Peptide synthesis (both solution and solid state) is of fundamental importance to the pharmaceuticals sector. They are therefore expected to play a major role in the future of drug discovery. Currently there are more than 60 peptide based medicines approved for use by the US FDA, around 140 peptide drugs currently in clinical trials and over 500 in preclinical trials. Consequently the peptide medicines market is currently worth an estimated US$14.1 billion, and is predicted to grow to around US$ 25.4 billion by 2018. As such, there is a resurgence of interest in the synthesis of synthetic peptides. Peptide synthesis is a highly optimised and automatable process, however, this has resulted in a very ungreen process which:

- Is carried out in undesirable solvents such as DMF and dichloromethane.
- Makes extensive use of auxiliary agents (protecting groups and coupling agents) which end up as waste.
- Uses large excess of reagents.

Of these, the solvent is the largest source of waste and in recent work we have shown that propylene carbonate can be used as a green replacement for DMF and dichloromethane in both solution and solid state peptide synthesis, thus solving the first problem. However, not all protected amino acid derivatives and coupling agents are soluble in propylene carbonate and the piperidine used to deprotect Fmoc groups reacts with propylene carbonate. Therefore, the aim of this studentship will be to address the remaining issues in greening peptide synthesis, particularly:

1. The peptide coupling agent. Many currently used coupling agents (uronium salts, carbodiimides etc) are large molecules which produce large amounts of waste and significantly lower the E-factor of the process, especially if an active ester has to be used as well. Therefore, the use of greener coupling agents such as amino acid fluorides and 2-propanephosphonic anhydride will be investigated in both solution and solid state reactions.

2. The use of other nucleophiles to cleave an Fmoc group will be investigated, aiming to find one which is still effective for this purpose, but which reacts very slowly (or not at all with propylene carbonate).

3. The replacement of the Fmoc protecting group by alternative amine protecting groups will be investigated. For example, β-sulfonylethoxy carbonyl based groups may have better solubility in propylene carbonate which still being cleavable under weakly basic conditions.

The solution to each of 1-3 will be compared to conventional peptide synthesis in terms of yield, purity and epimerisation and used in the synthesis of short peptides to demonstrate its effectiveness.

Application closing date: March 2017
Interview date: April 2017

Funding source: student to secure own funding
Eligibility: UK / EU / Overseas

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For more information contact chemgrad@york.ac.uk or see our web page: http://www.york.ac.uk/chemistry/postgraduate/
The Department of Chemistry holds an Athena SWAN Gold Award and is committed to supporting equality and diversity for all staff and students