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Therapeutic Potential of 1-Deazapurines as Alpha-Glucosidase Inhibitors: Molecular Docking and Pharmacokinetic Evaluation

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INTRODUCTION & AIM

Type 2 diabetes mellitus (T2DM) is the predominant form of diabetes, characterised by chronic hyperglycaemia that predisposes patients to cardiovascular disease, renal dysfunction, neuropathy, and retinopathy.

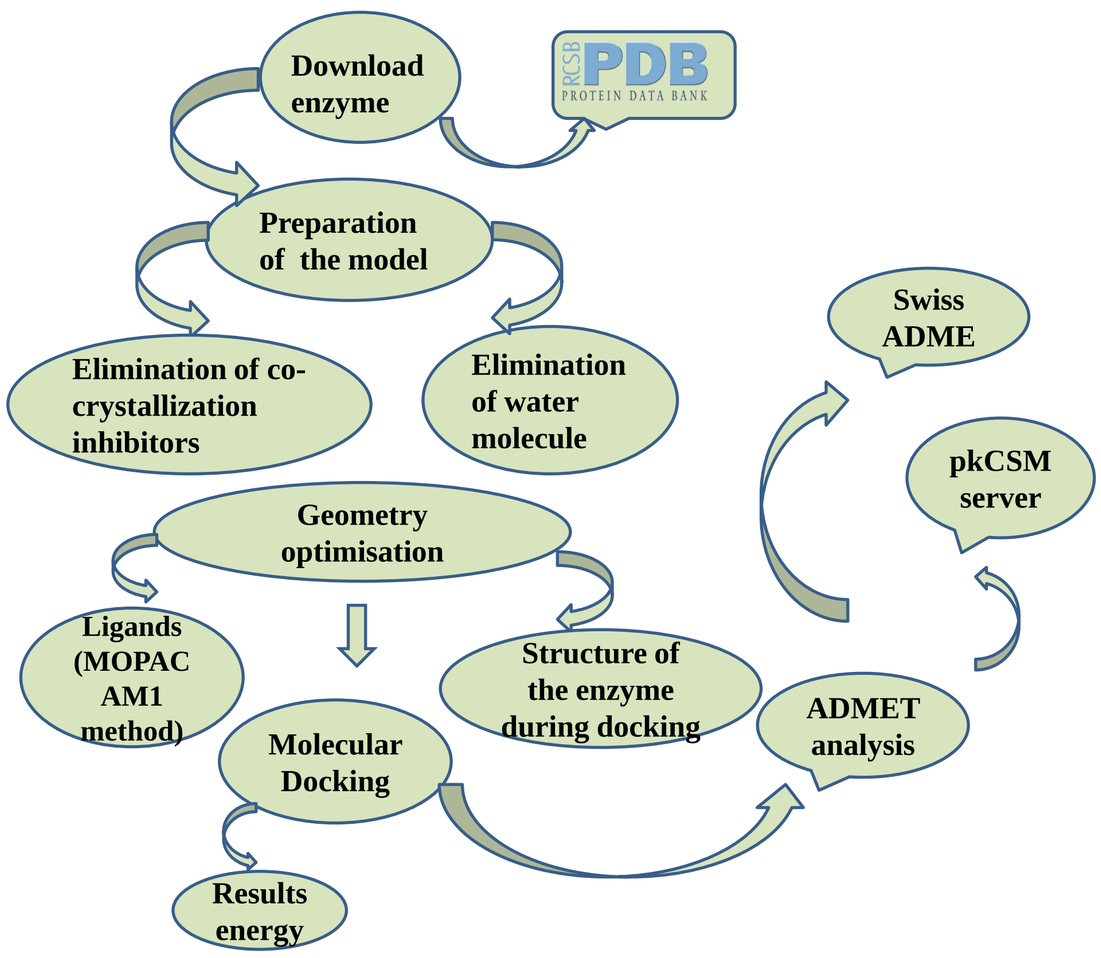
Among therapeutic strategies, alpha-glucosidase inhibitors (AGIs) are widely used to slow carbohydrate hydrolysis in the gastrointestinal tract, thereby moderating glucose absorption and postprandial glycaemia [1].

We aim to identify among the fifteen derivatives of 1-deazapurines the best complexs with strong binding affinity, assess stability within the enzyme active site, and predict pharmacokinetic suitability compared with existing therapeutic options. Computational techniques—molecular docking, molecular dynamics, and ADMET analyses—were employed

METHOD

Protein and ligand preparation : The crystal structure of alpha-glucosidase (PDB ID: 3L4Y; resolution 1.80 Å) was retrieved from the Protein Data Bank.

Fifteen derivatives of 1-deazapurines (compex 1to15) were designed and sketched using MOE 2014 software [2].



RESULTS & DISCUSSION

(A)3L4Y_L14 (Best complex)

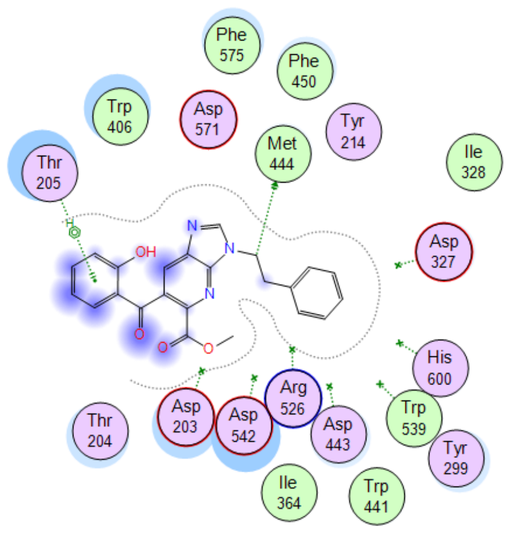


Table: **Score energy of differents complexs**

Code ligand	Score (kcal/mol)
Complex 2	-3.6741
Complex L8	-4.2295
Complex L12	-4.4261
Complex L1	-4.5406
Complex L5	-4.7096
Complex L6	-4.727
Complex L3	-4.9204
Complex L7	-4.9733
Complex L15	-5.3025
Complex L13	-5.3677
Complex L9	-5.4446
Complex L10	-5.4800
Complex L4	-5.5403
Complex L11	-5.703
Complex L14	-6.1247
Acarbose	-5.6234

✓ ADMET data reinforce the view that a subset of compounds, notably L14 and L11, combine high enzyme affinity with favourable pharmacokinetic behaviour.

Molecular dynamics simulations

The Molecular dynamics (MD) simulations were conducted on the three top-ranked ligands over a 100-ns timescale.

✓ Root mean square deviation (RMSD) trajectories revealed that L14 and L11 complex displayed a stable trajectory, in contrast to L4, which showed more significant fluctuations.

✓ Hydrogen-bond analysis showed L14 was maintaining a consistent number of bonds (0–1), while L11 exhibited a slightly higher range (0–2).

✓ The radius of gyration (Rg) and solvent-accessible surface area (SASA) values indicated that the ligands did not induce significant structural changes in the protein.

✓ The L11 complex demonstrated the lowest SASA value, suggesting a more compact and less solvent-exposed structure compared to L14 and L4.

✓ The MD data validate the docking predictions and reinforce the position of both L14 and L11 as the most promising lead candidates [5].

Pharmacokinetic predictions and ADMET profile

✓L14 and L11 adhered to both Lipinski and Veber's rules, suggesting their suitability for oral bioavailability.

✓The BOILED-Egg model positioned L14 and L4 in the "white region", reflecting good human intestinal absorption and a limited risk of blood-brain barrier penetration an advantageous property for antidiabetic agents, as central side effects are undesirable [3].

✓Toxicity analysis further indicated low hepatotoxicity and mutagenic risks for L14 and L11, in contrast to some derivatives bearing bulky aromatic substituents [4].

CONCLUSION

The computational evaluation of 1-deazapurine derivatives against α-glucosidase revealed that a subset of compounds, particularly L14 and L11, exhibit strong binding affinities, stable ligand–enzyme interactions, and favourable pharmacokinetic predictions. Molecular dynamics confirmed the persistence of key hydrogen bonds, while ADMET analyses highlighted their suitability for oral administration with limited toxicity risks. These outcomes suggest that selected deazapurines represent promising scaffolds for the design of novel α-glucosidase inhibitors with potential applications in type 2 diabetes management. Nonetheless, experimental validation remains essential to confirm efficacy and safety, and future optimisation may enhance potency and broaden therapeutic relevance.

FUTURE WORK / REFERENCES

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