY
3068260	HAT in vivo IN VIVO	T. b. brucei EATRO 110 ip	MSD	3 adm days 20 mg/kg	> 120.5	21-MAR-2008	Louis Maes
3068260	HAT in vivo IN VIVO	T. b. brucei EATRO 110 ip	MSD	4 adm days 20 mg/kg	= 12 day	10-APR-2008	LMPVTHATY
3068260	HAT in vivo IN VIVO	T. b. brucei EATRO 110 po	MSD	4 adm days 20 mg/kg	= 10.5 day	19-MAY-2008	Aixa Rodriguez
3068260	HAT in vivo IN VIVO	T. b. brucei EATRO 110 po	MSD	4 adm days 20 mg/kg	= 10.5 day	08-APR-2008	Aixa Rodriguez
3068260	HAT in vivo IN VIVO	T. b. brucei EATRO 110 po	MSD	4 adm days 20 mg/kg	= 10.5 day	14-JUN-2008	Aixa Rodriguez

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... access to and reporting of project data to/from all collaborators.



Collaborators in HAT Program



- DND*i*
 - Robert Don
 - Denis Martin
- Scynexis
 - Robert Jacobs
 - Matt Orr
 - Daitao Chen
 - Bakela Nare
 - Steve Wring
- Pace University
 - Cy Bacchi
 - Nigel Yarlett
- Antwerp University
 - Louis Maes
 - An Matheussen
- Sandler Center for Basic Research in Parasitic Diseases
 - James McKerrow
 - Maha Abdulla
 - Elizabeth Hansell
- Swiss Tropical Institute
 - Marcel Kaiser
 - Reto Brun
- Shanghai Jiao Tong University
 - Huchen Zhou
 - Dawei Li
- Anacor Pharmaceuticals
 - Jake Plattner
 - Yvonne Freund

