Synthesis and Evaluation of Small Molecule Inhibitors ofInterleukin (IL)-15: Towards IL-15 vs IL-2 Selectivity

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Interleukin (IL)-15, is a pleiotropic cytokine structurally close to IL-2, both sharing the IL-2Rβand γc receptor (R) subunits. IL-15 plays important roles in innate and adaptative immunity, supporting the activation and proliferation of NK, NK-T, and $CD8^+$ T cells. [1,2]

In case of dysregulation, high levels of IL-15 have been detected, leading to abnormal immune responses and autoimmune or inflammatory diseases such as polyarthritis rheumatoid or psoriasis[3]. Hence, our goal is to synthesize small molecule inhibitors that bind specifically to IL-15 on the IL-2Rβ interface.

Our presentation will describe two new families of IL-15 inhibitors (Figure). Taking advantage of our previous work IL-15[4], extending modifications were done on our first series called IBI[5]. On a second time, we applied a similar docking-based virtual screening of compounds libraries on a refined pharmacophore-based on IL-15 specific residues identified on the binding site of IL-15 with IL- 2Rβ giving so our second family named IBIS. These series of compounds were evaluated for their capacity to inhibit the binding to IL-15 to its cognate receptor, as well as the down-stream signalingof IL-15-dependent cells and their proliferation.

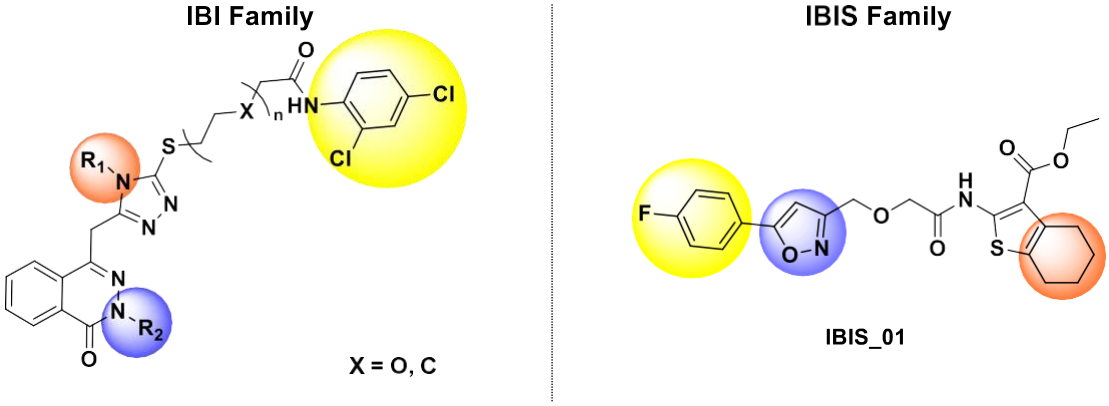

Figure: Structure-Activity Relationship Study. IBI Family: Modulations of *N*-triazole (orange), *N*-Phthalazinone (blue), Linker and Aromatic (yellow) moieties. IBIS Family: Modulations of Aromatic (yellow), Heterocyclic (blue) and Thiophene (orange) moieties.

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[5] J. Smadja & al, *Bioorg. Med. Chem.* **2021**, 39, 116161.