SAR OF TRIQUINAZINE, A CLASS OF POTENT JANUS KINASE INHIBITORS

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The development of new and improved drugs relies on the constant discovery of new chemical structures. Our group draws inspiration from the exploration of the chemical space to generate highly interesting novel molecules for medicinal chemistry. For this, we have developed the Generated Databases (GDBs)[1], in sillico libraries that contain billions of molecules created following several designs rules[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.

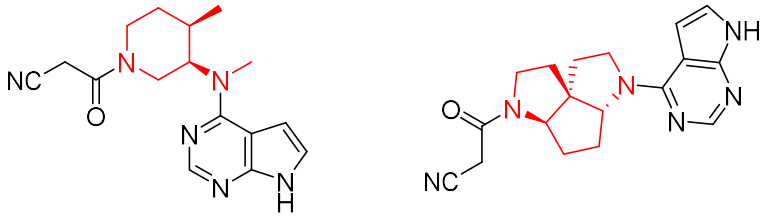

Fig 1. Different examples of Janus Kinase Inhibitors. **Tofacitinib**, a block buster drug in the market; **KMC 420**, triquinazine inhibitor.

[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.