

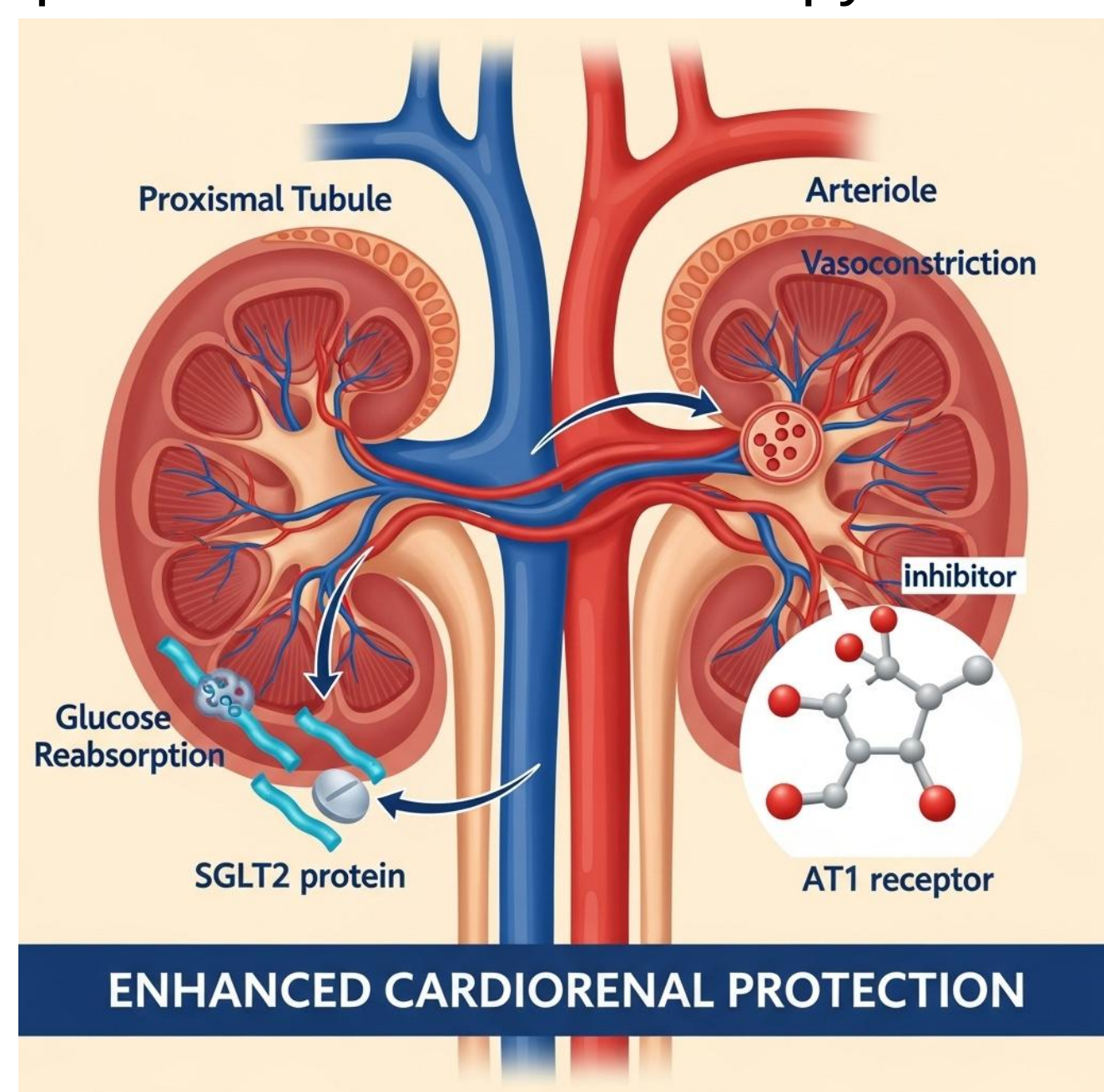
Structural design of hybrid molecules that exhibit dual inhibition of SGLT2 and AT1 for cardiorenal protection: a computational and medicinal chemistry strategy.

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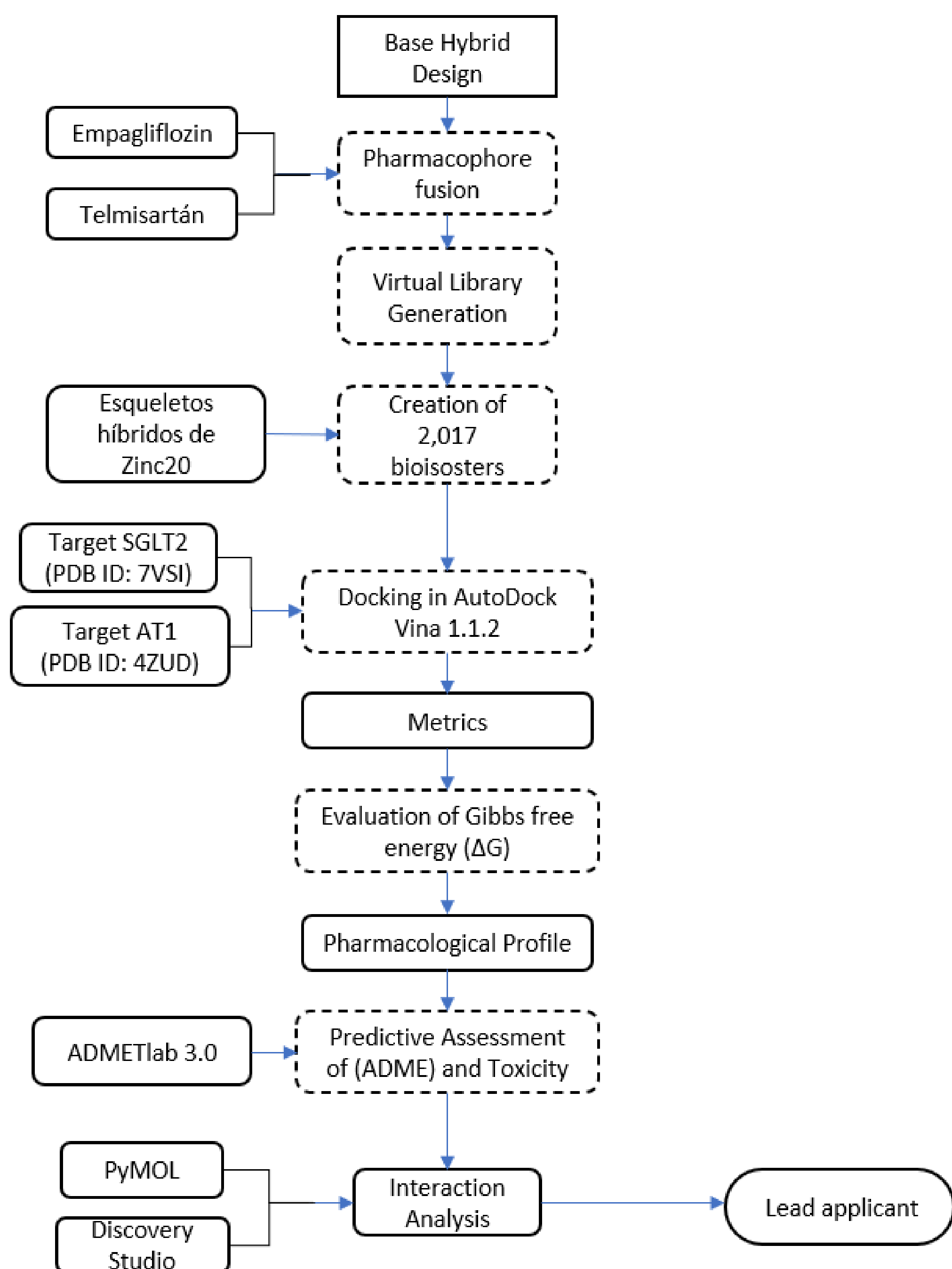
INTRODUCTION & AIM

AIM: Identify and computationally validate a dual ligand candidate with high affinity for both receptors (SGLT2 and AT1) and a favorable pharmacokinetic and safety profile for future optimized cardiorenal therapy.



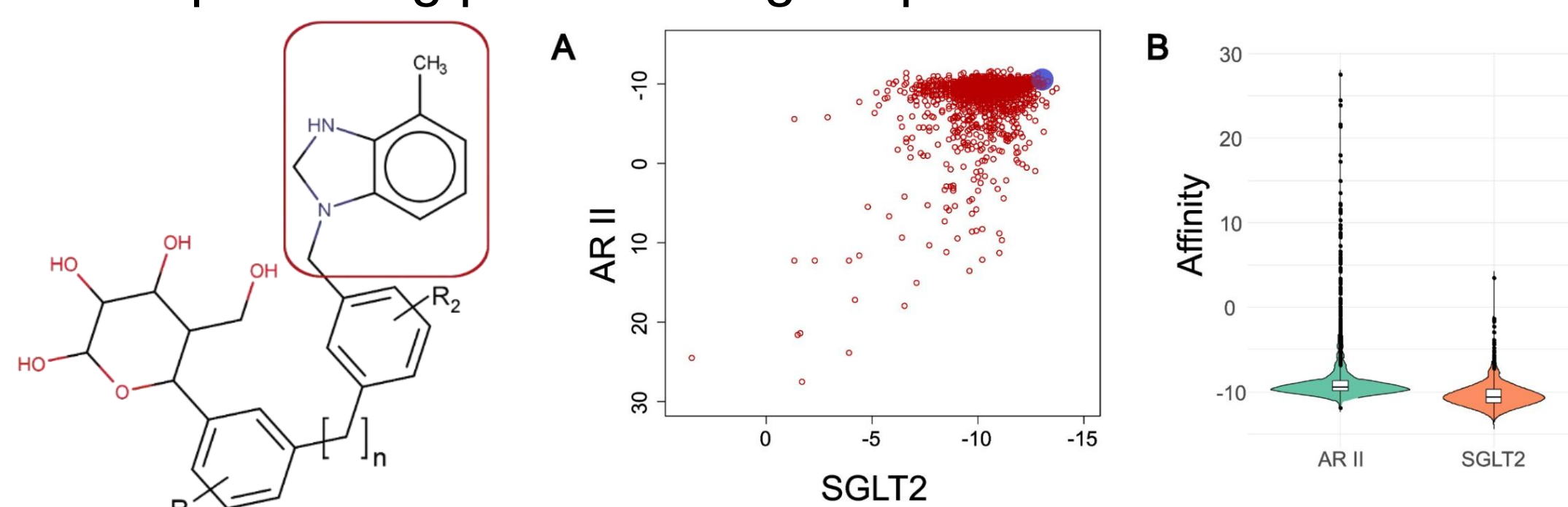
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METHOD



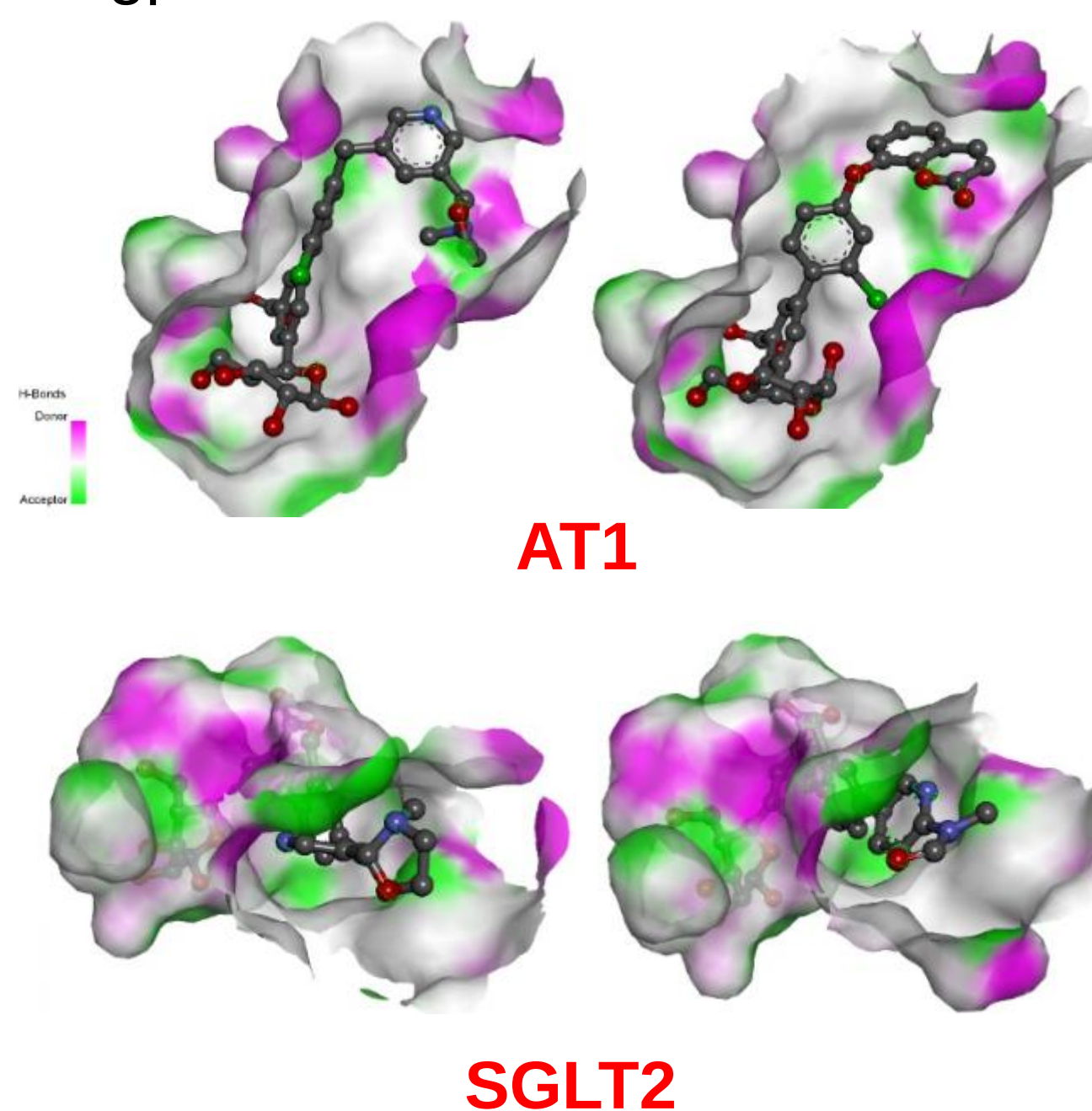
RESULTS & DISCUSSION

Virtual screening and profile analysis identified two lead candidates with exceptional potential for dual inhibition and a promising pharmacological profile.



The lead candidate demonstrates optimal, balanced, high-affinity dual inhibition toward both SGLT2 and AT1 receptors, confirmed as the superior performer in the library's upper distribution end (ΔG).

In silico ADME profiling predicts an excellent pharmacokinetic profile marked by high oral absorption (Caco-2/HIA), low risk of drug-drug interactions (DDI) due to non-significant CYP450 inhibition, and favorable non-P-gp distribution.



Molecular coupling validates the dual mechanism: SGLT2 binding is anchored by hydrogen bonds (PDB: 7VSI), and AT1 antagonism is confirmed by π - π stacking/salt bridges (PDB: 4ZUD), mimicking clinical ARA IIs.

CONCLUSION

Virtual screening and profile analysis identified two lead candidates with exceptional potential for dual inhibition and a promising pharmacological profile.

FUTURE WORK / REFERENCES

- Chemical Synthesis
- Preclinical *in vitro* Evaluation

References:

- Nuffield Department of Population Health Renal Studies Group, SGLT2 inhibitor Meta-Analysis Cardio-Renal Trialists' Consortium. Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. *Lancet* [Internet]. 2022;400(10365):1788–801. Available at : [http://dx.doi.org/10.1016/S0140-6736\(22\)02074-8](http://dx.doi.org/10.1016/S0140-6736(22)02074-8)