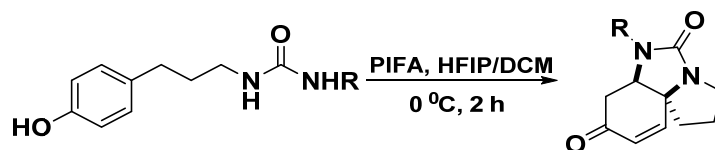


A 'TOP DOWN' APPROACH TO THE SYNTHESIS OF COMPLEX, DIVERSE LEAD-LIKE SCAFFOLDS

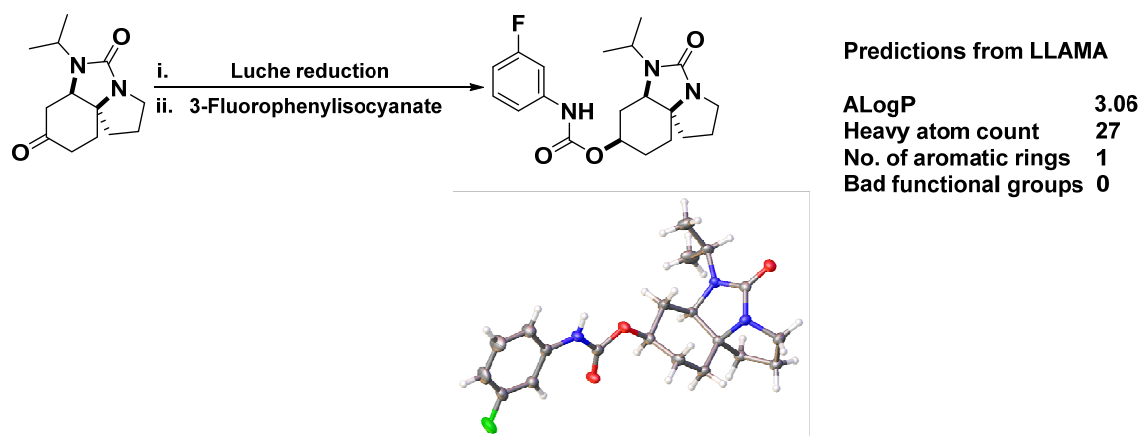
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Lead-oriented synthesis¹ (LOS) is a concept that seeks to underscore the usefulness of developing new methodologies suitable for making a diverse library of highly three-dimensional small organic molecules with controlled molecular properties that qualify them to most likely serve as lead compounds or be in the 'lead-like' space. The 'top down' approach² to LOS seeks to gain rapid access to complex polycyclic assemblies which can then be deconstructed or modified through ring addition, cleavage and expansion to generate multiple, diverse lead-like scaffolds. This strategy hopes to solve the problem of high attrition rates in drug discovery. A number of sp³-rich scaffolds have been synthesized through this means from relatively cheap and simple materials using a novel oxidative dearomatisation reaction as the complexity-generating step. Some of these scaffolds have been decorated along different vectors with exemplar medicinal chemistry capping groups, with their molecular properties assessed by LLAMA (Lead-likeness and Molecular Analysis, an in-house computational tool³) prior to their decoration, and shall be tested for biological activity against a wide range of targets.



Scheme 1. Last step of complexity generating reactions



Scheme 2. Exemplar decoration for a final compound for biological screening

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