Automated Multi-Target Docking Pipeline to Identify Fucosidic Ligands for Lectins

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Glycans are abundant and diverse natural products that coat the surface of every cell. The structural diversity of this “glycocalyx” encodes vast biological information that is deciphered by lectins, a specialized class of Glycan-Binding Proteins (GBPs). Interactions between the glycocalyx and lectins regulate critical immunopathological processes, including bacterial and viral infection, fibrosis, homeostasis and cancer proliferation [1].

Fucosylated glycans such as Lewis and ABO antigens, bearing a unit of L-6-deoxy-galactopyranose, are key players in these processes. For instance, the altered expression of these antigens is a hallmark of many carcinomas and correlates with patient prognosis. Furthermore, many pathogens exploit these glycoconjugates, using lectins with high affinity for fucose to bind human tissues [2].

Modulating or inhibiting these recognition events with glycomimetic ligands represents a promising yet challenging therapeutic strategy, primarily due to the limited druggability of lectins and poor pharmacokinetics of carbohydrate-based ligands.

In this context, and to better understand the structural requirements for receptor engagement, an automated multi-target docking workflow was implemented via the Schrödinger Suite Python API [3], ensuring efficiency, customization and reproducibility. This approach was used to assess the binding potential of a virtual, combinatorial library of synthetically accessible fucosides to multiple selected targets. Thorough analysis of the most promising docking poses, further refined through molecular dynamics (MD) simulations [4], enabled the identification of high-potential chemotypes and alternative binding modes not previously observed for several fucose-binding lectins. These findings provide a structural foundation for the rational design of new glycomimetics and offers candidates for subsequent experimental validation.

References

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