DNDI-VL-2098: a nitroimidazooxazole as clinical candidate to treat visceral leishmaniasis

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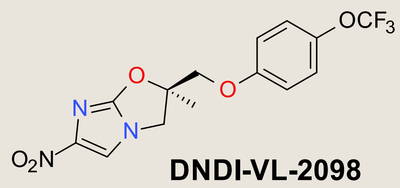
ABSTRACT

DND*i* (Drugs for Neglected Diseases *initiative*) is a collaborative, patients' needs-driven, not-for-profit organization whose mission is to develop new drugs for the most neglected tropical diseases, including visceral leishmaniasis (VL).

The nitroimidazole class, well known for its anti-infective properties, became the focus of our research effort and quickly led to the identification of DNDI-VL-2098 as a potential candidate for VL. This compound is expected to fulfill DND*i*'s Target Product Profile, including:

a. effectiveness against *L. donovani* in East Africa and India (including drug resistant strains)
b. 95% clinical efficacy
c. no contraindications
d. oral formulation
e. dosing once a day for a maximum of 10 days
f. cost under $10 per course.



DNDI-VL-2098

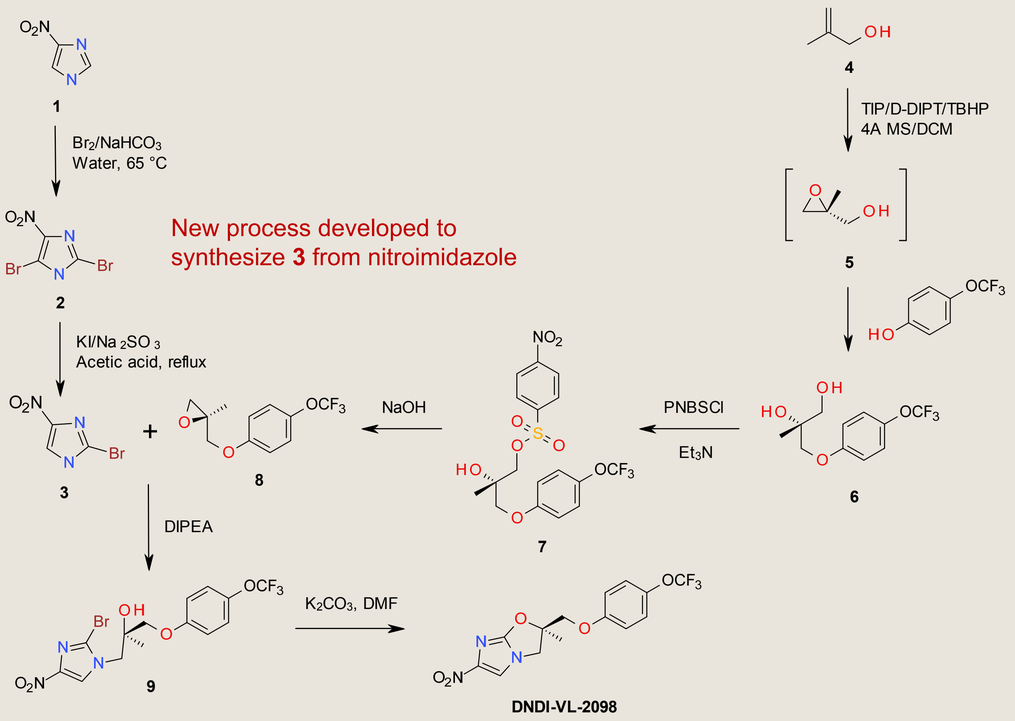
(2R)-2-methyl-6-nitro-2-[[4-(trifluoromethoxy)phenoxy]methyl]-3H-imidazo[2,1-b]oxazole

INTRODUCTION

Screening of a representative selection of nitroimidazoles quickly led to the identification of DNDI-VL-2001 as a lead compound. Further investigation of this racemate and its 2 enantiomers showed superiority of the R enantiomer: DNDI-VL-2098. DND*i* therefore decided to develop the latter as a candidate for Visceral Leishmaniasis. We describe here the synthesis of DNDI-VL-2098, its main *in vitro* and *in vivo* characteristics and early safety profile.

SYNTHESIS

A process chiral route was developed for synthesis of DNDI-VL-2098, in order to improve yields of the synthetic route and limit the use of purifications. 2-Bromo-4-nitroimidazole **3** and the oxirane derivative **8** were identified as key building blocks that, upon condensation and cyclisation, lead to DNDI-VL-2098 in 2 steps, with 44% yield and 99.5% chiral purity.



IN VITRO PROFILE

Potency against Leishmania strains (IC_{50} in µM)

VL strains	DNDI-VL-2098	SbV*	Amphotericin B	Miltefosine
L. donovani Dd8	0.03		0.023	2.5
L. donovani HU3	0.09		0.05	2.05
L. donovani BHU1[a]	0.29	> 150	0.2	3.8
L. donovani SUKA001[b]	< 0.74	10.6	0.053	4.6
CL strains				
L. major LV39	0.83	> 50	0.01	> 30
L. tropica A021/p	1.34		0.11	8.22
L. braziliensis M2903	< 0.63		0.02	8.49
L. mexicana B379	6.67		6.55	6.55

*Pentavalent Antimonials, [a]SbV-resistant strain, [b]recent clinical isolate

DNDI-VL-2098 shows broad-spectrum *in vitro* activity against a range of standard visceral (VL) and cutaneous (CL) *Leishmania* strains, comparing favourably with currently used drugs (SbV, Amphotericin B and Miltefosine). The compound did not have any toxic effect on the host cells and the selectivity index was very high (> 100).

ADMET profile

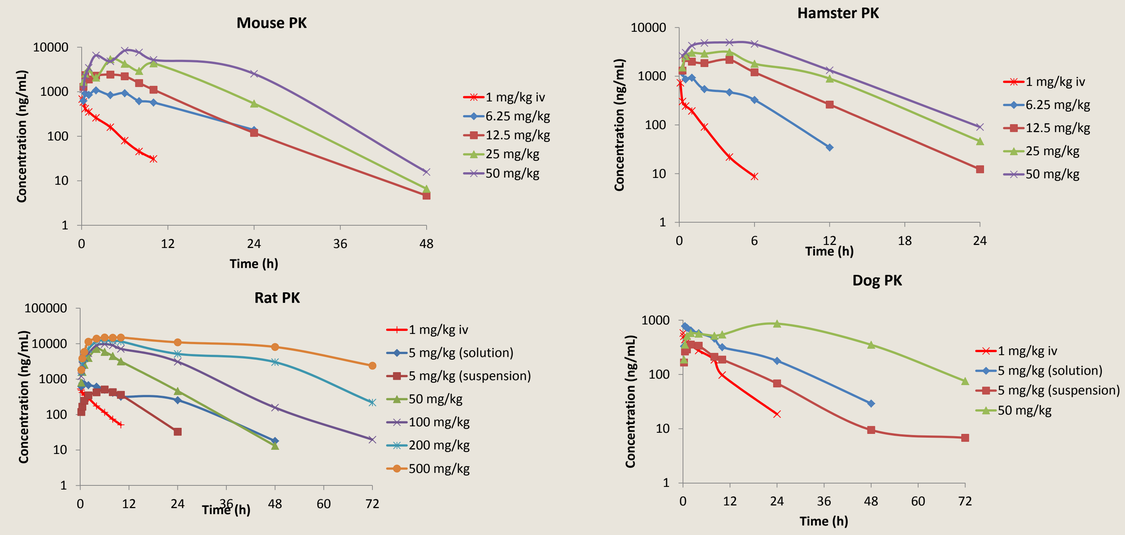
- High permeability in CaCo-2 cells - not a substrate for efflux transporters
- Stable in recombinant human CYPs, human liver microsomes and hepatocytes - projected to have low intrinsic clearance and long elimination half-life in humans
- Among all CYPs, inhibitor of CYP2C19 only (IC_{50} = 0.5 µM) - considered to have a limited potential for drug-drug interactions
- Moderate to high plasma protein binding (94.4% in human, 96.6% in mouse), uniform blood/plasma distribution (blood-to-plasma ratio: 0.5 in human, 1.4 in mouse)

Overall, the *in vitro* data generated indicate that DNDI-VL-2098 is a stable, high permeability and low clearance molecule with limited potential for drug-drug interactions.

IN VIVO PROFILE

Pharmacokinetics

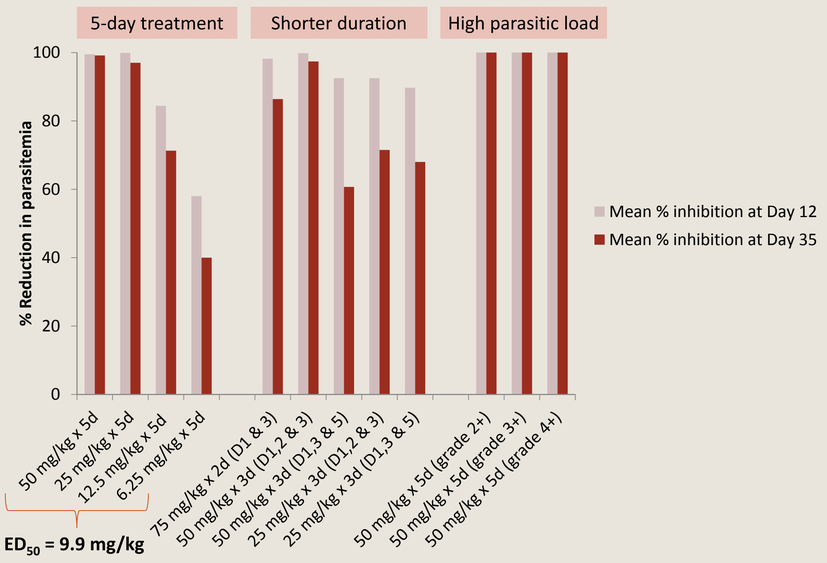
The pharmacokinetic profile of DNDI-VL-2098 was assessed in four different species.



In all rodent species, the compound exhibited low (26 mL/min/kg in hamster) to moderate (2 mL/min/kg in mouse) clearance and excellent oral bioavailability (70% in rat to 100% in mouse and hamster). In the dog, clearance was low (5 mL/min/kg) and oral bioavailability was moderate/variable.

Efficacy

- In the BALB/c mouse - *L. donovani* model of the disease, experiments conducted at 3.125, 6.25, 12.5, 25 and 50 mg/kg once a day for 5 days led to an average ED_{50} value of 2 mg/kg.
- In the Golden Syrian hamster – *L. donovani* model of the disease, ED_{50} was evaluated to be 9.9 mg/kg at Day 12 after beginning of treatment. No sign of relapse was observed up to Day 50 after treatment at doses as low as 25 mg/kg qd for 5 days.



- Additional *in vivo* efficacy studies conducted on *L. infantum* hamster model and followed by promastigote transformation assay suggested the compound induces full parasitological cure when dosed at 50 mg/kg qd for 5 days.

SAFETY PROFILE

- DNDI-VL-2098 moderately inhibited the hERG channel (in transfected Chinese Hamster Ovary cells), with an IC_{50} of 10.5 µM. A telemetry study in male Beagle dogs showed no modification of QTc up to the highest dose tested (250 mg/kg).
- DNDI-VL-2098 was shown to be neither clastogenic *in vitro* nor mutagenic both *in vitro* and *in vivo*.
- DNDI-VL-2098 did not induce any effect on CNS and respiratory functions up to highest dose tested (500 mg/kg).
- In mice and rats, after single dose oral administration, the No-Observed-Effect Level (NOEL) was > 2000 mg/kg.

According to allometric scaling predictions for human PK, the minimum efficacious dose in human beings (50 kg) is expected to be in the range of 200 to 350 mg, with a once a day oral administration (estimated long human elimination half-life).

SUMMARY

Nitroimidazooxazole DNDI-VL-2098 was extensively studied as a drug candidate for Visceral Leishmaniasis and results showed it had:

- Potent anti-leishmanial activity against a range of strains *in vitro*
- Significant reproducible activity following oral administration *in vivo*: the minimally effective dose in the mouse model was 6.25 mg/kg, and 25 mg/kg in the hamster model for a treatment duration of 5 consecutive days
- Advantageous PK and safety profile

The compound is currently in the final stages of preclinical development at DND*i*.

In conclusion, DNDI-VL-2098 shows promise for development as a clinical candidate to treat visceral leishmaniasis.

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