A TOP-DOWN APPROACH TO DIVERSE LEAD-LIKE MOLECULAR SCAFFOLDS

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Control of molecular properties is essential in the design of new bioactive compounds, due to the inherent link between molecular properties of lead compounds and their successful progression through the stages of clinical development. Through the optimization process compounds tend to gain in molecular weight, lipophilicity and complexity, therefore a set of guidelines have been established to aid the design of lead-like molecules. In order to realise efficient lead-oriented synthesis a "top-down" approach has been employed whereby complexity is encoded to give a key polycyclic intermediate. It is vital that this intermediate contains functionality that can facilitate annulations, ring contractions and ring cleavage reactions. The use of this approach will be demonstrated using [5+2] cycloaddition chemistry as the complexity generating reaction in the synthesis of a library of highly 3-dimensional compounds, which have the correct properties to target lead-like chemical space. A toolkit of reactions has been applied to the parent compound creating a diverse range of lead-like scaffolds. Each scaffold contains a number of functional handles which can be decorated to create a large number of lead-like screening compounds.