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Computational investigations of D-glucofuranose-based derivatives: DFT, MEP, NBO, ADMET, PASS, and molecular docking toward antidiabetic targets

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Abstract. A chronic metabolic disease characterized by persistently elevated blood sugar levels, diabetes mellitus is typically caused by inadequate insulin synthesis or function. Because natural monosaccharides and carbohydrates such as D-glucofuranose share structural similarities, they present a promising foundation for the development of antidiabetic drugs. 3-*O*-Acyl derivatives were produced by the unimolar one-step acylation of D-glucopyranose. Computational methods were used to investigate the potential antidiabetic effects of D-glucofuranose (**1**) and its derivatives (**2-9**). The frontier molecular orbital (FMO) characterizes reactivity by analyzing the energy difference between the HOMO (highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) orbitals, whereas the electrostatic potential map (MEP) shows the charge distribution of a molecule, highlighting regions prone to electrophilic and nucleophilic interactions, and global reactivity indicators such as hardness, softness, and electrophilicity characterize a molecule's overall reactivity, which is the outcome of density functional theory (DFT) calculations to optimize the molecule's stable geometric configuration. To estimate the binding affinities and interaction patterns, molecular docking experiments were conducted with human glucokinase (PDB IDs: 3IMX and 1V4S). Compound **7** exhibited the highest binding affinities (-9.0 and -8.2 kcal/mol) and formed persistent interactions with the TRP99, HIS218, VAL62 and IEL211 residues in the glucokinase active site. ADMET estimates were used to evaluate drug similarity, pharmacokinetics and toxicity profiles. *In silico* tests *via* PASS prediction against bacteria and fungi revealed that the compounds containing D-glucofuranose derivatives had outstanding antibacterial and antifungal effectiveness. Overall, these results show that D-glucofuranose derivatives have the potential to be lead molecules for glucokinase regulation and offer a logical framework for further validation *in vitro* and *in vivo*.

***Keywords*:** D-glucofuranose; FMO; MEP; pharmacokinetics; human glucokinase; molecular docking; ADMET.

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