SCYX-7158

DNDi
Drugs for Neglected Diseases *initiative*

RIO-ICTMM Sept.2012

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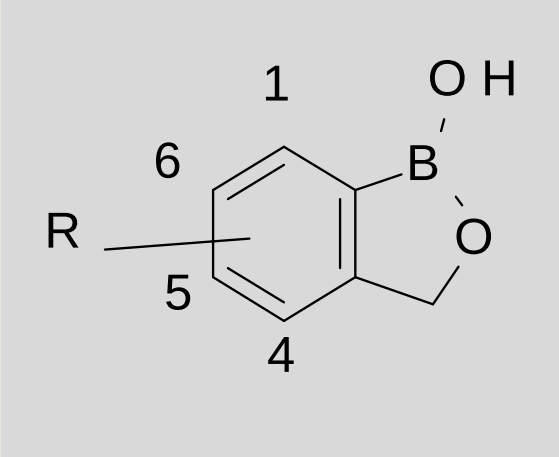
Oxaboroles SCYX-7158
First DNDi Preclinical Candidate for HAT
From Lead Optimization Program



2-bromo phenylboronic acid

Key partners include:

- SCYNEXIS
- Pace University
- Anacor Pharmaceuticals

- Identified as hit against *T. brucei* at the Sandler Center of UCSF
- Innovative chemistry with potential activity for HAT, VL, and Chagas disease
- Hundreds of analogs were made and tested
- Top candidate, SCYX 7158, starting clinical phase 1 studies in Q12012

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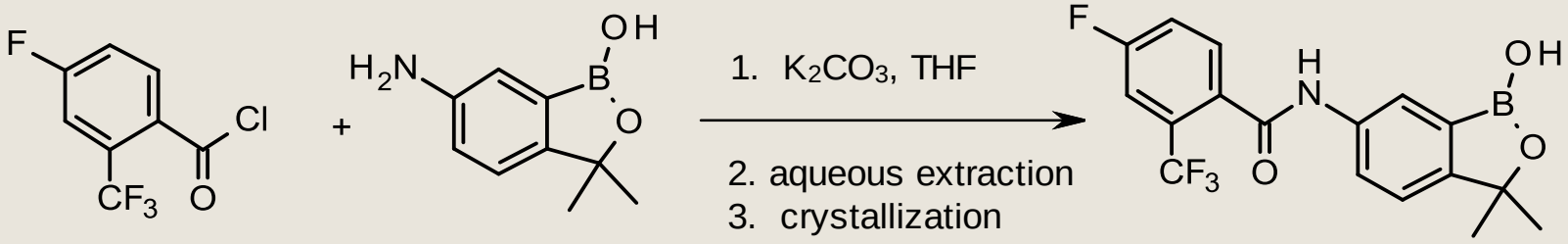
SCYX-7158 - General information

SCYX-7158

PM = 367.11 g/mol
pKa=9.61
LogD ph7.4 = 3.51



1

Chloride

2

Aniline

SCYX-7158
(016SXS031)

Chemical name: (4-Fluoro-N-(1-hydroxy-3,3-dimethyl-1,3-dihydro-benzo[c] [1,2] oxaborol-6-yl)-2-trifluoromethyl benzamide)

OXABOROLE-6 BENZAMIDE

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SCYX-7158 - In Vitro efficacy

***T. brucei* Strain Tested**	**SCYX-7158** IC_{50} **(µg/mL)**
T. b. brucei SBRI 427*	0.267
T. b. rhodesiense STIB 900	0.294
T. b. gambiense 40R	0.363
T. b. gambiense 108R	0.165
T. b. gambiense DAL 1402	0.065
T. b. gambiense ITMAP 141267	0.092
T. b. gambiense Drani	0.129

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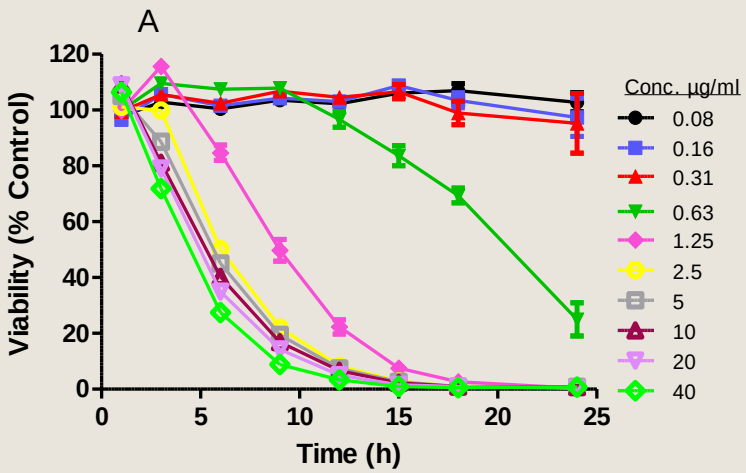
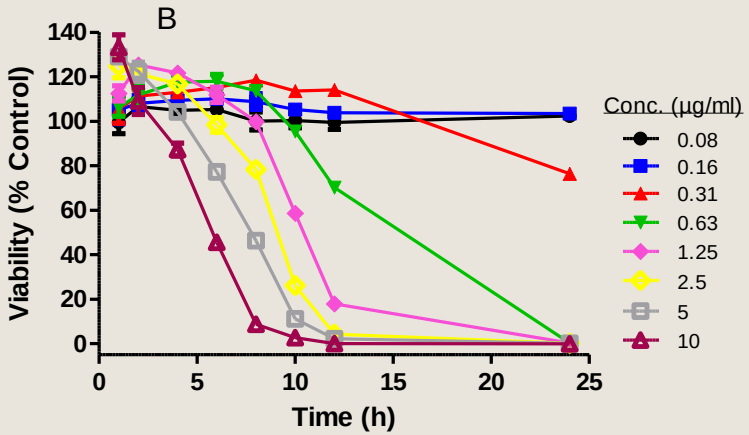
SCYX-7158 - Time to kill plots





A= Time to kill

B = rate to kill

- 24H continuous exposure to SCYX- 7158
- 10-12h pulse exposure of SCYX-7158, medium was washed, survival were evaluated at 72 h after initiation of incubation

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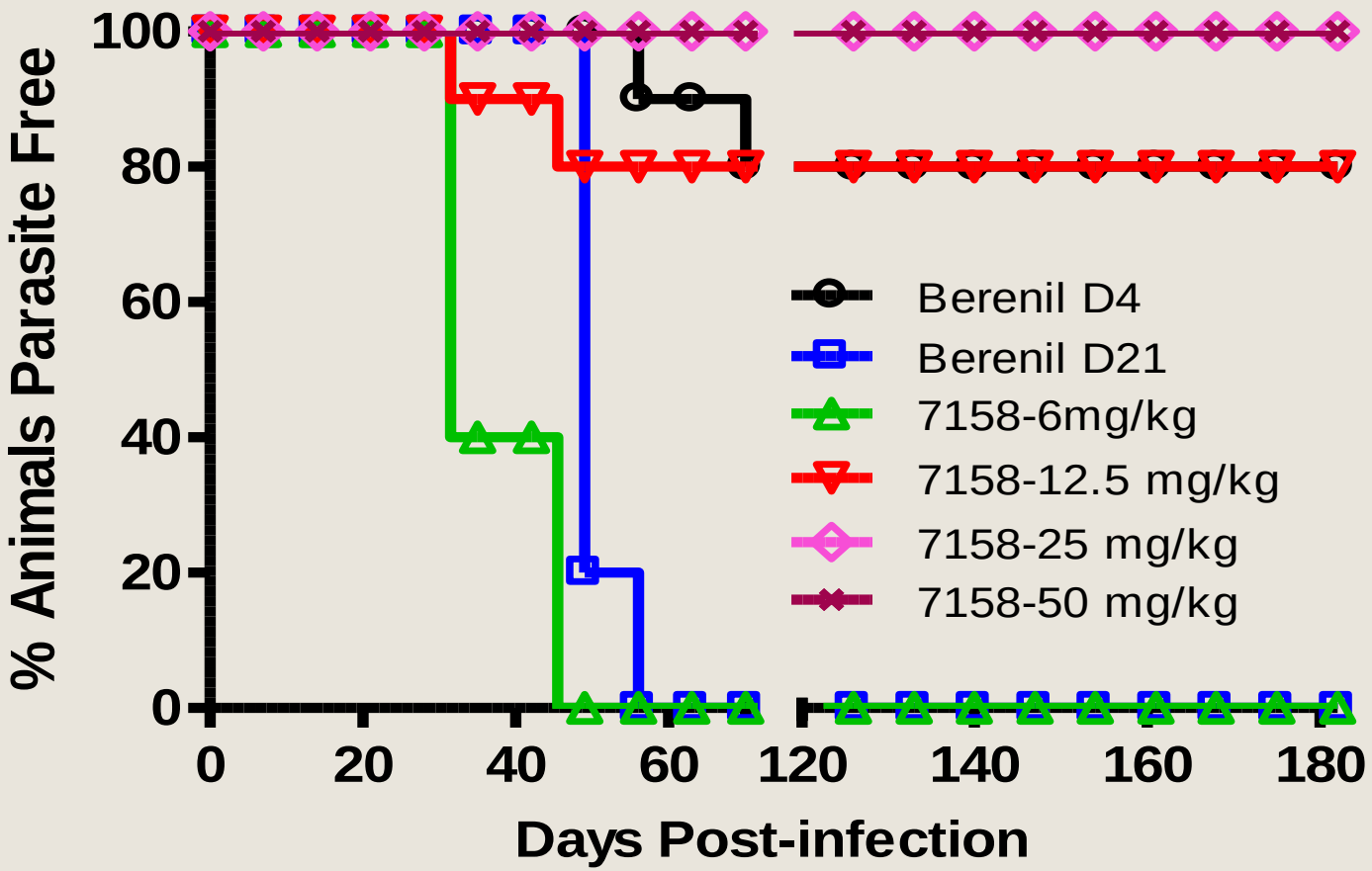
SCYX-7158 - In vivo Efficacy – Stage 2 HAT model in murine



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SCYX-7158 - Safety pharmacology (1)

Safety Pharmacology (GLP)

- Standard genotoxicity battery
  - Ames
  - In vivo micronucleus test
  - In vitro chromosomal aberration
- hERG
- Telemetry (cardiovascular) Dog
- Respiratory in Rat
- Functional Observation Battery in Rat

Toxicokinetics

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SCYX-7158 - Safety Pharmacology (1)

- Standard genotoxicity battery
  - Ames — negetive
  - In vivo micronucleus test — negative
  - In vitro chromosomal aberration — negative
- hERG (10,30,60,100µM)
  IC50 >100µM
- Telemetry Dog (5, 15, 40 mg/kg) — No observations
- Respiratory in Rat (15, 40, 80 mg/kg) — No observations
- Functional Observation Battery in Rat
  - (15, 40, 80 mg/kg) — No observations

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SCYX-7158 - DMPK

- **Absorption**
  - **In vitro** MDR1-MDCK cells system

    High absorption potential
    High distribution in brain
    No significant effflux
  - **In vivo** Dog ≈ 100% in dog
    Monkey ≈ 80%
    Rat ,Mouse ≈ 50%
- **Bioavailability Tmax** 4.5- 9.5 H in all species
  linearity dose proportional
- **Volume of distribution :** ≈ 0.6 – 0.7 l/kg in all species
- **$T_{1/2}$ elimination** ≈ 25H
- **High protein binding** ≈ 95 % in all species

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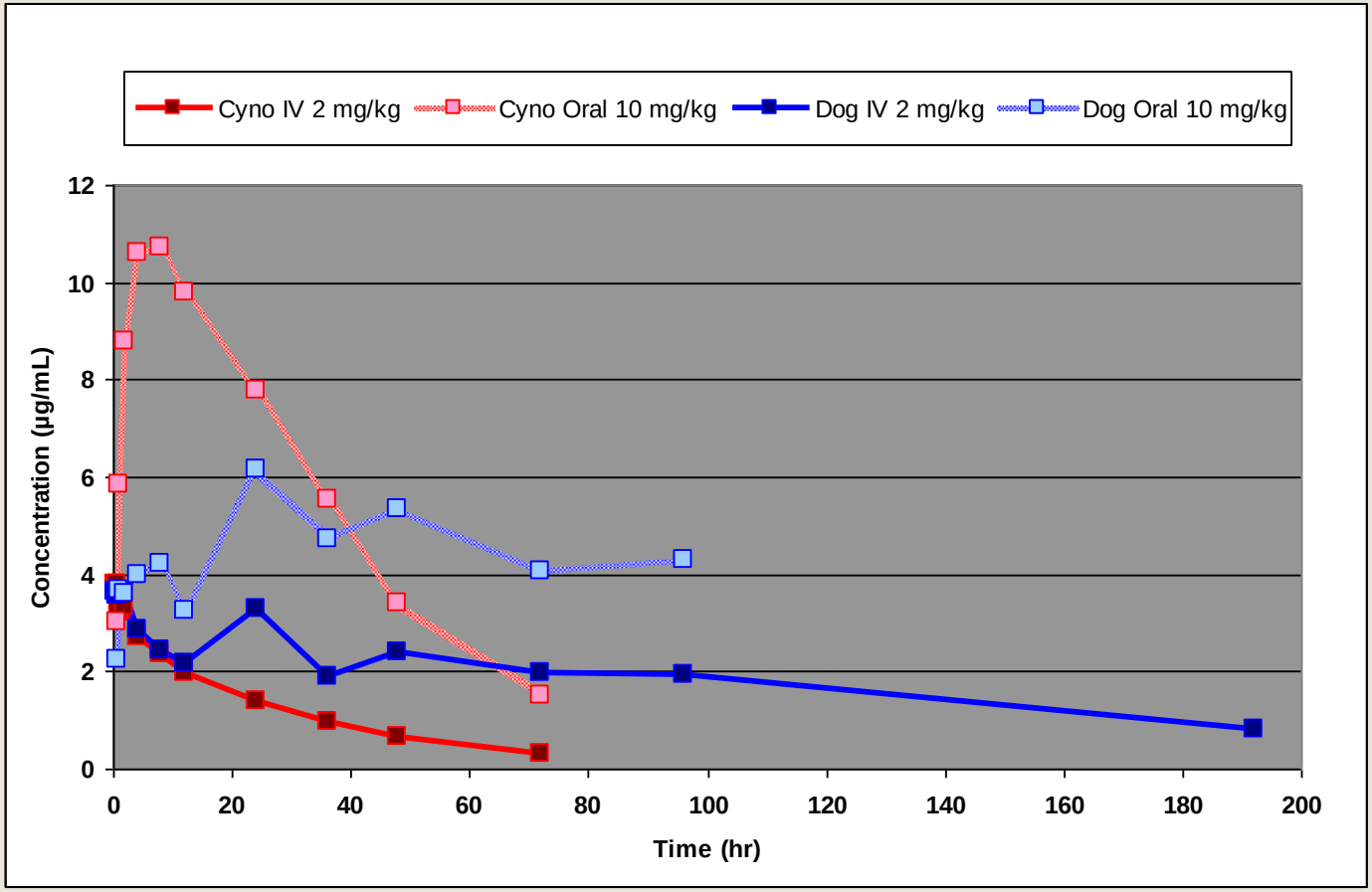
SCYX-7158 pk profil data normalised



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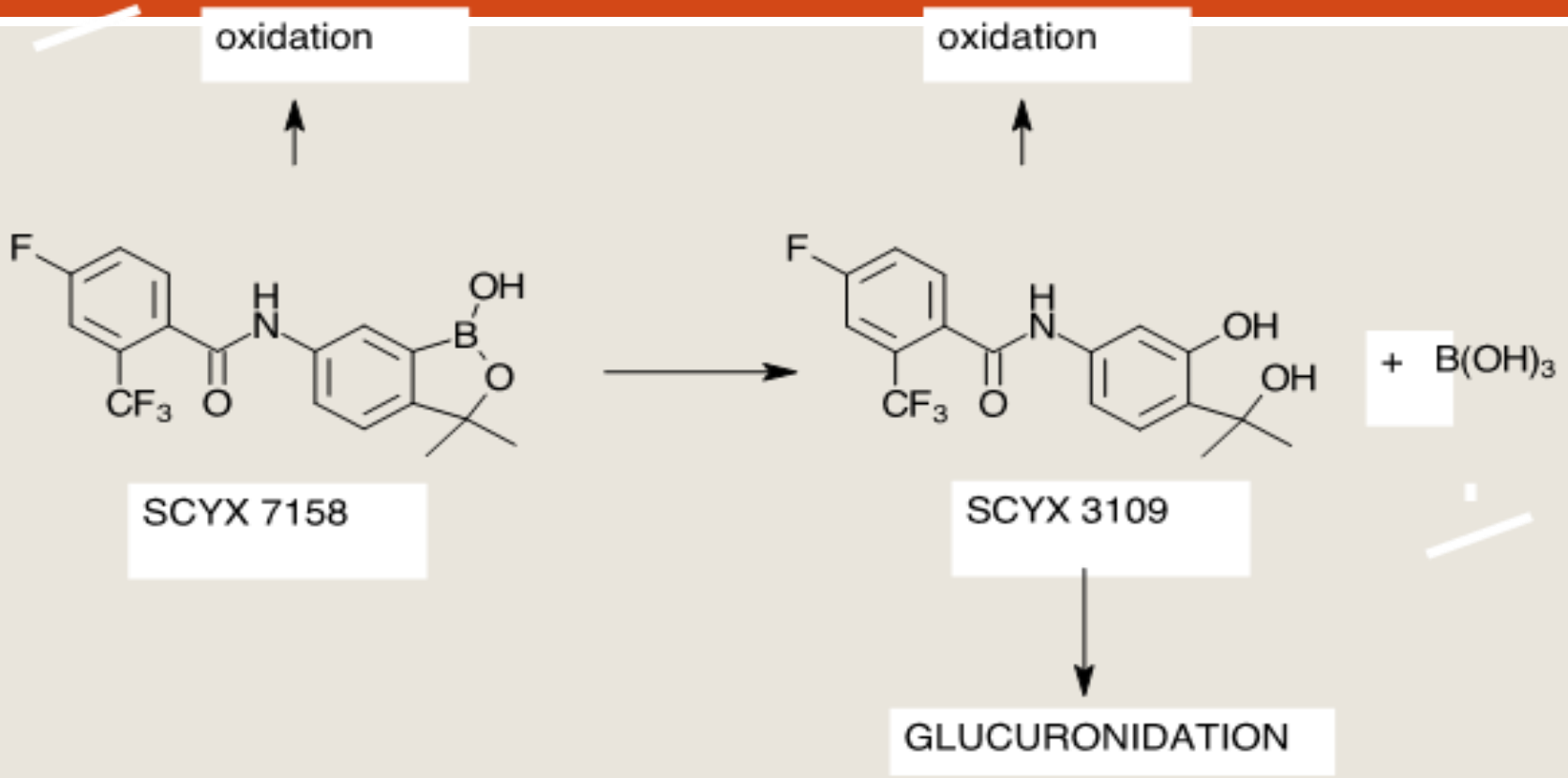
SCYX-7158 - Metabolism



CYP Induction

- Inducer of CYP 2B6 and 3A4

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SCYX-7158 - ADME

Mass balance in rats

	Faeces	Urine	F + U	Total measured
Male	66%	20%	86%	89%
Female	73%	14%	87%	90%

Excretion after 14 days

Tissue distribution

- Well distributed in all tissues Brain Rat ≈ 44% Mouse ≈ 38%
- Highest levels in liver kidney and subcutaneous fat
- Lowest levels in eye and brain 1.5 -2 fold lower than blood

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SCYX-7158 - Rat Toxicokinetics

Toxicokinetics

- 7 days TK in rat 50, 140, 400mg/kg
  - weight loss and loss of appetite
  - Histopathology : stress related changes
- 28 days TK in rat 5, 15, 40, 80 mg/kg
  - Loss of appetite and weight loss at 80 mg/kg
  - Main target organ RBC : ↓ RBC:9-11%, ↓Hb 9%,↓Hct 8-10%, ↑ Reticulocyte:75- 80%
  - No signs of bleeding nor hemolysis but
  - ↑ Extra medullar hematopoiesis
  - Histopath : no signs of bleeding no hemolysis ,
  - clinical chemistry: No abnormal signs
- **NOAEL = 15 mg/kg**

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SCYX-7158 - DOG Toxicokinetics

Toxicokinetics

- 7 days study TK in Dog 5, 20, 50 mg/kg
  - weight loss and loss of appetite
  - Histopathology : stress related changes
  - Reduced weight of thymus and spleen
- 28 days TK in dog 5, 15, 40 mg/kg
  - Loss of appetite and weight loss (emesis) at 40 mg/kg
  - Main target findings ; decrease in food consumtion
  - clinical chemistry: - 40 mg/kg/d Hb, Ht, decrease

    -15 and 5 mg/kg: only anecdotic, ancillary variations (Haemato and BC)

NOAEL =15 mg/kg

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SCYX-7158 -Preclinical Pharmacokinetic data

Mean Pharmacokinetic Parameters of SCYX-7158 after Oral Administration of SCYX-7158 in Animal Species.

	Dose (mg/kg)	T_{max} (h)	C_{max} (µg/mL)	AUC (µg/mL.h)	F* (%)	$T_{1/2}$ (h)
Mouse	12.5	6	6.96	104	54.5	7.7
	25	0.5	9.75	134	45.3	6.93
	39.9	4.0	24.4	320	71.4	5.5
Rat	10	8.0	12.7	362	53.	16.9
Dog	10	4.5	8.36	1032	100	37.65
Monkey**	10.4	9.5	11.5	477	88.8	20.3

*The ratio AUC_{po}/ AUC_{iv} was used for bioavailability (%F) calculation. The i.v. dose was 2 mg/kg in the dog and the monkey

**Nasogastric administration

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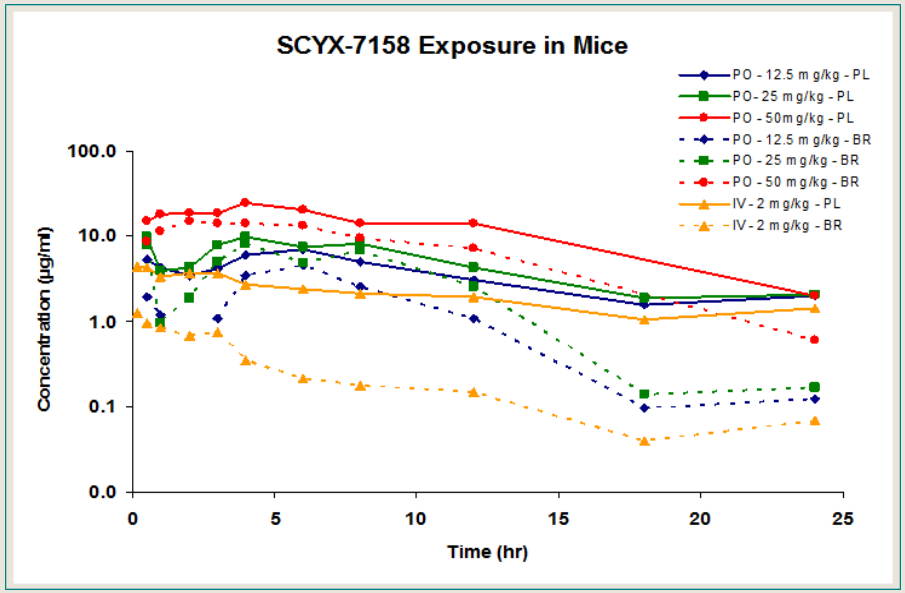
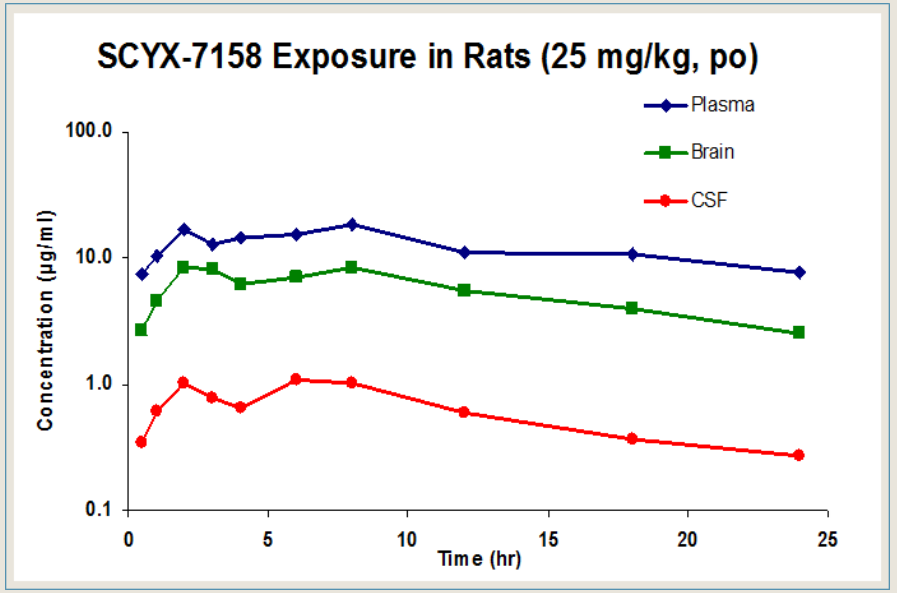
SCYX-7158 -Plasma Concentrations (1)

PK in INFECTED MICE



Exposure in Rats



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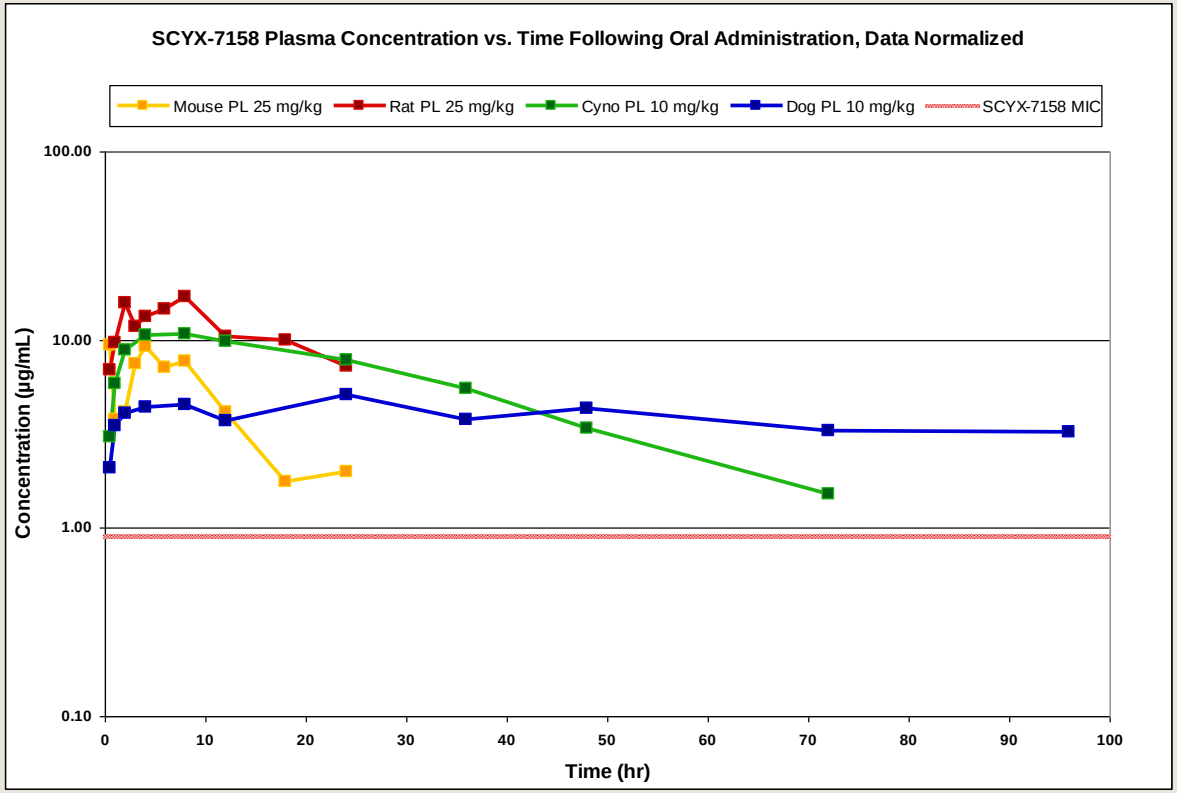
SCY-7158 - Plasma Concentrations

- **25 mg/kg 100% cure dose in mouse model**



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SCYX-7158 - Conclusion

- **New family of drug :** OXABOROLE-6 BENZAMIDE
- **Exhibit a high in vitro potency vs *t. brucei brucei***
- ***physicochemical properties compatible with high brain penetration***
- ***Active in acute and chronic HAT disease mouse model***
- ***PK properties compatible with a once a day dosing***
- ***NOAEL : 15mg/kg in rat and dog***

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Thank you

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