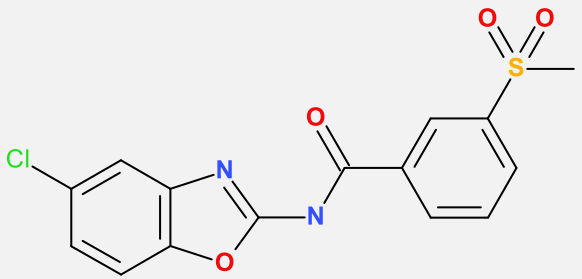
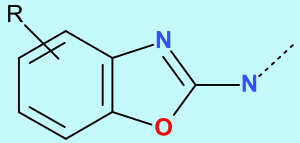
Project P5 – Benzoxazole amide Hit to lead

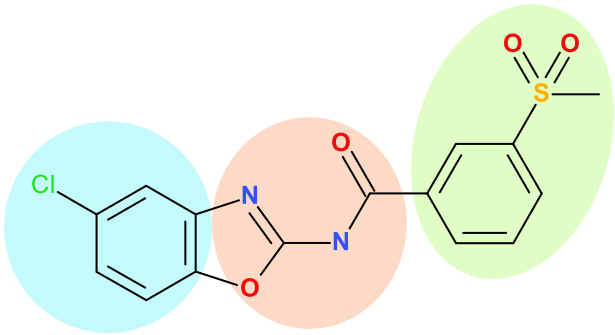


DNDI0003202883
L. donovani (axenic) IC50: 0.34 uM
L. donovani (cell) IC50: 3.2 uM
Background cell cytotox (THP1) IC50: >50 uM

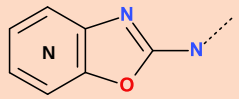
- Compound identified from High Throughput Screen of a large (>200,000 compound) commercial library conducted by DNDi in 2017
- 2 close analogues display similar efficacy

Work Package A: Alternative substitution on benzoxazole

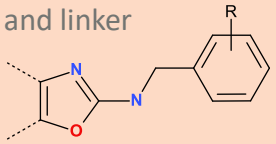


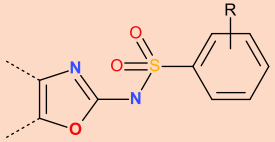


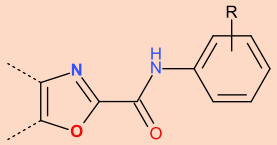
Work Package B: Explore core heterocycle and linker



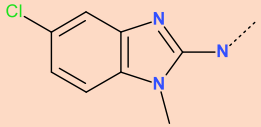
Incorporate additional N

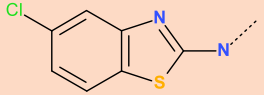


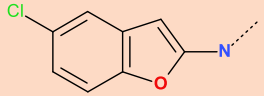




Alternative linkers

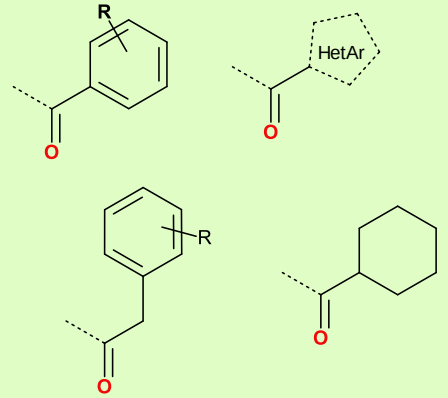






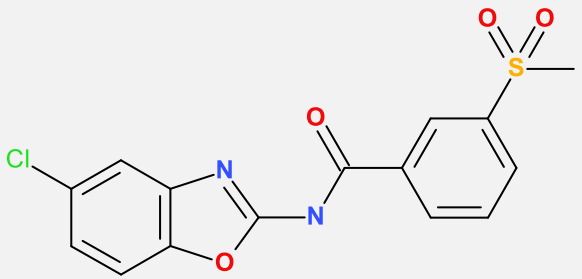
Alternative heterocycles

Work Package C: Scan around the phenyl ring



- **OSN Challenge:**
  - Early Hit to Lead exploration to validate efficacy and build SAR
    - Driven via empirical scanning of the chemotype
  - Evaluation of series once we have ~30-50 compounds in hand
- **Objective:** Elaborated SAR via ~40 compounds, including compounds with improved potency against *leishmania* parasite

Project P5 – Available data, Med chem plan



DNDI0003202883
L. donovani (axenic) IC50: 0.34 uM
L. donovani (cell) IC50: 3.2 uM
Background cell cytotox (THP1) IC50: >50 uM

Initial data generated by University of Dundee
- Potency demonstrated in both Axenic (extracellular) and infected cell (macrophage) assay
- Cell based assay (THP1 cells)
- Compound demonstrated good efficacy, no background toxicity

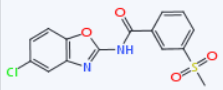
OSN compounds will be tested at University of Antwerp
- *Leishmania infantum* Cell based assay (PMM cells)

- Data set available (3 compounds)

Dundee data

File Edit Data Chemistry Database List Macro Help

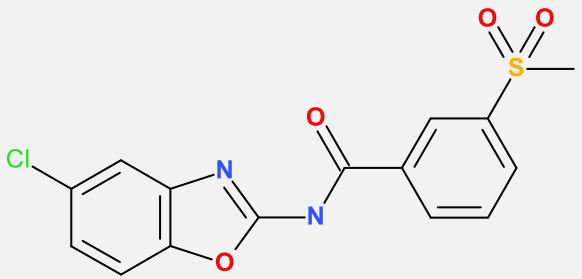
Table

	Structure	Molecule Name	L dond axenic IC50 (Du...	L don IC50 (Dundee)	CC50 THP1	Compound
1		DNDI0003202883	0.34	3.2	50	
		DNDI0002673563		50.12	25.12	

- **Project Plan**
  - Resynthesisze sample of hit and confirm activity (priority)
  - In parallel synthesize ~20 analogues probing chemotype
  - Profile in *L inf* Assay at LMPH
    - If compounds are not active at LMPH, run second confirmation at Dundee
  - Identify compounds with both improved and reduced *L inf.* potency – indicative of valid structure – Activity relationship (SAR)
    - If SAR is evident after ~20 analogues, project will continue
    - If SAR is not evident, project will stop
  - If series demonstrates SAR, publish initial findings and continue optimization

- **Design of Analogues**
  - "Wanted List" of DNDi designed analogues available (OSN P5 Master list.sdf)
  - OSN institutions and invited to propose their own design ideas based on available data set (OSN P5 data set.sdf)

Project P5 – Benzoxazole amide synthetic chemistry



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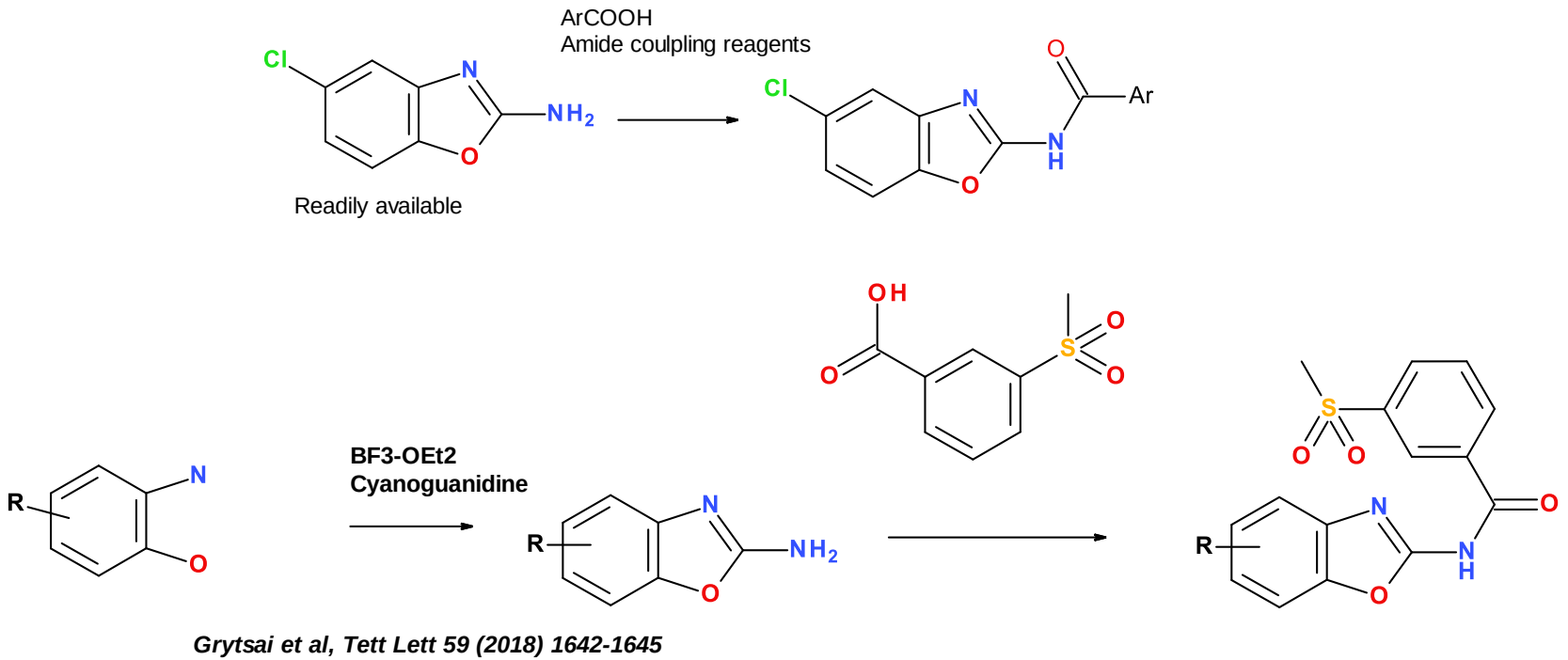
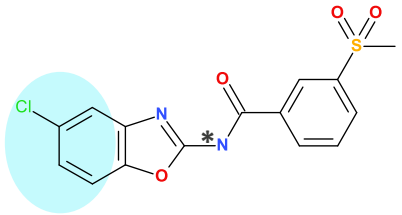
- Compound identified from High Throughput Screen of commercial library
- 2 close analogues display similar efficacy

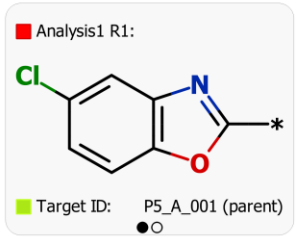


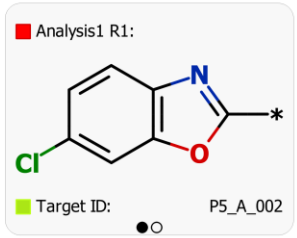
Grytsai et al, Tett Lett 59 (2018) 1642-1645

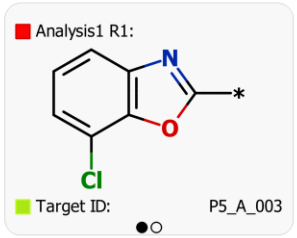
- Relatively straightforward chemistry with final compounds available in 1-3 steps

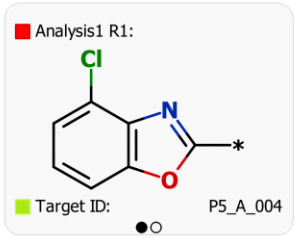
Project P5 – Work Package A: Initial targets

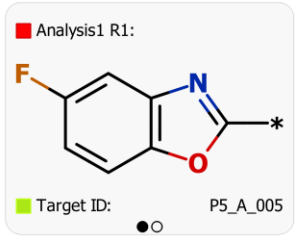


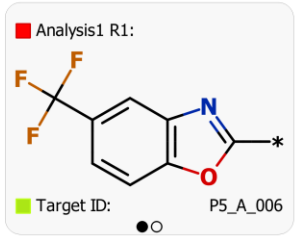


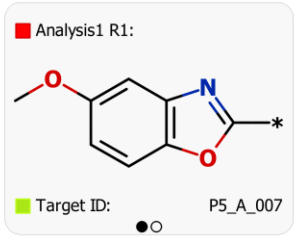


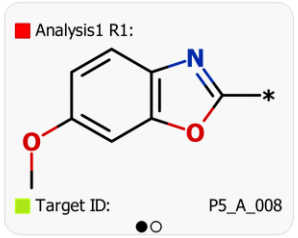


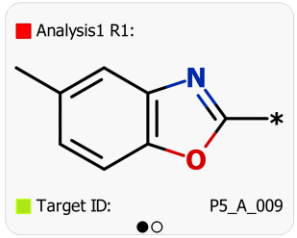


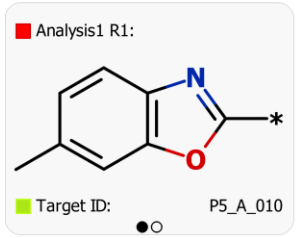




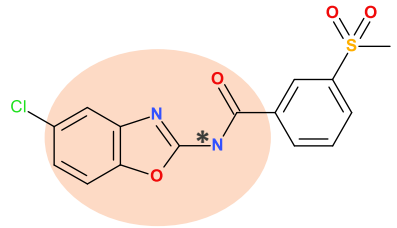


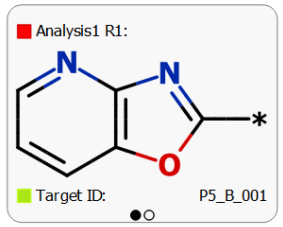


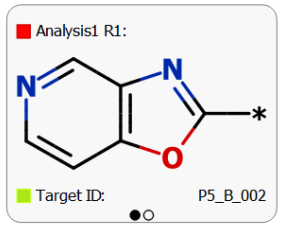


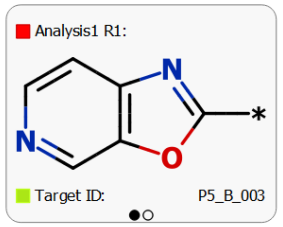


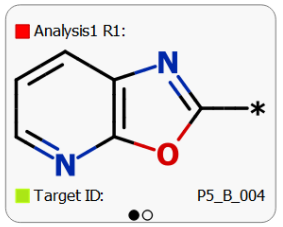
Project P5 – Work Package B: Initial targets

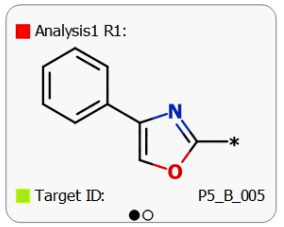


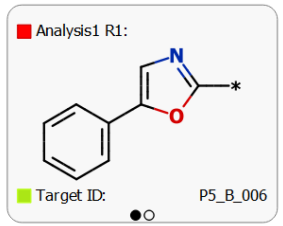


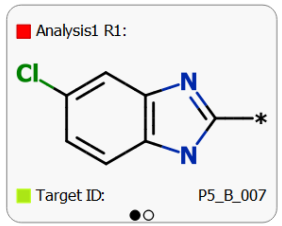


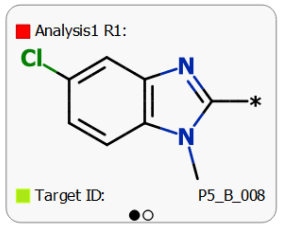


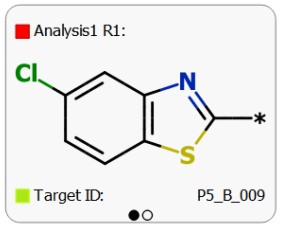


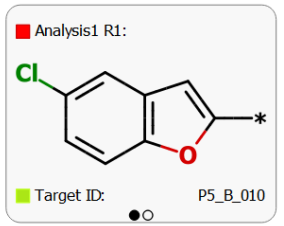


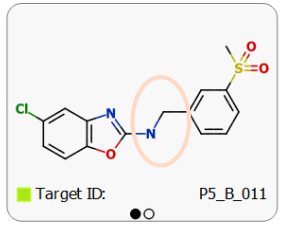


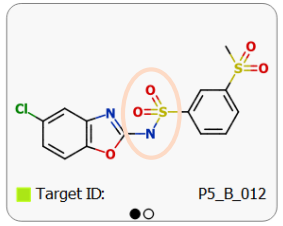


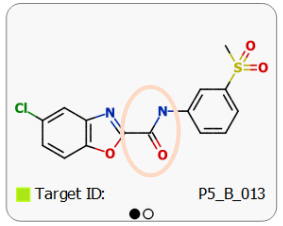












Project P5 – Work Package B: Initial targets