Using small molecules to solve big problems

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DIVERSITY-ORIENTED SYNTHESIS (DOS)

![Diagram showing the process of DOS](image)

**Figure 1** left: overall synthetic strategy used in traditional combinatorial synthesis, right: branching DOS pathway.

**EXAMPLE: MACROCYCLES**

![Diagram showing macrocycles](image)

**Figure 2**: macrocycles are present in more than 100 marketed drugs but are rare in screening libraries due to synthetic intractability.

**MACROCYCLES VIA ADVANCED BUILD/COUPLE/PAIR**

- DOS based on advanced build/couple/pair (B/C/P) whereby building blocks are synthesised (build), coupled together (couple) and cyclised to form macrocyclic scaffolds (pair).
- Structural diversity defined by the building blocks employed, and by the linking motif installed by various aza-Wittig coupling reactions.
- ‘Click’ and enyne metathesis used as the pairing reactions.

![Diagram showing macrocycle synthesis](image)

**Figure 3**: outline of the synthetic strategy used for the construction of the macrocyclic DOS library.

- 73 Macrocycles based around 59 discrete scaffolds were prepared.
- Principal moment-of-inertia analysis was used to illustrate the broad shape diversity of the macrocycles.
- Advanced B/C/P algorithm since extended to include a multidimensional pair phase utilising Sonogashira and Graser couplings, Pauson-Khand and olefin metathesis reactions.

**KEY REFERENCES**


PROTEIN-PROTEIN INTERACTIONS (PPIs)

![Diagram showing PPIs](image)

**Figure 4** left: crystal structure of MDM2-p53 (1YCR), middle: crystal structure of MDM2-Nutlin-2 (1RV1), right: Nutlin-2.

**EXAMPLE: POLO-LIKE KINASE 1 (PLK1)**

![Diagram showing PLK1](image)

**Figure 5** left: crystal structure of Pk1 (4J7B), right: crystal structure of LHeSpTA-PBD (3FVH).

**KEY RESULT 1**: IDENTIFICATION OF A CELL-ACTIVE PHOSPHOPEPTIDOMIMETIC

- 1 caused a dose response increase in mitotic index (EC50 = 13 μM)
- HeLa cells treated with 1 predominantly showed the ‘metaphase’ with non-congressed chromosomes phenotype typical of PBD inhibition

![Diagram showing PLK1 inhibition](image)

**Figure 6** left: U2oS cells treated with 25 μM 1; Hoechst stained for DNA; PH3 stained for phospho histone h3, right: confocal microscopic images of HeLa cells treated with DMSO and 1; scale bar = 5 μm.

**KEY RESULT 2**: SEMINAL CRYSTAL STRUCTURE OF A SMALL MOLECULE INTERACTING WITH THE PBD TYROSINE POCKET

- Phosphopeptidomimetics were soaked into PBD-CREST crystals
- 2 was found to interact with the tyrosine pocket at the PPI interface

![Diagram showing PLK1 inhibition](image)

**Figure 7** left: crystal structure of PBD tyrosine pocket interacting with Map205, right: crystal structure of 2 interacting with the tyrosine pocket.

**CONCLUSIONS AND FUTURE WORK**

- 1 causes mitotic arrest and appears to induce the PBD cellular phenotype, although investigations are ongoing to confirm this
- A 2.68 Å resolution crystal structure of 2 interacting with the tyrosine pocket has been obtained
- A fragment program has been initiated in an effort to uncover hit compounds that inhibit PBD function via binding to the hydrophobic tyrosine pocket

**KEY REFERENCES**