Polymer supported reagents in fully automated multi-step solution-phase organic synthesis

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Introduction
In recent years, considerable effort has been expended to develop immobilised reagents and scavengers to facilitate high-throughput solution phase synthesis.1 The simplicity afforded by the use of such reagents allows development of automated methods for compound library production (Fig. 1).

In this proof of concept study, we report the first fully automated multistep polymer assisted solution phase (PASP) synthesis of a compound array. The synthesis is performed in a single solvent and intermediate inline purifications are achieved through the use of scavenger resins and ‘catch and release’ strategies. Conventional purification is limited to a single prepreparative step at the end of the synthesis to give pure compounds in suitable amounts for initial biological assays.

Figure 1: Schematic of an automated synthesis

Biological Target
Histone deacetylase (HDAC) inhibitors currently constitute an important medicinal chemistry drug target with potential benefits in, for example, the treatment of cancer.

Figure 2: Representation of open and closed forms of chromatin.
HDAC enzymes play a key biological role in chromatin remodelling and in the regulation of gene transcription2 (Fig. 2). Recently, the hydroxamic acid 1 was reported to be a potent HDAC inhibitor.3 We therefore elected to prepare a small compound array 2 based upon 1 as an automated lead optimisation exercise.

Synthesis
The synthetic route below (Scheme 1) was adopted for library production and trialed for the preparation of the lead 1.

DMF was identified as the best overall solvent compatible with all transformations in the proposed synthesis (Scheme 2).

Sulfonylation of the aniline 3 with PS-DMAP tosyl chloride complex gave the intermediate 4 with no evidence of bis-sulfonylation. Heck olefination was achieved with little dehalogenation upon exposure to microencapsulated Pd (II). The carboxylic acid 6 was ‘captured’ on resin to effect an inline purification prior to ‘release’ from the solid phase and conversion to the hydroxamic acid 1.

With a PASP synthesis established the multi-step sequence was repeated in a flow-through manner transferring the reaction solution iteratively through the synthetic steps without isolation of intermediates or solvent concentration.

HPLC analysis was conducted at each stage to provide a profile of the complete synthetic sequence (Table 1). A final HPLC purification of the material obtained gave 1 (20% overall; >95% purity).

Automated Synthesis of HDAc inhibitors
To implement the automated PASP synthesis, a series of modular liquid handling and filtration protocols were first developed. These were run on the Zinsser Sophas M6 robotic platform (Fig. 3). This instrument was determined to be well-suited to automate PASP synthesis due to its ability to repeatedly filter and wash concentrated resin suspensions and to transfer the filtrate between different reaction blocks.

The protocols devised were then linked according to Scheme 3 and the process was validated in 2 parts. Finally, the complete flow-through synthesis was performed to prepare the hydroxamic acid 1.

Samples of intermediates were analysed and this data is contrasted to that obtained for the manual synthesis (Table 1). A similar reaction profile was observed for both the manual and unattended, fully automated multi-step syntheses.

Importantly, the use of automation significantly reduced the overall time for the synthesis.

Conclusions
• Immobilised reagents can be used to perform a series of orchestrated transformations in a single solvent.
• PASP synthesis is well-suited to full automation.
• The unattended fully automated PASP synthesis of an array of HDAC inhibitors 2 has been achieved on a Zinsser Sophas M6 demonstrating a significant time saving over the manual synthesis.

Acknowledgements
Tony Parkhouse (GSK), Adrian Pipe (GSK) and Fiona Payne (Zinsser Analytic UK) for help with the automation.

References