Development of an *in silico* tool for the prediction of new small molecules targeting cytokines

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Cytokines are a family of small proteins that act as chemical messengers between cells, playing an essential role in orchestrating and regulating the immune response. They can have pro-inflammatory or anti-inflammatory effects and bind to their specific target receptors. Due to their essential role in the immune system, an imbalance in their expression or regulation can lead to the pathophysiology of various inflammatory and autoimmune diseases, making them major therapeutic targets [1–3].

Biological agents such as monoclonal anti-cytokine antibodies are already commercially available for a minority of these proteins, but small molecules could represent a complementary asset [4]. Therefore, our objective is to develop an open access *in silico* tool for predicting new small molecules targeting cytokines.

The first step of this project is the construction of a database dedicated to cytokines structures and ligands. We set up a pipeline retrieving all the experimental and computational structures already available in the Protein Data Bank for each cytokine, linked to their UniProt code. These structures, in mmCIF files, were then parsed to extract the necessary data, which enabled us to build a relational database. The next step is the identification of the different receptors associated with each cytokine in order to predict these complexes, using deep learning tools. For these complexes, their structures were predicted, including all the domains of the cytokine receptors, using Boltz-2 [5]. These structural complexes will subsequently be used to identify potential binding sites for small molecules. Indeed, protein-protein interfaces will be of particular interest in the case of cytokines.

Bibliography:

[1] Meager, A. ; Wadhwa, M. Encyclopedia of Life Sciences (2013).

[2] Kany, S. ; Vollrath, J.T. ; Relja, B. Int. J. Mol. Sci. 20 (2019) 6008.

[3] Khaiboullina, S. Int. J. Mol. Sci. 27 (2026) 876.

[4] Raavi ; Koehler, A.N. ; Vegas, A.J. Chem. Rev. 125 (2025) 4528–4568.

[5] Passaro, S. et al. bioRxiv (2025).