Fexinidazole: a rediscovered nitroimidazole drug candidate moving into clinical development for HAT

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DNDi Best Science for the Most Neglected

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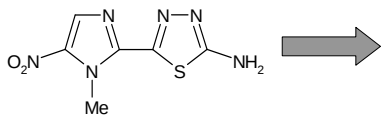
Compound mining to create innovation for neglected diseases

- Megazol:
  - Existing compound (1968) from the nitroimidazole family
  - Shown to have potent oral trypanocidal activity *in vivo*
    - Several publications in 1980s-1990s
  - Toxic (mutagenic)
- Other anti-infective drugs exist in this family: metronidazole, tinidazole, benznidazole,…



Megazol

Can we identify existing compounds with a better activity/toxicity profile?

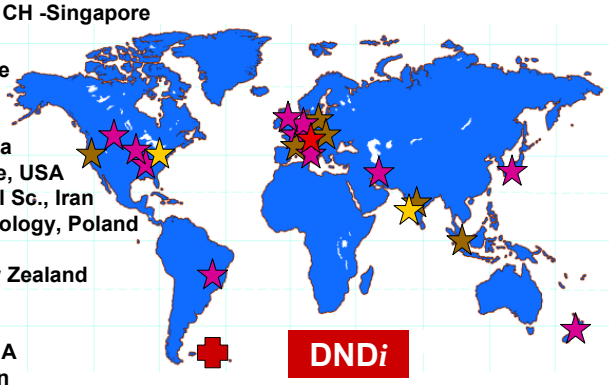
DNDi

Over 600 nitroimidazoles obtained and assessed as drug leads during 2005-7

Pharma
- sanofi-aventis, France - Germany
- Roche, CH
- Novartis (NITD), USA - CH -Singapore
- Alkem, India

Academics
- Swiss Tropical Institute
- Fiocruz, Brazil
- Glasgow Univ, UK
- Univ of Alberta, Canada
- ENH Research Institute, USA
- Tehran Univ of Medical Sc., Iran
- Silesian Univ of Technology, Poland
- LaSpienza Univ, Italy
- Univ of Auckland, New Zealand
- Univ of Dundee, UK
- Univ of Parma, Italy
- Univ of Tennessee, USA
- Tokushima Univ, Japan

other
- TB Alliance
- retired pharma chemist , India



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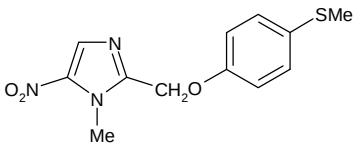
Fexinidazole

- 5-nitroimidazole
- in preclinical development by Hoechst in 80s as broad-spectrum anti-protozoal
  - Not progressed



- DNDi profiling
  - Literature + Hoechst reports (s-a)
  - New studies: pharmacology – ADME/PK – toxicology

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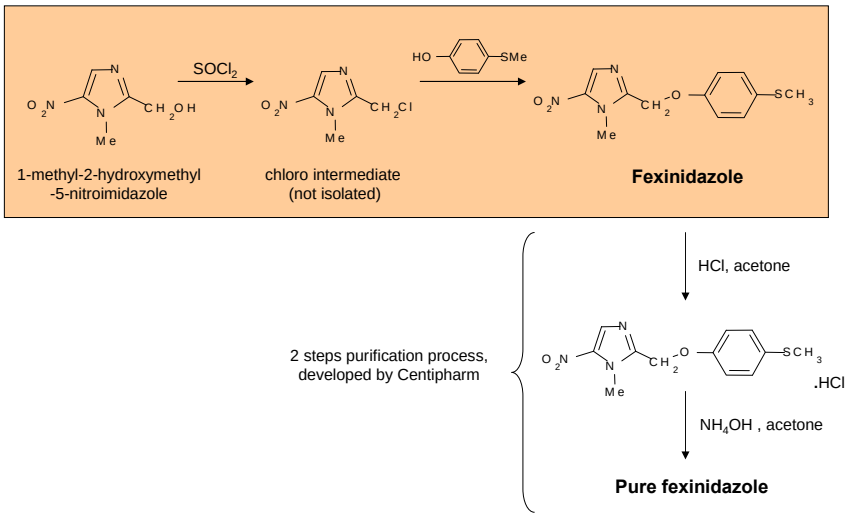
2-step synthesis of fexinidazole



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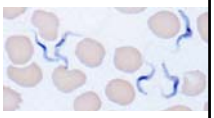
Pharmacology (1)

- Selective *in vitro* anti-trypanosomal activity



IC_{50} in µg/ml (µM)	*T. b. rhodesiense* STIB 900	*T. b. gambiense* STIB 754	cytotoxicity L-6 (rat skeletal myoblast cells)
Fexinidazole	**0.72 (2.57)**	**0.32 (1.14)**	**>90 (>322)**
Reference compounds			
Megazol	0.02 (0.10)		57 (254)
Melarsoprol	0.004 (0.009)	0.0015 (0.004)	1.3 (3.3)
Eflornithine	0.90 (3.80)	0.40 (1.67)	12 (51)
Nifurtimox	0.41 (1.44)	0.31 (1.08)	25 (87)
Pentamidine	0.003 (0.009)	0.002 (0.01)	3 (9)

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Pharmacology (2)

- *In vivo* activity in mouse model of acute infection (*T.b.rhodesiense* STIB900 - stringent model)

Compound	#days x daily dose in mg/kg	route	Cured/ infected	Mean survival (days)
control	-		**0/4**	7-8
fexinidazole	4 x 25	po	**0/4**	15.75
	4 x 50	po	**1/4**	>34
	4 x 100	po	**4/4**	>60
	4 x (2 x 12.5) (bid)	po	**0/4**	17.5
	4 x (2 x 25) (bid)	po	**2/4**	>39.5
	4 x (2 x 50) (bid)	po	**4/4**	>60
	1 x 200	po	**3/4**	>51.75

- pentamidine and eflornithine are inactive in this model
- nifurtimox requires 4 x 200 mkd p.o (inactive at 4 x 100 mkd)
- melarsoprol cures at 4 x 8 mkd ip

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Pharmacology (3)

- *In vivo* activity in mouse model of chronic infection with CNS-involvement (*T.b.brucei* GVR35)

Compound	dose: #days x mg/kg	mode	Cured/ infected	MSD
Study 1				
Diminazene diaceturate	1 x 40	ip	0/4	63
fexinidazole	5 x 100	po	**3/5**	>145
fexinidazole	5x (2 x 100) - *bid*	po	**5/5**	>180
Study 2				
Diminazene diaceturate	1 x 40	ip	0/4	63
melarsoprol	1 x 10	ip	2/8	>122
fexinidazole	5 x 50	po	**0/8**	63.8
fexinidazole	5 x 100	po	**2/8**	>107
fexinidazole	5 x 200	po	**7/8**	>169

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In vitro ADME fexinidazole

- Good intestinal permeability (Caco-2)
  - no limiting factor for absorption
- Good potential for BBB permeability (MDR1-MDCK)
- High plasma protein binding
  - 95% (human); 93% (mouse)
- *In vitro* hepatocyte metabolism: < 1% remaining after 1h

Species	$t_{1/2}$ (min)	*In vitro* CL_{intr} (mL/min/kg)
Mouse	1.4	4312
Rat	1.2	2890
Dog	1.1	5042
Monkey	0.6	6467
Human	13.4	124

- 2 major metabolites: sulfoxide (M1) and sulfone (M2)

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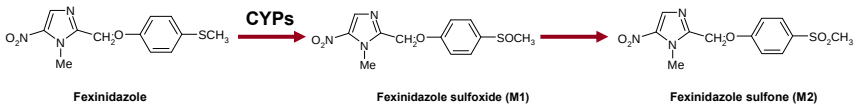
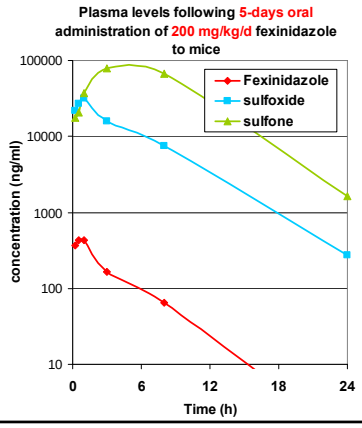
Fexinidazole metabolism / PK



Fexinidazole — Fexinidazole sulfoxide (M1) — Fexinidazole sulfone (M2)

IC50 in µg / mL	*T.b.rhodesiense* STIB900
Fexinidazole (batch 1)	1.265
Fexinidazole (batch 2)	0.719
Fex-sulfoxid (M1)	0.487
Fex-sulfon (M2)	0.354

	pH	solubility (aqueous sol) µg/ml	logD
fexinidazole	*1.2*	5.89	2.51
	7.4	2.55	2.83
fexinidazole sulfone	*1.2*	84.1	0.52
	7.4	51.6	0.74
fexinidazole sulfoxide	*1.2*	>1000	0.19
	7.4	942	0.52



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Fexinidazole distribution
(after oral administration)

- Plasma levels & AUC metabolites >> fexinidazole
  - Similar profiles in mouse – rat – dog
- Fexinidazole / metabolites are widely distributed over all tissues
  - Including brain

dose: 25 mg/kg po	Brain concentration (ng/mL of brain homogenate)		
Time (min)	fexinidazole	sulfoxide	sulfone
15	1136	nd	nd
30	267	1105	156
60	254	1624	394

  - Elimination of fexinidazole and metabolites is rapid (about 90% within 48h) and mainly with feces (~60%)
  - No/limited accumulation over repeated administration

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Toxicology

Completed regulatory toxicology studies

- GLP safety pharmacology
  - hERG (CVS)
  - Irwin screen (CNS)
  - Respiratory function
  - Dog telemetry (CVS)
- Secondary pharmacology (receptor screen)
- *In vitro* phototoxicicity
- Repeated dose toxicology, incl toxicokinetics
  - 7d dose range and MTD in rat
  - 4-weeks repeated dose toxicokinetics in rat - GLP
  - 7d dose range and MTD in dog
  - 4-weeks repeated dose toxicokinetics in dog – GLP
- Genetic toxicology (details below)

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Safety pharmacology

- ***In vitro* hERG:**
  - Concentrations tested: 1, 5, and 30 µM
  - Fexinidazole and the sulfoxide **do not affect** hERG peak tail current
  - Fexinidazole sulfone showed a significant decrease (-33%) on hERG peak tail current at the 30 µM concentration only
- ***In vivo* cardiovascular parameters in the Beagle Dog (dog telemetry)**
  - Dose levels: 100, 300 and 1000 mg/kg oral
  - **NOEL CV parameters and ECG intervals ≥1000 mg/kg**
  - Overrules positive hERG signal
- **Irwin test in rat**: general behavior and body temperature
  - Dose levels: 100, 300 or 1000 mg/kg oral
  - **NOEL ≥ 1000 mg/kg**.
- **Respiratory Parameters** in unrestrained Conscious Male Rat
  - Dose levels: 100, 300 and 1000 mg/kg oral
  - **NOEL ≥1000 mg/kg**.

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4-week repeated dose Toxicokinetics – Rat & Dog

Doses: 0, 50, 200 and 800 mg/kg/day, oral

- For both species, the dose of 200 mkd is considered the **NOAEL** (No-observed-adverse-effect-level)

$AUC_{0\text{-}24h}$ mcgxh/mL at NOAEL (Day 28)

Species	Dose	Sex	**fexinidazole**	**sulfoxide**	**sulfone**
rat	200 MKD	M	2,320	122,100	341,333
		F	4,437	138,333	342,333
dog	200 MKD	M	0.395	42,200	258,000
		F	0.377	33,800	277,000

- For both species, the top dose of 800 mkd is considered as **"well-tolerated"** :
  - In rat: slightly decreased body weight (M) and increased liver weight (F) with minimal/slight hypertrophy of hepatocytes
  - In dog: slight reduction in food intake and decreased body weight (mainly F) but no histological findings
- **No particular issues identified**

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Genetic Toxicology: new GLP-studies
(to confirm previous evidence from Hoechst-DNDi studies)

Test	Result	Top dose
In vitro Bacterial Ames test	Positive*	1000 µg/plate
In vitro Human lymphocyte micronucleus test	Negative	220 µg/mL
In vivo Rat Liver UDS	Negative**	2000 mg/kg
In vivo Mouse micronucleus	Negative**	2000 mg/kg

*Decreased in NR-deficient strains
**with PK to confirm fexinidazole and both metabolites are being formed

Conclusion: fexinidazole and metabolites are unlikely to pose a genotoxic risk to volunteers or patients

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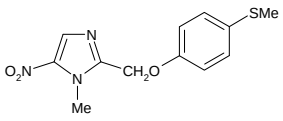
Fexinidazole is promising drug candidate for clinical development for HAT



- Complies with ideal Target Product Profile:
  - Oral treatment for stage 2 HAT
    - Ideally useful for both stage 1 and 2 (if practical and very safe)
  - Active on *T.b.gambiense* + *T.b.rhodesiense*
  - Short course, affordable
- **Decision to progress to First-in-Human phase I trials**
  - Objective: assess bioavailability/PK and tolerability (MTD) in healthy volunteers (SAD, MAD, food effect)
    - Assess prototype tablets
  - Planned to start Q2-2009
- Registration by 2014 if successful development

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A multidisciplinary team effort to advance fexinidazole into clinical development

DNDi project team

- **Els Torreele**: DNDi project manager
- **Michael Bray**: pharmaceutical project management consultant
- **Bernadette Bourdin**: chemistry project support & documentation
- **Guy Mazué**: toxicology, preclinical development
- **Jean-René Kiechel**: CMC, formulation, pharmacology
- **Pierre-Etienne Bost**: chemistry, preclinical development
- **David Tweats**: toxicology, in particular genetic toxicology
- **Daniela Sassella**: clinical development
- **François Chappuis**: clinical HAT expert
- **Matthias Dormeyer**: regulatory advise, IMPD
- **Eloan Pinheiro**: formulation and manufacture expert
- **Christian Burri**, **Gabriele Pohlig**: HAT clinical trials experts

Operational partners

- **Main preclinical package**
  - **Accelera**, Italy: preclinical formulation, regulatory toxicology, safety pharmacology, pharmacokinetics, bioanalytics
  - **Covance**, UK: genotoxicology
- **Disease models**
  - **STI**, Swiss Tropical Institute, Switzerland: mouse models
  - **TRC**, Trypanosomiasis Research Centre, Kenya: monkey model
- **CMC**
  - **Axyntis** (ex Orgasynth), France: chemistry, GMP-production
  - **Aptuit**, UK: clinical formulation development and batch supply

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Financial support

- Project specific funding:
  - Private Swiss Foundation
  - French Ministry of foreign Affairs (MAEE)
- DNDi core funding:
  - MSF
  - UK DFID

Thank you!

DNDi

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DNDi HAT symposium at ASTMH 2008

Bayside BC
Sheraton
New Orleans
USA

For more information, please visit DNDi's booth (#209) at ASTMH 08 or www.dndi.org

Addressing the R&D challenges

in making new drugs available for human African trypanosomiasis: potential in the pipeline and recent clinical results

Monday, December 8, 2008
10:15 am - 12:00 pm

CHAIRS:

Leon Kazumba
HAT Platform, Kinshasa, DRC

Pere Simarro
WHO, Geneva, Switzerland

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Drugs for Neglected Diseases *initiative*

Addressing the R&D challenges
in making new drugs available for human African trypanosomiasis (HAT): potential in the pipeline and recent clinical results

HAT symposium, ASTMH 2008
Sheraton New Orleans, USA
Monday, December 8, 2008

DNDi
Drugs for Neglected Diseases initiative

- **HAT Platform - Success to date, and challenges/opportunities ahead in overcoming difficulties in clinical research of HAT drugs & in developing regional research platform**
  Fred Kansiime, HAT Platform, Coordination Office for Control of Trypanosomiasis in Uganda, Kampala, Uganda
- **Phase III results of multi-center study evaluating nifurtimox-eflornithine combination for treatment (NECT) of Stage 2 HAT**
  Gerardo Priotto, Epicentre, Paris, France
- **Research results evaluating the diamidine class for the treatment of HAT**
  Carol Olson, Immtech Pharmaceuticals, Vernon Hills, IL, United States
- **Fexinidazole: a rediscovered nitroimidazole drug candidate moving into clinical development for HAT**
  Els Torreele, Drugs for Neglected Diseases initiative, Geneva, Switzerland

Interventions by **Christian Burri**, Swiss Tropical Institute, Basel, Switzerland, and **Constantin Miaka Mia Bilenge**, HAT National Control Program, Kinshasa, Democratic Republic of the Congo (DRC), followed by a Q&A session

DNDi's HAT symposium will be followed by film broadcast on HAT: "Sleeping sickness: the deadliest disease", BBC series "Survival", produced by Rockhopper TV.
At 12:15 pm, Room: Bayside BC