Design and synthesis of original heterocyclic scaffolds and application to the discovery of novel neutraligands of chemokines.

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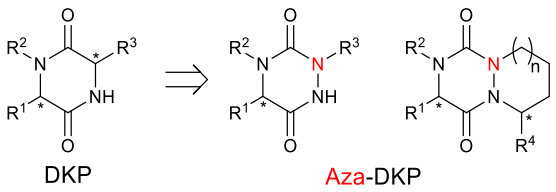
Low molecular-weight organic molecules are a major source of pharmacological probes and/or drug candidates [1]. Recent achievements in Pd-catalyzed C(sp2)–C(sp2) coupling reactions have greatly facilitated the syntheses of small-size compounds. While these advances have largely contributed to drug discovery, mainly compounds with greater unsaturation, aromatic and flatness characters were obtained. However as recently reported [2], such compounds are less likely to succeed in clinical trial than saturated ones. Indeed, increasing saturation in molecules results in more complex three dimensional 3D-shaped structures to better complement the spatial subtleties of target proteins, thus increasing their selectivity and reducing off-target liabilities. In addition, saturation also greatly improves aqueous solubility and as a consequence ameliorates pharmacokinetical properties while decreasing potential toxicity [3].

In this context, we embarked on a general program aiming at designing efficient and facile routes to complex 3D-shaped molecules containing sp3 hybridized carbons and stereocenters with potential application in medicinal chemistry. In this communication we will describe the synthetic routes to access to novel aza-diketopiperazine (aza-DKP) scaffolds to enrich the chemical diversity of our library. Based on a high-throughput screening approach of this library, we will present also the discovery of novel small compounds that displays an original mechanism of action as they bind to the chemokine CXCL12, not to its receptor CXCR4 and neutralize its biological activity. These compounds have been termed “neutraligands” by analogy with neutralizing antibodies with potential therapeutic approach to treat inflammatory diseases, such as asthma.



References:

[1] B. R. Stockwell, *Nature* **2004**, *432*, 846-854. [2] W. P. Walters, J. Green, J. R. Weiss and M. A. Murcko, *J. Med. Chem.* **2011**, 54, 6405-6416. [3] F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.* **2009**, *52*, 6752-6756. [4] (a) P. Regenass, D. Bosc, S. Riche, P. Gizzi, M. Hibert, L. Karmazin, A. Ganesan, D. Bonnet, *J. Org. Chem.* **2017**, *82*, 3239-3244; (b) P. Regenass, S. Riche, F. Peron, D. Rognan, M. Hibert, N. Girard, D. Bonnet, *Org. Biomol. Chem.* **2016,** *14*, 8859-8863; (c) P. Regenass, J. F. Margathe, A. Mann, J. Suffert, M. Hibert, N. Girard and D. Bonnet, *Chem. Commun.* **2014**, *50*, 9657-9660.