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Vectorial Functionalisation of Heteroaromatic "Rings of the Future" for Fragment-Based Drug Discovery

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1. INTRODUCTION

- The "rings of the future" form a virtual library of heteroaromatic ring systems published by Pitt *et al.*[1] with the aim to uncover novel scaffolds that explore unchartered areas of chemical space and break away from the relatively limited set of ring systems routinely used in constructing drug-like molecules.
- Heterocycles are prevalent in biologically-active molecules meaning these novel scaffolds are valuable inputs for medicinal chemists. Their molecular size and functional group density lends itself well to FBDD. Any fragment-based approach (figure 1) typically involves several rounds of elaboration to introduce new protein-ligand interactions. Heterocycles complicate this synthetic elaboration as new substituent patterns often require *de novo* synthesis and strategies for late-stage functionalisation are still lacking. This is particularly true when the fragments are based on novel scaffolds.
- Here we present strategies for the synthesis and vectorial functionalisation of one of these "rings of the future": the pyrazolo[3,4-c]pyridine scaffold **1**.

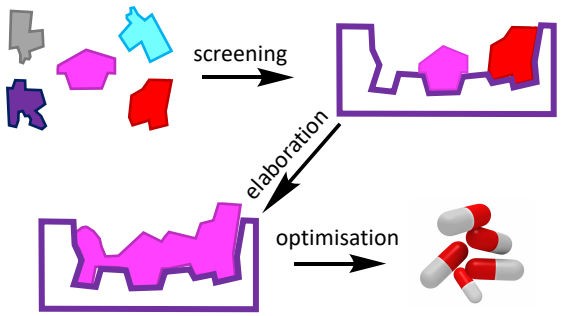
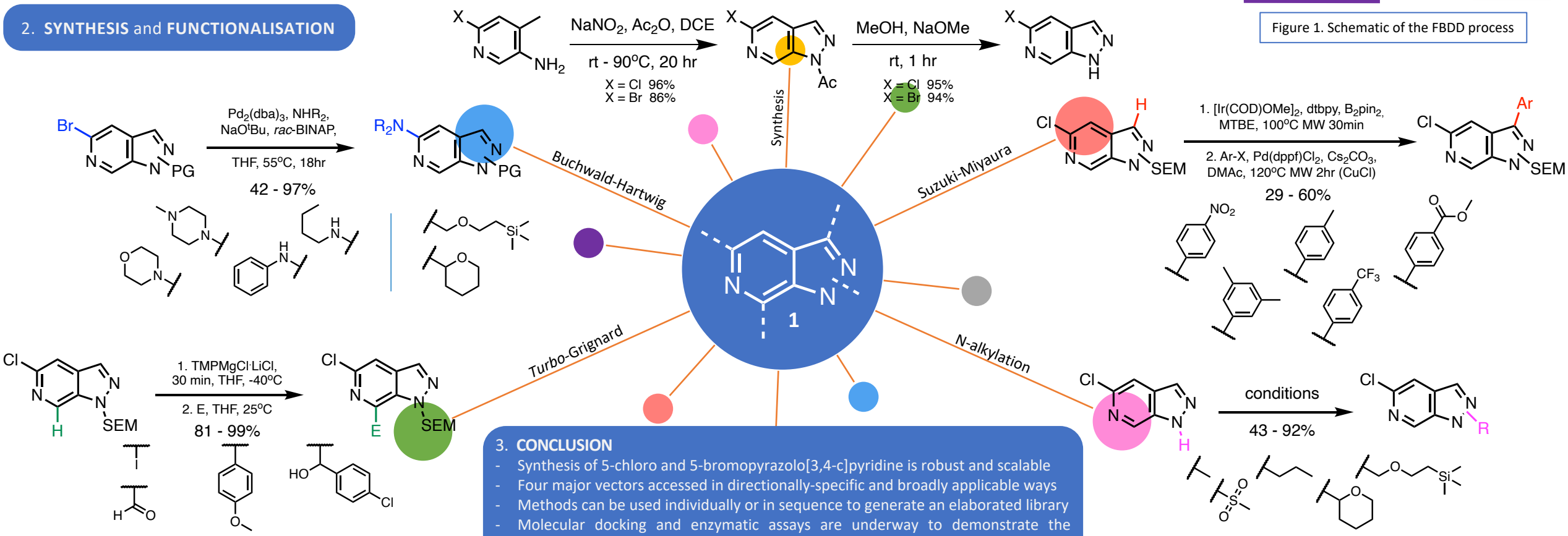


Figure 1. Schematic of the FBDD process

2. SYNTHESIS and FUNCTIONALISATION



3. CONCLUSION

- Synthesis of 5-chloro and 5-bromopyrazolo[3,4-c]pyridine is robust and scalable
- Four major vectors accessed in directionally-specific and broadly applicable ways
- Methods can be used individually or in sequence to generate an elaborated library
- Molecular docking and enzymatic assays are underway to demonstrate the application to a FBDD strategy targeting the Sirtuin2 enzyme of Trypasomatids

1. *J Med Chem.* **2009**, 52(9), 2952-2963.