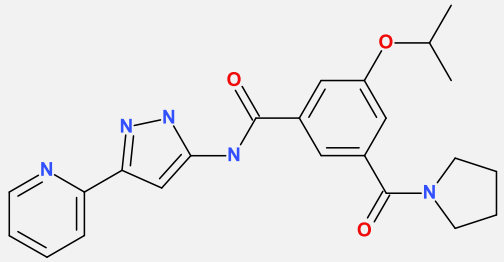
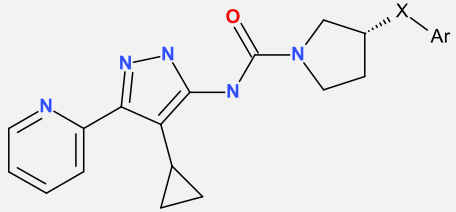
Project P1 – Aminopyrazole lead optimization – next gen compounds



SCYX0001780041 – Hit compound
L. donovani IC50: 5.8 uM

Previous work: >1200 analogues

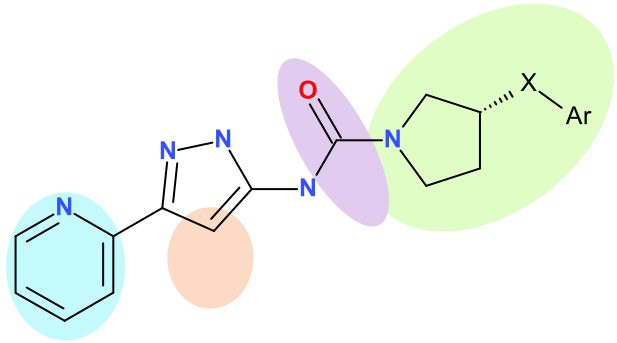


DNDI5561-chemotype
Lead and candidate compounds
L. donovani IC50: <0.5 uM

OSN: Further investigation

Next gen back up candidates

- **OSN Challenge:**
  - Series was investigated thoroughly between 2010 and 2016, leading to clinical candidate for visceral leishmaniasis DNDI5561
  - DNDi5561 profiling in preclinical studies is ongoing
  - Following standard protocol, we aim to identify next gen compounds to support DNDI5561
    - Rapid follow on in the event DNDI5561 preclinical reveals liabilities
    - Next gen compounds may display improved anit-parasitic activity or selectivity for particular strain
- **Objectives:**
  - *Leishmaniasis:* Explore the various areas of the chemotype which have not yet been investigated or were put on hold / under resourced during the discovery of DNDi5561.
  - *T. cruzi*: Investigate the emerging Trypanosoma Cruzi SAR



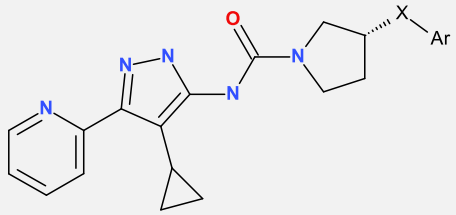
Right hand side (RHS)
- Plenty of scope to make changes and modulate potency – goal is to find alternative RHS chemotype which retains profile (potency, metabolic stability) of 3-substituted pyrolidines whilst being as "different" as possible

Left hand side (LHS)
Moveing away from 2-pyridyl has proven very difficult, however shifting the nature of the RHS may free up more space to investigate LHS and move away from unsubstituted 2-pyridyl

Pyrazole – 4 position
Substituents at 4 position of pyrazole are beneficial but synthetically challenging to incorporate

Linker
Amide and urea tolerated; removal of the carbonyl completely leads to parasite-hop into anti-T. cruzi space

Project P1 – Available data, Med chem plan



DNDI5561-chemotype
Lead and candidate compounds
L. donovani IC50: <0.5 uM

OSN compounds will be tested at University of Antwerp

- *Leishmania infantum* Cell based assay (PMM cells)

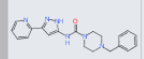
- Data set available (>400 compounds)

LMPH parasitology data – leish (IC50 and C550 on PMM background cell line)

LMPH parasitology data – T. cruzi (IC50 and C550 on MRC5 background cell line)

Mirosomal stability data – various species

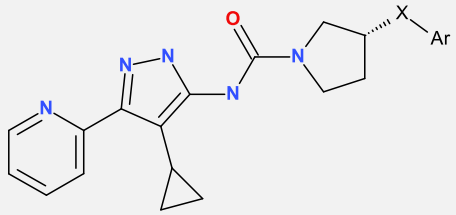
Solubility data / permeability data

Structure	COMPOUND ID	L. infantum IC50 (u...	PMM CC50 (uM)	T. cruzi IC50 (u...	MRC5 CC50 ...	MouseLM Cli...	HamsterLM ...	HLM Clint (u...	RatLM Clint (...	Kinetic solub...	Kinetic solub...	MDCK A-B (...	MDCK B-A (...	St
	DNDI0002427762	5.214595	64.0	55.71355	64.0	11.95	40.0	11.9	13.75	72.49	35.87	20.35	30.65	Fr
	DNDI0002427763	64.0	64.0	29.49169	64.0									Fr

- **Project Plan**
  - Investigate various regions of the molecule to find changes away from the DNDI5561 structure but which are tolerated and retain the antiparasitic drug-like profile of DNDI5561
  - Identifiy additive changes in more than 1 region of the molecule which can be combined to yield next generation candidate compound which differentiates structurally from DNDI5561-chemotype in at least two distinct regions of the molecule

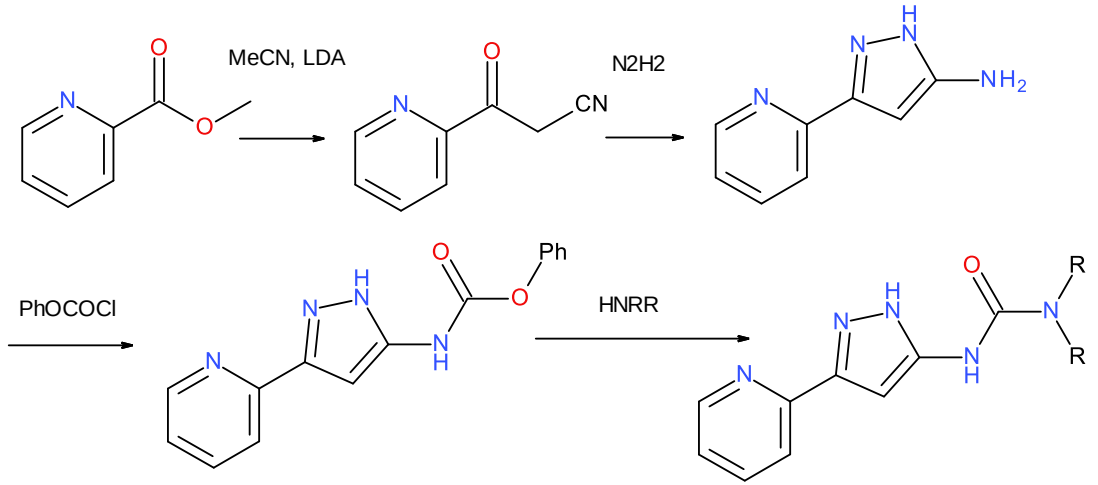
- **Design of Analogues**
  - "Wanted List" of DNDi designed analogues available (OSN P1 Master list.sdf)
  - OSN institutions and invited to propose their own design ideas based on available data set (OSN P1 data set.sdf)

Project P1 – Benzoxazole amide synthetic chemistry

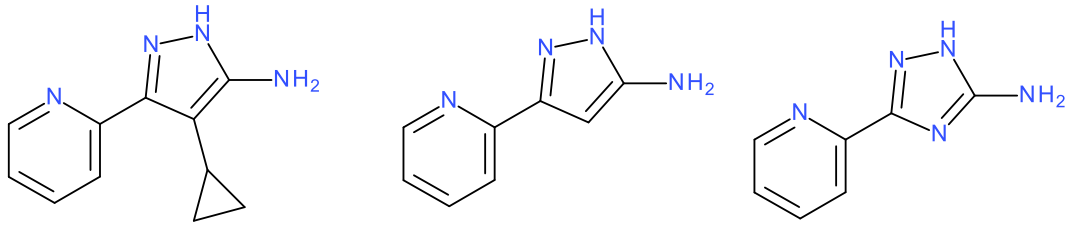


DNDI5561-chemotype
Lead and candidate compounds
L. donovani IC50: <0.5 uM

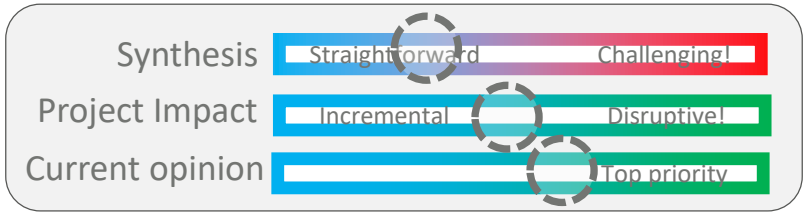
- Large supply of synthetic information available (representative synthesis below)



- Key intermediates available for shipment (~5g scale)



Project P1 – Work Packages A & O:

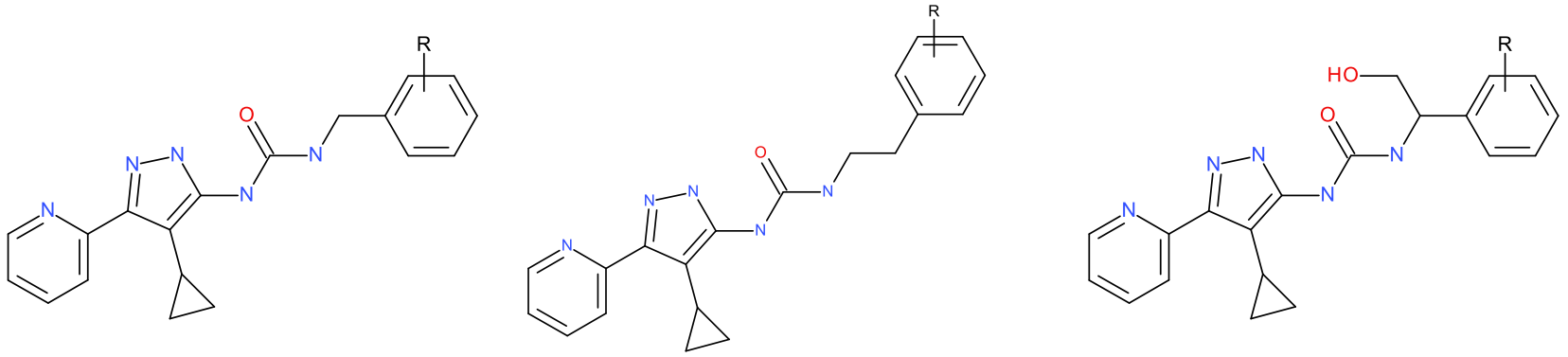


- Handful of acyclic alkyl ureas have been made; activity observed but initially deprioritized
- Recent breakthroughs by OSN participants identified ureas with hydroxy sidechains as being of key interest (good potency, potential for good metabolic stability
- DNDi will provide data set of compounds made within this sub-series
- Stability in rodent microsomes seems to be an issue / area for improvement.
    - Balance of ClogP is key for keeping potency and achieving metabolic stability
  - Focus of work package: Improve potency and improve rodent microsomal stability via exploration / combination approach:

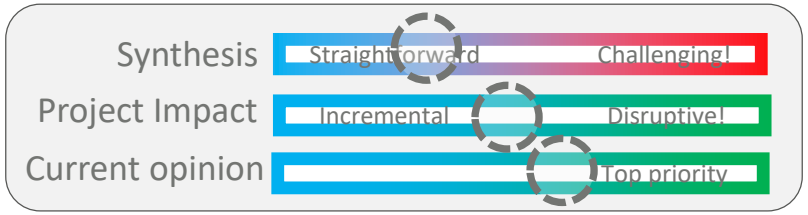
Examples of target compounds:

Library scans

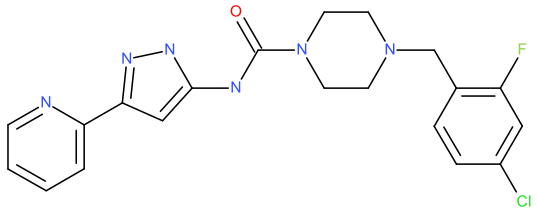
(suitable for parallel synthesis from common intermediate)



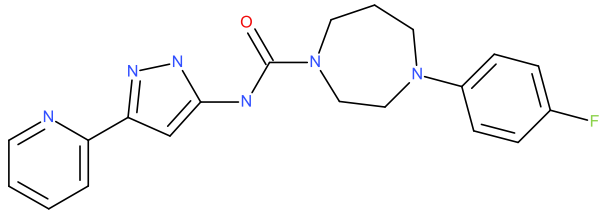
Project P1 – Work Packages B & K:



- Examples of piperazine and homopiperazine ureas have been made (approx. 35 analogues), with activity observed.
- Data set of existing piperazines and other compounds will be provided
- Metabolic stability and optimization of potency needs to be addresses



DNDI0002491055
L.Infantum IC_{50}: 0.732 µM
HLM 51 µL/min/mg.pr

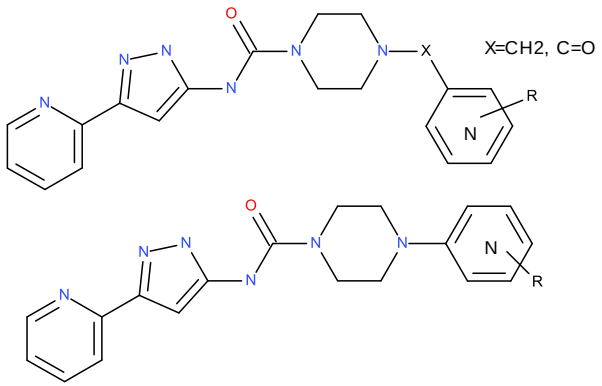


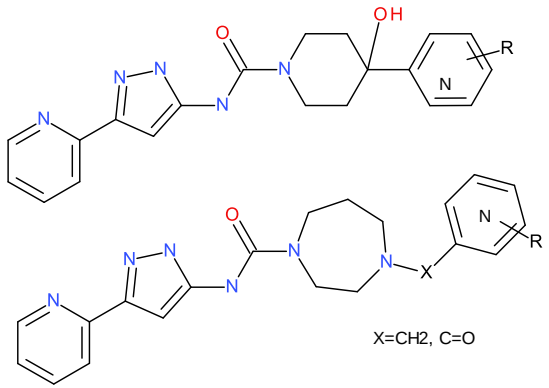
DNDI000296578
L.Infantum IC_{50}: 0.45 µM
HLM 51 µL/min/mg.pr

Examples of target compounds:

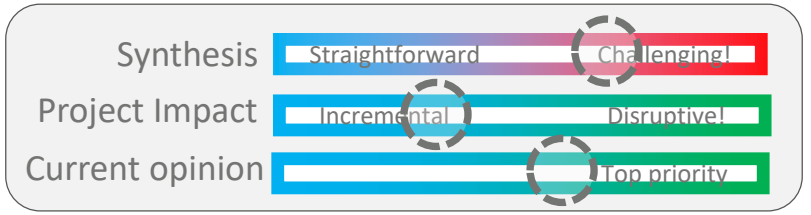
Library scans

(suitable for parallel synthesis from common intermediate)



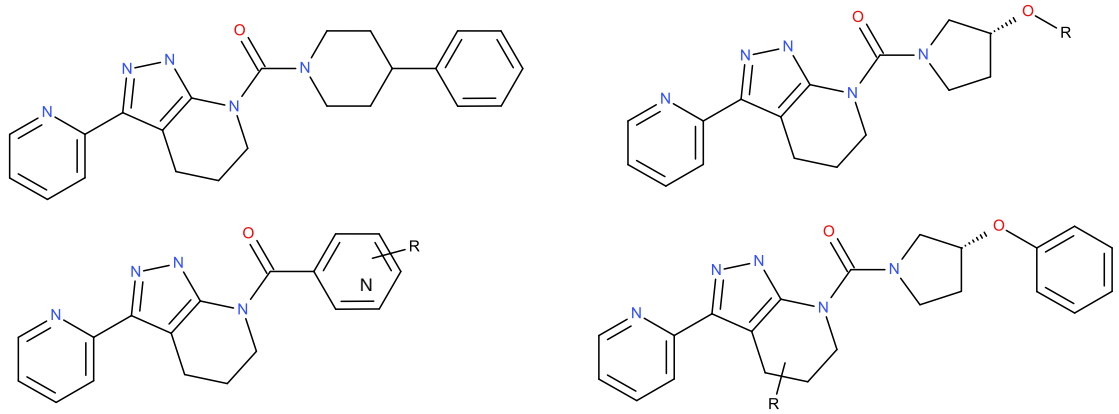


Project P1 – Work Packages C:

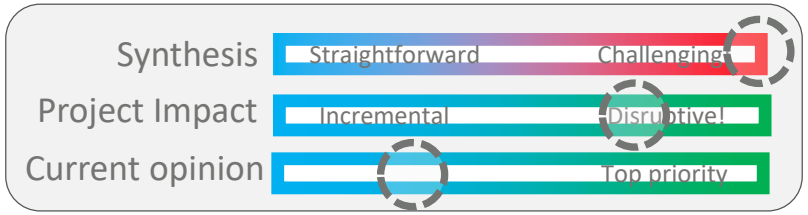


- Cyclization of the core to give a partially saturated [5.6] system has demonstrated some potential but is relatively unexplored
- Relevant data set will be provided (4 compounds)
- Exploration of this chemical sub-series may require development of target-specific chemistry

Examples of target compounds:

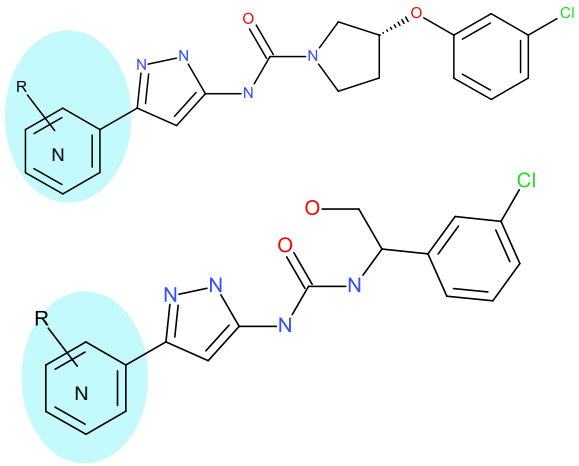


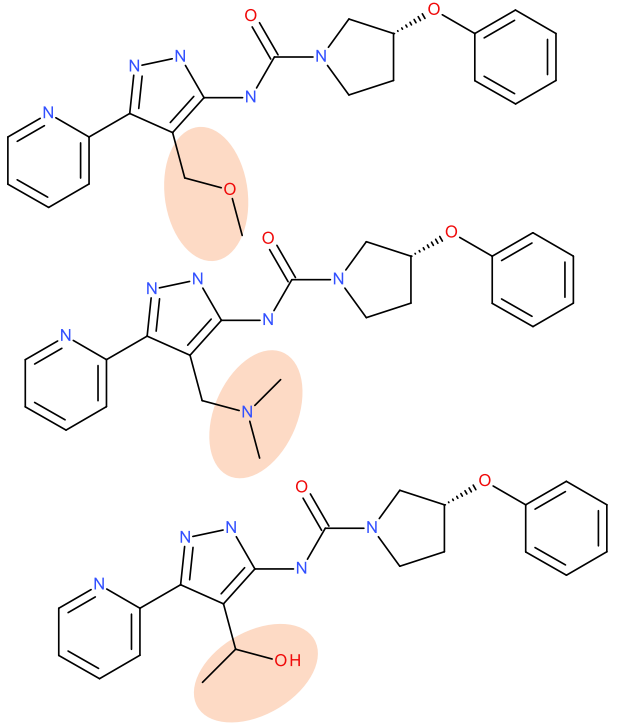
Project P1 – Work Packages D&F:



- Replacement of 2-pyridyl on left-hand side (LHS) has been investigated, but not necessarily for more advanced right hand sides (RHS)
- Relevant data set will be provided (approx. 20 compounds)
- New chemistry could be developed to allow parallel synthesis; otherwise this requires bespoke synthesis for each analogue (approx. 4 steps)
- Substitution of the 4-position of the pyrazole has been shown to be advantageous, however certain analogues have yet to be synthesized:
- Expected to be Synthetically challenging

Examples of target compounds:

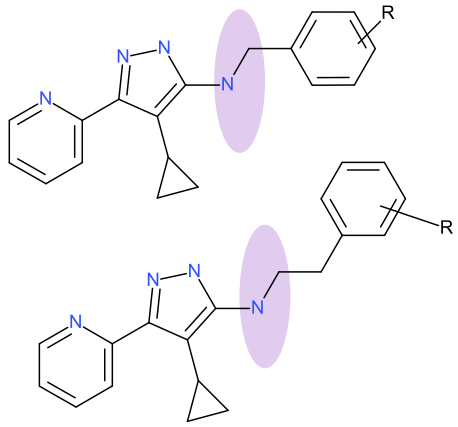




Project P1 – Work Package H:

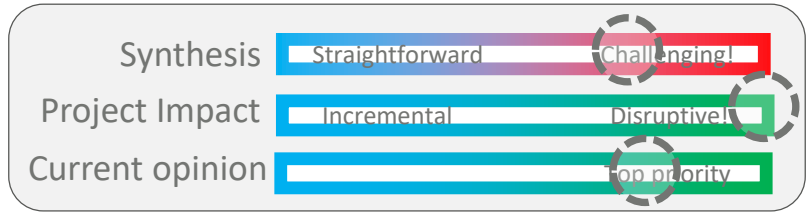
- 5-N-alkyl analogues
- Some early SAR suggested that 5-N-alkyl (instead of 5-N-amide or 5-N-ures) pyrazoles may have activity against both leishmania and also *trypanosoma cruzi*, causative agent of Chagas disease
- This was not pursued further in the initial investigations but recent OSN results have confirmed activity and intertest

Examples of target compounds:



OPEN SYNTHESIS NETWORK

Project P1 – Work Package N:



- In collaboration with leading Artificial Intelligence (AI)-driven med chem design company IKTOS, we have designed some highly innovative and exciting possible scaffold hops away from the lead compounds and into new chemical space.
- Work package N takes the best of these AI designed molecules and tries to makes these entirely novel and untested compounds a success.
- **High Risk, High Reward** ! Active molecules identified from work package N would have MAJOR impact on the project, delivering entirely new chemotypes for leishmaniasis and/or Chagas disease

Examples of target compounds: