IN3-Structure: AI-Enhanced Ligand–Receptor Profiling for Drug Repurposing

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G-protein-coupled receptors (GPCRs) constitute one of the most important protein families in human biology, regulating key physiological processes, such as metabolism, immune responses, and neuronal signalling[1,2]. They are also among the most widely targeted proteins in pharmacology, with approximately 40% of FDA-approved drugs acting on GPCRs. However, their intrinsic structural flexibility and the limited number of experimentally resolved structures pose significant challenges for drug discovery and repurposing.[3-6] [5,6]

Recent advances in Artificial Intelligence (AI) have transformed structural biology[7,8]. Models such as AlphaFold2, and more recently AlphaFold3, enable high-accuracy prediction of protein structures and complexes, while emerging tools such as Boltz-2 allow for quantitative estimation of ligand–receptor affinity[9,10]. Leveraging these developments, we present IN3-STRUCTURE, an AI-driven computational pipeline that integrates structure prediction and affinity modelling to systematically explore GPCR–drug interactions.

Our approach combines AlphaFold3-based structural modelling with Boltz-2 affinity scoring to generate and evaluate GPCR–drug complexes in both active and inactive conformational states for all currently FDA-approved drugs and Class A GPCR families. As a paradigm, we focus on cardiovascular-relevant Class A GPCR families, including adrenergic, muscarinic, purinergic, sphingosine-1-phosphate, lysophosphatidic acid, prostanoid, dopamine, and cannabinoid receptors, providing a pharmacologically diverse testbed.

By integrating confidence metrics from both AI models into a unified scoring framework, we evaluated 61,851 receptor–drug pairs. The top-ranked interactions exclusively corresponded to clinically validated drug–target relationships, demonstrating high predictive precision and zero false positives within the top hits.

Overall, IN3-STRUCTURE highlights how AI can bridge 3D (structural biology) and 1D (multi-omics, translational biomarkers) data, empowering our IN3© engine (*in silico, in vitro, in/ex vivo*) by enabling scalable, data-driven drug repurposing.

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References

1. Yang, D., Zhou, Q., Labroska, V., Qin, S., Darbalaei, S., Wu, Y., Yuliantie, E., Xie, L., Tao, H., Cheng, J., Liu, Q., Zhao, S., Shui, W., Jiang, Y., & Wang, M.-W. (2021). G protein-coupled receptors: Structure- and function-based drug discovery. *Signal Transduction and Targeted Therapy*, *6*(1), 7. https://doi.org/10.1038/s41392-020-00435-w
2. Conflitti, P., Lyman, E., Sansom, M. S. P., Hildebrand, P. W., Gutiérrez-de-Terán, H., Carloni, P., Ansell, T. B., Yuan, S., Barth, P., Robinson, A. S., Tate, C. G., Gloriam, D., Grzesiek, S., Eddy, M. T., Prosser, S., & Limongelli, V. (2025). Functional dynamics of G protein-coupled receptors reveal new routes for drug discovery. *Nature Reviews Drug Discovery*, *24*(4), 251–275. https://doi.org/10.1038/s41573-024-01083-3
3. Zhang, M., Chen, T., Lu, X., Lan, X., Chen, Z., & Lu, S. (2024). G protein-coupled receptors (GPCRs): Advances in structures, mechanisms and drug discovery. *Signal Transduction and Targeted Therapy*, *9*(1), 88. https://doi.org/10.1038/s41392-024-01803-6
4. Hilger, D., Masureel, M., & Kobilka, B. K. (2018). Structure and dynamics of GPCR signaling complexes. *Nature Structural & Molecular Biology*, *25*(1), 4–12. https://doi.org/10.1038/s41594-017-0011-7
5. Congreve, M., De Graaf, C., Swain, N. A., & Tate, C. G. (2020). Impact of GPCR Structures on Drug Discovery. *Cell*, *181*(1), 81–91. https://doi.org/10.1016/j.cell.2020.03.003
6. Addis, P., Bali, U., Baron, F., Campbell, A., Harborne, S., Jagger, L., Milne, G., Pearce, M., Rosethorne, E. M., Satchell, R., Swift, D., Young, B., & Unitt, J. F. (2024). Key aspects of modern GPCR drug discovery. *SLAS Discovery*, *29*(1), 1–22. https://doi.org/10.1016/j.slasd.2023.08.007
7. Zheng, Y., Koh, H. Y., Ju, J., Yang, M., May, L. T., Webb, G. I., Li, L., Pan, S., & Church, G. (2025). Large language models for drug discovery and development. *Patterns*, *6*(10), 101346. https://doi.org/10.1016/j.patter.2025.101346
8. Jumper, J., Evans, R., Pritzel, A., Green, T., Figurnov, M., Ronneberger, O., Tunyasuvunakool, K., Bates, R., Žídek, A., Potapenko, A., Bridgland, A., Meyer, C., Kohl, S. A. A., Ballard, A. J., Cowie, A., Romera-Paredes, B., Nikolov, S., Jain, R., Adler, J., … Hassabis, D. (2021). Highly accurate protein structure prediction with AlphaFold. *Nature*, *596*(7873), 583–589. https://doi.org/10.1038/s41586-021-03819-2
9. Abramson, J., Adler, J., Dunger, J., Evans, R., Green, T., Pritzel, A., Ronneberger, O., Willmore, L., Ballard, A. J., Bambrick, J., Bodenstein, S. W., Evans, D. A., Hung, C.-C., O'Neill, M., Reiman, D., Tunyasuvunakool, K., Wu, Z., Žemgulytė, A., Arvaniti, E., … Jumper, J. M. (2024). Accurate structure prediction of biomolecular interactions with AlphaFold 3. *Nature*, *630*(8016), 493–500. https://doi.org/10.1038/s41586-024-07487-w
10. Passaro, S., Corso, G., Wohlwend, J., Reveiz, M., Thaler, S., Somnath, V. R., Getz, N., Portnoi, T., Roy, J., Stark, H., Kwabi-Addo, D., Beaini, D., Jaakkola, T., & Barzilay, R. (2025). *Boltz-2: Towards Accurate and Efficient Binding Affinity Prediction*. Molecular Biology. https://doi.org/10.1101/2025.06.14.659707