Traditionally, medium sized rings and macrocycles are made by forming a chemical bond between the two ‘ends’ of a long linear molecule (A), but competing side reactions and/or dimerisation reactions usually dominate in such processes, leading to inefficient reaction processes. This research is based on a new system for macrocycle synthesis in which the difficult macrocyclisation step is completely avoided, and instead, macrocycles are ‘grown’ via the iterative expansion of smaller ring systems via Successive Ring Expansion (SuRE, B). In SuRE, a smaller cyclic molecule (or ‘starter unit’) undergoes a simple chemical transformation to attach a linear ‘linker’ molecule onto it. A reactive group attached to this linker can then attach itself to the ‘starter unit’ (to briefly form another smaller ring fused onto its side) and then fragment to form a single, larger ring; overall, this corresponds to the insertion of the ‘linker’ into the original ring of the ‘starter unit’. A crucial factor in the reaction design is the fact that the chemical groups present in the ‘starter unit’ are replicated in the expanded product, therefore the same series of steps can then be repeated with a new linker to form an even larger ring; indeed, the sequence can theoretically be repeated indefinitely, allowing the synthesis of macrocycles of virtually any ring size and composition.

In this work, it is planned to use SuRE for the synthesis of medium sized rings and macrocycles, to facilitate to discovery of new pharmaceutical lead compounds using our published ring expansion method (see Angew. Chem. Int. Ed. 2015, 54, 15794). By varying the size, properties and functionality of both the cyclic starter unit and linear fragment, an enormous range of functionalised macrocycles, and medium sized ring scaffolds should be accessible. For example, performing a single iteration of the ring expansion sequence, the 8 simple β-keto esters and 14 linear fragments shown below (the majority of which were shown to be compatible with SuRE in our published study) will allow access to 168 unique lactam and lactone frameworks. It is not planned to synthesize all of these targets; instead it is planned to employ a combination of physicochemical predictive tools and traditional biological screening results to help to prioritise which compounds to make, in order maximise the chances of identifying new pharmaceutical lead compounds. Further functionalisation/derivatisation of the scaffolds shown will likely be necessary to improve their drug-like properties. This will be done in two ways: a) by installing more varied functionality in the cyclic starter unit or linear fragment; b) by post-functionalisation of the scaffolds.

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

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