Using small molecules to solve big problems

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DIVERSITY-ORIENTED SYNTHESIS (DOS)

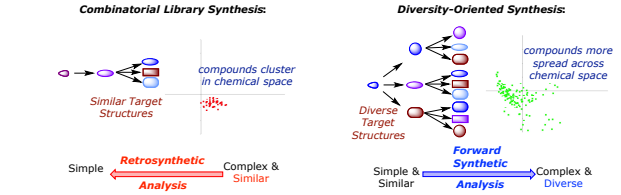

Figure 1 left: overall synthetic strategy used in traditional combinatorial synthesis, right: branching DOS pathway.

EXAMPLE: MACROCYCLES

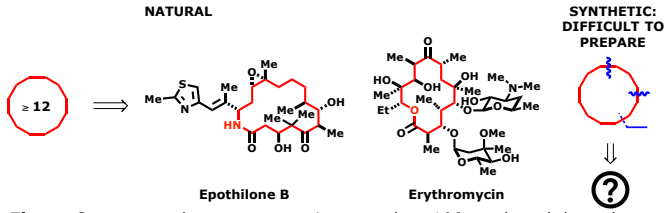

Figure 2: macrocycles are present in more than 100 marketed drugs but are rare in screening libraries due to synthetic intractability.

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

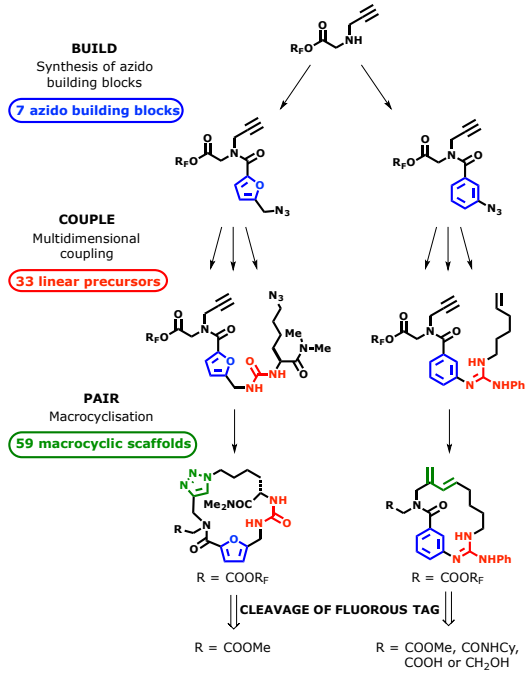

Figure 3: outline of the synthetic strategy used for the construction of the macrocyclic DOS library.

- 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 Glaser couplings, Pauson-Khand and olefin metathesis reactions

KEY REFERENCES

- W. R. J. D. Galloway *et al.*, *Nature Commun.*, 2010, **1**, 80.
- H. Beckmann *et al.*, *Nature. Chem.*, 2013, **5**, 861-867.
- See also: Grossmann *et al.*, *Angew. Chem. Int. Ed.*, 2014, **53**, 13093-13097; Llobet *et al.*, *Proc. Natl. Acad. Sci. USA*, 2011, **108**, 6793-6798.

PROTEIN-PROTEIN INTERACTIONS (PPIs)

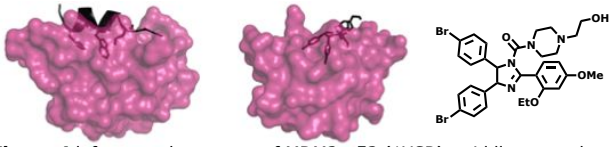

Figure 4 left: crystal structure of MDM2-p53 (1YCR), middle: crystal structure of MDM2-Nutlin-2 (1RV1), right: Nutlin-2.

EXAMPLE: POLO-LIKE KINASE 1 (PLK1)

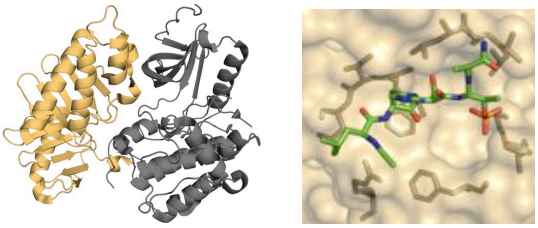

Figure 5 left: crystal structure of Plk1 (4J7B), right: crystal structure of LHSpTA-PBD (3FVH).

KEY RESULT 1: IDENTIFICATION OF A CELL-ACTIVE PHOSPHOPEPTIDOMIMETIC

- **1** caused a dose response increase in mitotic index (EC_{50} = 13 μM)
- HeLa cells treated with **1** predominantly showed the 'metaphase' with non-congressed chromosomes phenotype typical of PBD inhibition

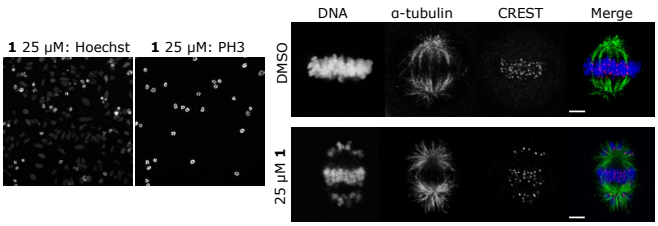

Figure 6 left: U2oS cells treated with 25 μM **1**; Hoechst stained for DNA; PH3 stained for phospho histone h3, right: confocal microscopic images of HeLa cells treated with DMSO and **1**; scale bar = 5 μm.

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

- Phosphopeptidomimetics were soaked into $PBD_{371-594}$ crystals
- **2** was found to interact with the tyrosine pocket at the PPI interface

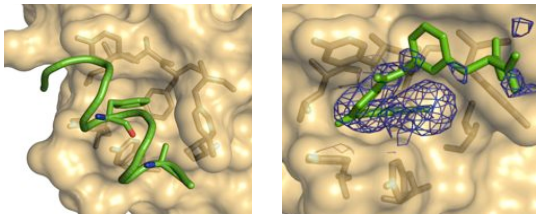

Figure 7 left: crystal structure of PBD tyrosine pocket interacting with Map205, right: crystal structure of **2** interacting with the tyrosine pocket.

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

- J. A. Wells and C. L. McClendon, *Nature*, 2007, **450**, 1001-1009.
- K. Strebhardt and A. Ullrich, *Nat. Rev. Cancer*, 2006, **6**, 321-330.
- S-M. Yun *et al.*, *Nat. Struct. Mol. Biol.*, 2009, **16**, 876-883.