ENABLING FRAGMENT GROWTH WITH PHOTOREDOX CATALYSIS THROUGH HIGH-THROUGHPUT EXPERIMENTATION

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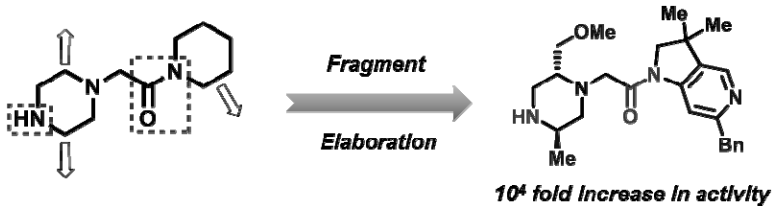
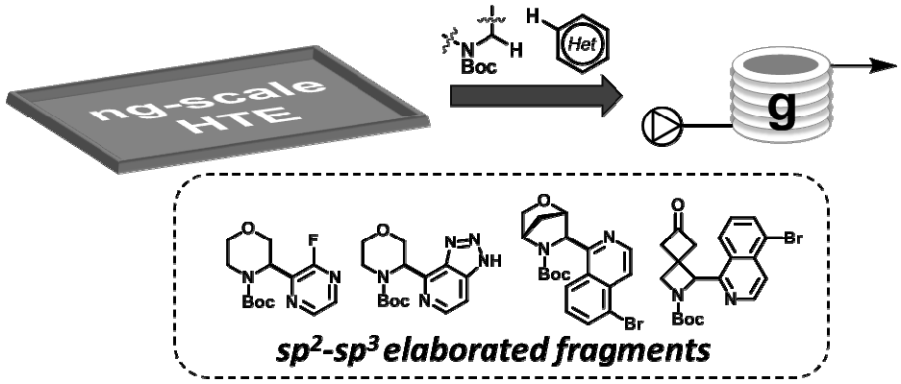
Fragment based drug discovery (FBDD) is an established technique in both industry and academia for the identification of novel starting points for drug discovery.[1] Robust organic chemistry is essential to synthesise new fragments and to elaborate these weakly binding (mM to µM) hits into nM leads through growth at selected vectors whilst maintaining key polar interactions (fig. 1).[2] This requires synthetic methodology that is compatible with significant amounts of polar functionality.[3]



To expedite synthesis in FBDD, we established a nanogram-to-gram workflow to enable synthetic transformations on native fragments, such as the direct C–H functionalization of saturated and unsaturated heterocycles. This novel approach deploys high-throughput experimentation (HTE) in 1,536-well microtiter plates facilitated by liquid handling robots to screen reaction conditions on nanomolar scale; subsequently the reaction is upscaled in continuous flow to generate gram-quantities of material (fig. 2). To date this workflow has been applied to uncover two photoredox-mediated C–H functionalisation reactions: the first of which – the cross-dehydrogenative coupling of amines and heteroarenes was recently reported.[4] These methods exhibit excellent functional group tolerance to unprotected polar motifs and common synthetic handles and make them highly applicable to synthesis in FBDD and medicinal chemistry in general.



[1] *Nat. Rev. Drug Discovery*, **2013**, *12*, 5 – 7.

[2] *J. Med. Chem.*, **2015**, *58*, 6574 – 6588

[3] *Angew. Chem. Int. Ed.*, **2016**, *55*, 488 – 492

[4] *Chem. Sci.*, **2019**, *10*, 2264 – 2271