EXPLORING THE FUNCTIONAL AND SYNTHETIC IMPORTANCE OF FOUR-MEMBERED HETEROCYCLES IN PRENYLATED NATURAL PRODUCT CHEMISTRY

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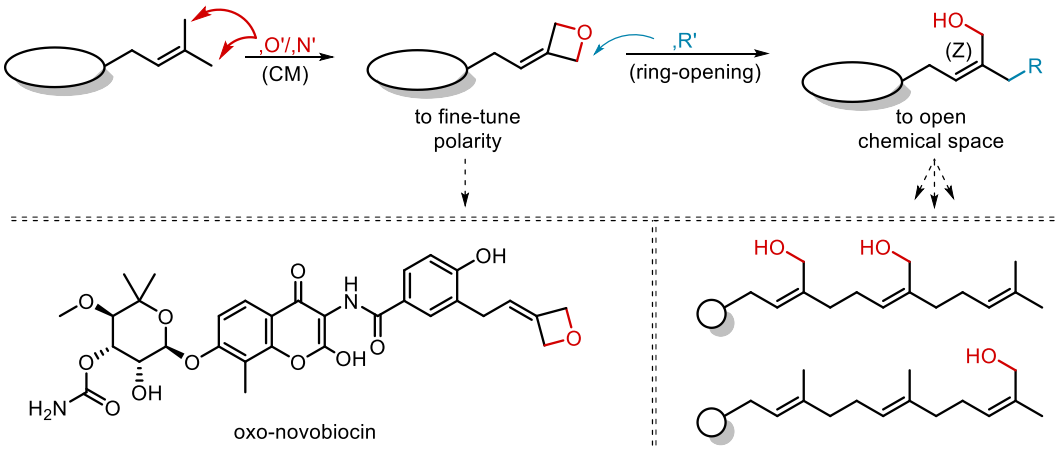
In contemporary drug discovery, the use of four-membered heterocycles has emerged as a strategic tool, particularly for polarity-modifying bioisosteric replacements. Their incorporation into drug molecules often leads to improved bioavailability, selectivity, and potency, while their utilization opens new vistas in the exploration of new chemical space. [1] [2]

Encouraged by the immense functional potential of four-membered heterocycles, we became interested in extending this concept to the late-stage polarity fine-tuning of prenylated natural products and drug candidates by the selective, orthogonal introduction of these four-membered heterocycles into the prenyl moiety. This isosteric replacement was expected to open new opportunities for fine-tuning of the ADMET properties of prenylated natural products. To achieve this goal, we developed a strain-driven olefin cross-metathesis (CM) methodology to formally insert oxygen and nitrogen between the methyl groups of the prenyl site [3].

Subsequently, this unique synthetic methodology enabled us to explore the synthetic utility of 3-alkylideneoxetane derivatives, particularly in their further synthetic elaboration via ring opening. These efforts led to the development of an efficient and highly selective synthetic platform for the synthesis of *Z*-hydroxylated prenyl, geranyl and farnesyl derivatives in a modular and iterative fashion, opening an unprecedented route to the synthesis of difficult-to-access natural and non-natural terpenoid derivatives.[4]



[1] Juan J. Rojas and James A. Bull *J. Med. Chem.* **2023**, 66, 18, 12697–12709
[2] Georg Wuitschik, Erick M. Carreira, Bjorn Wagner, Holger Fischer, Isabelle Parrilla, Franz Schuler, Mark Rogers-Evans and Klaus Muller *J. Med. Chem.* **2010**, *53 (8), 3227–3246*
[3] Krisztián Albitz, Dániel Csókás, Zoltán Dobi, Imre Pápai and Tibor Soós *Angew. Chem.Int. Ed.* **2023**, *62,e202216879*
[4] Unpublished results