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SAR OF TRIQUINAZINE, A CLASS OF POTENT JANUS KINASE INHIBITORS

Kleni Mulliri, Kris Meier, Jean-Louis Reymond

Department of Chemistry and Biochemistry, University of Bern, Freiestrasse 3, 3012 Bern.
kleni.mulliri@unibe.ch

Chemical space involves organizing molecules with potential therapeutic interest into a structured search space based on their structural and functional similarities, thereby facilitating the discovery of new drugs. We investigate the generated database (GDBs) [1], to access novel, challenging and unknown molecules with high potential in medicinal chemistry.This sillico libraries contain billions of molecules created following several designs rules giving us a huge chemical space of choice[2]. From GDBs, we have selected and synthesised a tricyclic diamine dubbed triquinazine, which is used as the core of some of the most potent and selective Janus Kinase Inhibitors to date (IC_{50} = 1.0 nM for JAK1) **KMC 420**[3] (Fig 1). Inspired by these results we are synthesizing a series of compounds by diversifying the diamine core of our lead compound **KMC 420**. In addition to the SAR that will improve the understanding JAK1 pharmacology, our compounds have the potential to provide new selective inhibitors for the other isoforms of this enzyme family.

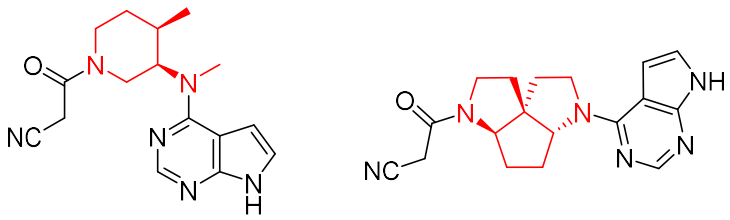

Fig 1. Examples of Janus Kinase Inhibitors. **Tofacitinib**, a block buster drug in the market and **KMC 420**, triquinazine inhibitor.

[1] Meier, K.; Bühlmann, S.; Arús-Pous, J.; Reymond, J.-L. Chimia. 2020, 74 (4), 241–246.
[2] Visini, R.; Arús-Pous, J.; Awale, M.; Reymond, J.-L. J. Chem. Inf. Model. 2017, 57 (11), 2707–2718.
[3] Meier, K.; Arús‐Pous, J.; Reymond, J.-L. Angew. Chem. Int. Ed. 2021, 60 (4), 2074‐2077. …