## How Ring-Size, Stereochemistry and Substituents Modulate the Activity of a Nanomolar JAK1 Inhibitor

K. Mulliri<sup>1</sup>, K. Meier<sup>1</sup>, J. Reymond<sup>1</sup>\*

<sup>1</sup>University of Bern

We investigate the generated database  $(\text{GDBs})^1$ , to access novel, challenging and unknown molecules with high potential in medicinal chemistry. These in sillico libraries contain billions of molecules created following several designs rules producing a huge chemical space<sup>2</sup>. We have selected and synthesized a tricyclic diamine dubbed triquinazine, which is used as the core of one of the most potent and selective Janus Kinase Inhibitors to date (IC<sub>50</sub> = 1.0 nM for JAK1) **KMC 420**<sup>3</sup> (Fig 1). Inspired by these results we are synthesizing a series of compounds by diversifying the diamine core of our lead compound **KMC 420**. Our synthetic approach involves a seven-step linear sequence, that allows for the control of the ring size and diastereochemistry. Through the deconstruction of triquinazine, we obtained a diverse set of analogues, focusing on those closely resembling the core structure. Stereochemistry was crucial for bioactivity where a one pot two step Mitsunobu, Staudinger protocol was implemented to obtain the compounds with the desired stereochemistry. Further functionalization of the amines with the deazapurine and four other selected functionalities, furnished more then 20 final compound which were tested for biological activities. **KM-174** showed to be selective on JAK1 with IC<sub>50</sub> = 25 nM, improving the understanding JAK1 pharmacology.



Fig 1. KMC 420, triquinazine inhibitor,  $IC_{50} = 1$  nM and KM-174,  $IC_{50} = 25$  nM on JAK1.

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