Synthesis and Biological assessments for RhoGTPases' inhibition

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Over the years, numerous studies have shown a significant link between human diseases (cancers, neuronal disorders, pulmonary and cardiovascular diseases) and aberrant activity of small GTPases of the Rho protein family. [1–5] These RhoGTPase proteins have long been deemed "undruggable" because of their smooth structure devoid of pockets which prevent small inhibitors to strongly interact with them. However, their activity due to the catalysis of a binded molecule of GDP into GTP through the interaction with a guanine nucleotide exchange factor (GEF) could be a relevant target for the study of the Rho/GEF complex inhibition. The elucidation of new inhibitors of this protein-protein interaction provides an attractive alternative by bypassing the direct inhibition of Rho protein. In 2020, Dr. Camille Trouillet's researches have led to two molecule series (Kheops & Felouk) exhibiting a great potential for the inhibition of this protein-protein interaction.[6] According to the biological assays and the computer modeling studies, numerous analogues have been confirmed as remarkable inhibitors for the inhibition of RhoA/Arghef1 complex. Our presentation will describe the synthesis of new multifunctional compounds to build on a chemical library with better inhibition potency (Fig. 1), and it will also discuss about the difficulties encountered in the chemical synthesis of these Kheops' molecule series.

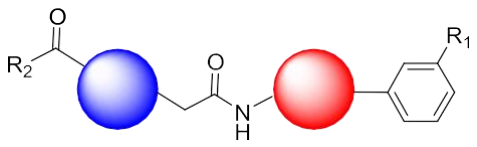

Figure 1: Kheops' series analogues

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