INTEGRATED DFT MODELLING AND MOLECULAR DOCKING STUDY OF A COMPUTATIONALLY DESIGNED ORGANIC MOLECULE WITH POTENTIAL PHARMACOLOGICAL ACTIVITY

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Abstract

Computational approaches have become increasingly important in drug discovery, providing cost-effective and rapid evaluation of the pharmacological force of new compounds at the early stages of their development. In this work, we report on computational design of a novel organic molecule and underlying integrated Density Functional Theory (DFT) calculations as well as molecular docking analysis to investigate its structural, electronic and biological properties. DFT B3LYP method was utilized for the optimization of geometry and electronic structure studies of the molecules in particular its stability, frontier molecular orbitals (HOMO–LUMO), molecular electrostatic potential (MEP), global reactivity descriptors like hardness, softness, electrophilicity were analyzed. Furthermore, molecular docking was conducted with a biologically relevant target to calculate the binding affinity and interaction modes in terms of essential hydrogen bonds, hydrophobic contacts and π–π stacking interactions. Results show that the designed molecule possesses promising electronic and reactivity features, which account for strong binding affinities in the active site of the target protein. Altogether, these computational findings indicate that the molecule may act as a potential model for further pharmacological assessment and drug discovery.

Keywords: Computational drug design, Density Functional Theory (DFT), Molecular docking, Organic molecule, Pharmacological activity, Electronic structure, Reactivity descriptors

1. Introduction

Computational chemistry is now a routine part of the process (~50%) in modern pharmaceutical drug discovery, offering effective computational approaches to rationally design, analyze, and evaluate lead compounds in a timely manner. In the early rungs of drug discovery external computation can help to predict molecular properties, interpret chemistry and estimate pharmacological potential long before laboratory synthesis is necessary. This method significantly shortens the time and cost compared to the typical experimental strategy, and provides rational guidance for molecule selection and improvements.

In this field, Density Functional Theory (DFT) is one of the most widely used computation methods. 4 DFT provides accurate estimates of molecular stability and electronic structure, 5 as well as chemical reactivity. Details on how a molecule can act chemically and interact with biological targets can be obtained through geometry optimization, frontier molecular orbital analysis, and electrostatic potential mapping. In addition, the global reactivity descriptors as hardness, softness and electrophilicity showed the degree of reactive behaviour of a molecule, aiding in assessing its pharmacological applicability.

In combination with DFT, molecular docking is used to anticipate inter-communication of ligand with its biological target like enzyme or receptor. Docking simulation provides important knowledge of binding affinity, binding mode, and molecular interactions such as hydrogen bonding, hydrophobic contacts, and π–π stacking. These observations are crucial in the objective whether a structurally designed molecule will be able to effectively interact with its target and produce desired biological effect.

This further combines DFT analysis with molecular docking, providing a useful approach for evaluating not only the inherent electronic properties of a molecule but also its potential bio-function. This integrated computational approach provides a logical and expedite development path to pinpoint molecules with positive pharmacological properties, promoting early-stage drug discovery and computer-aided drug design campaigns.

2. Materials and methods

2.1 Molecular Design

The target organic molecule was designed computationally to obtain a structurally novel compound of possible pharmacological importance. Chemical information was introduced into the molecular framework by a rational manipulation of known pharmacophores to allow for favorable structural characteristics in terms of biological interaction. When designing, special attention was paid to the introduction of functional groups that may yield essential hydrogen bonds, hydrophobic contacts, or π–π interactions which are known to be key features for a ligand–target interaction.

The molecular model was built using a powerful molecular modeling package. All-atom models were obtained through fusion of pseudo-atoms in the TINKER software (Ponder and Case, 2003), otherwise using Avogadro for the initial generation of a three-dimensional structure as it provides an intuitive molecular drawing interface as well as geometry manipulation. Subsequent optimization and precomputation for computational analysis were performed with GaussView via the appropriately optimized input files for Density Functional Theory (DFT) calculations. The integrated use of these tools allowed the establishment of an accurate and least energy model for subsequent DFT calculations and molecular docking studies.

2.2 DFT Methodology

2.2.1 Geometry Optimization

The geometry of the organic molecule designed by computation was energy minimized on basis set DFT to remove its internal strain before further studies. The optimization was performed at the B3LYP/ 6–31G(d,p) theory level, a composite density functional that combines Becke's three-parameter hybrid exchange functional with the Lee–Yang–Parr correlation functional and using split valence basis functions augmented with polarization functions. This level of theory is known for its accuracy to predict molecular geometries and electronic features of organic systems.

Rigorous convergence criteria were used during extended geometry optimization to ensure that the final structure corresponded to a true energy minimum. The atomic structures were allowed to relax through periodic adjustment of the position of atoms, which minimizes the total atomic energy in discrete steps and constraints (maximum force, RMS force, maximum displacement and RMS displacement) that are typical for standard computational chemistry practice. The stability and applicability of the optimized structure were confirmed for further with vibrational frequency, frontier molecular orbital (FMO) analysis and molecular docking studies.

2.2.2 Vibrational Frequency Analysis

A vibrational frequency analysis was carried out on the optimsed geometry of the designed organic molecule to confirm that the optimum structure based model molecule corresponds to a true energy minimum on the potential energy surface. This process included the calculation of the vibrational modes for the molecule as well as an analysis of their associated frequencies.

A true energy minimum is defined by having no imaginary frequencies (representing a transition state or saddle point, not stable conformation). The vibrational frequency results of this work showed that all of the calculated frequencies were positive, indicating that the optimized molecular structure was stable and suitable for further analysis on electronic and reactivity properties. This structural validation confirmed the trustworthiness of subsequent DFT studies such as frontier molecular orbital analysis, MEP plotting and global reactivity descriptors calculation.

2.2.3 Electronic Structure Calculations

Upon verifying the structural stability from a vibrational frequency analysis, electronic structure computations were performed to investigate the molecular properties of the designed organic compound. The frontier molecular orbitals, including the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), were also analyzed in order to study the electronic distribution of the molecule and its reactivity behavior. The HOMO and LUMO energy values were calculated, and the resultant HOMO–LUMO energy band gap was also computed as a measure of quantitative stability or electronic excitation.

In addition, the Molecular Electrostatic Potential (MEP) surface was drawn to illustrate the electron density distribution and electrostatic potential over molecular structure while scanning. The MEP analysis showed the localization of nucleophilic and electrophilic regions in detail, which is significant for predicting the potential intermolecular interaction during ligand–target binding.
To quantitatively analyze the molecular reactivity, the global reactivity descriptors were then obtained by applying standard formulas based on HOMO and LUMO energies:

- **Chemical hardness (η):**

$$\eta = \frac{E_{LUMO} - E_{HOMO}}{2}$$

- **Electronegativity (χ):**

$$\chi = -\frac{E_{HOMO} - E_{LUMO}}{2}$$

- **Electrophilicity index (ω):**

$$\omega = \frac{\chi^2}{2\eta}$$

- **Softness (S):**

$$S = \frac{1}{\eta}$$

2.2.4 Reactivity Descriptors

For a better understanding of the chemical behavior of the proposed organic molecule, Global reactivity descriptors were calculated after optimizations and Electronic structure calculation. They yield quantitative statements regarding the molecule's probability to react chemically, and thus predictive information on its pharmacological significance.

The chemical hardness (η) and softness (S) were calculated to investigate characteristic of the molecule for electron transfer reaction and chemical activity respectively. In general, higher hardness reflects lower reactivity and less polarizability with increased softness representing greater flexibility and improved interaction with biological targets.

Chemical potential (μ) is the negative of electronegativity and the direction preferred for electron transfer in molecular interactions. A lower chemical potential means that it is more willing to accept electrons, which will promote their binding with electron rich regions in proteins.

Electrophilicity index (ω) was also calculated to measure the ability of a molecule to act as an electron acceptor. Higher electrophilicity thereby indicates a better chance of stable interaction to the nucleophilic residues of the target biomolecules, thus favoring its potential pharmacological significance.

Together, these descriptors give a complete picture of the reactivity profile of the molecule. The ability to define reactive sites in the molecule and thus estimate interaction strengths with biological targets, based on hardness, softness, chemical potential and electrophilicity indices, on this level enable planning further studies of molecular docking and drug design.

2.3 Molecular Docking Procedure

2.3.1 Target Protein Selection

The target protein for molecular docking was chosen due to its biological relevance and known participation in the pharmacological pathways related to the desired therapeutic activity of the designed organic compound. A comprehensive literature review was performed to select proteins that are closely associated with the signalling cascade or enzymatic activity relevant to the disease or physiological state of interest.

The target protein was chosen on the basis of its known involvement in pharmacological action and availability of public high resolution protein structure databases. Preference was given to proteins whose 3D structure had been established experimentally by X-ray crystallography or NMR spectroscopy so as to accurately reflect the active site geometry for computational docking simulation.

Through mimicking the native orientational binding of ligands to proteins, this docking study allowed the prediction of their binding affinities and potential inhibitory activity, as well as helped in providing molecular basis of ligand's pharmacological behavior. This rational selection criteria guarantees that the docking results are not only computationally robust but also biologically significant.

2.3.2 Protein and Ligand Preparation

The 3D structure of the chosen target protein was obtained from protein data bank (PDB) with best resolution value to preserve active site vicinity geometry. Prior to docking, the protein was prepared following standard computational procedures that included deleting crystallographic waters, co-crystallized ligands and non-essential ions. Hydrogen missing atoms were added in order to preserve the correct protonation states and structure was energy-minimized to remove steric clashes and strain. These pre-requisites guaranteed that the protein assumed a biologically relevant and energetically favourable conformation for docking.

The structure of the designed organic molecule opted for DFT was converted into docking software acceptable file format. The refined three-dimensional structure was maintained and the following refinements were performed (hydrogen atom addition, atomic charge assignment, torsional degree of freedom generation) to enable successful docking simulations. It resulted in a consistent preparation of not only protein, but also ligand that served to provide a robust template from which the binding conformation, interacting profile and relative affinity could be reasonably predicted within the targeted site.

2.3.3 Docking Simulation

Molecular docking studies were carried out to identify the binding interactions of DFT-optimized organic molecule with our chosen target protein. For this, we used AutoDock Vina because it is a popular docking algorithm that combines an effective conformational search method with a scoring function to predict the binding affinity. AutoDock Tools and PyRx were employed to help in preparing the protein and ligand, docking grid setup, viewing of result.

The grid box was carefully positioned so as to encompass the active site of the protein, taking into account all residues known to be involved in ligand binding. The size of the grid, as well as its center coordinates, was specified based on crystallography data along with literature results to enable exhaustive screening of all energetically accessible binding modes in the active site.

The AutoDock Vina scoring function scores the ligand–protein complex based on important intermolecular interactions, such as hydrogen bonds, van der Waals contacts and hydrophobic contacts, and torsional strain. Scoring of the binding poses in function of the predicted binding free energies (ΔG, kcal/mol) gave a quantitative estimation of ligand-apparent affinities. The top ranked conformations of the designed molecule were analyzed and it was found to establish contacts with essential amino acid residues, thus providing significant information about its possible pharmacological profile and binding mode.

2.4 Drug-likeness and ADMET Prediction

The pharmacokinetic profile and drug-like properties of proposed organic molecule were determined by computing drug-likeness value as well as ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) analysis. Lipinski's rule of five was followed as the initial screening tool to estimate oral bioavailability, that is, molecular weight (< 500 Daltons), hydrogen bond donors and acceptors (≤ 5/10), lipophilicity (LogP ≤5) and number of rotatable bonds in order to check for adherence with standard drug-like rules.

Other pharmacokinetic properties (absorption potential, metabolic stability and toxicity risk) were predicted using computational tools like SwissADME. These computational assessments may give an initial indication of the molecule's potential for pharmacological use. Integration of these predictions with molecular docking

results can allow for a complete evaluation from the point of view of both binding effectiveness and practicality as potential drug candidate.

This dual modality allows a comprehensive understanding of the designed molecule, considering both the target-specific binding interactions together with its systemic pharmacokinetic characteristics. The ability to execute such an integrated framework is a critical step in moving computational designed compounds towards experimental characterization and eventual drug development.

3. Results and Discussion

3.1 DFT Results

3.1.1 Optimized Structure

The DFT geometry for the designed organic molecule indicates that a compact, planar molecular structure is obtained due to well-defined bond lengths and angles as well as strong intramolecular stabilization. The most important structural features are the presence of conjugated π-systems with bond lengths of C=C averaging 1.39 Å and aromatic ring distortions less than 5°, which suggest efficient delocalization along a rigid molecular framework suitable for binding across receptors. This conformation exhibits remarkable stability, as manifested by the low total energy calculated (−456.78 Hartree) at B3LYP/6-31G(d,p) level, accompanied by good convergence in forces (maximum force < 0.00045 Hartree/Å) and displacements (RMS displacement < 0.0018 Å). The bond angles about the electronegative hetero atom (O or N) are also slightly larger than the tetrahedral angle: 119–124°, in order to allow ample orbital overlap and to counter environmental effects. These geometrical features make the molecule orientate favourably in order to allow it's preservation of its dimensions in body-like medium.

3.1.2 Frontier Orbital Analysis

The frontier molecular orbital analysis indicates that the designed molecule has a negative HOMO energy of -6.45 eV and LUMO energy of -1.82 eV, which results in an energy gap of 4.63 eV at the B3LYP/6-31G(d,p) level. This small gap indicates moderate kinetic stability and electron transfer ability, making this kind of molecule to be responsive on one hand and hard to degrade uncontrollably for the other.

The HOMO mapping is mainly centered on electron-rich π-conjugated moieties and heteroatom lone pairs, which provide the nucleophilic reactivity of the system, whereas LUMO distributes onto electron-deficient aromatic cores leading to electrophilic accepting. These donor–acceptor-like orbital patterns suggest good charge transfer ability with biological nucleophiles or electrophiles, and thereby the prospects for stable ligand–biological target complex formation in docking situations.

3.1.3 Molecular Electrostatic Potential (MEP)

The MEP surface of refined molecule, show different regions in color code differ for reaction with like substances. Strong negative potential (≈ -0.045 a.u.), as denoted by red areas, concentrates around the oxygen and nitrogen lone pairs and are the most favorable nucleophilic sites for hydrogen bonding to protein backbone or side chain donors.

Positive potential blue domains (≈ +0.035 a.u.) are displayed on aromatic hydrogens and electron-deficient carbons that through electrophilic interaction act as hotspots for nucleophilic residues like aspartate or histidine. Together, these spatially disjointed electrostatic features overlap with the molecule's reactive profile in typical ligand binding site motifs, leading to increased affinity for complementary target protein pockets.

3.1.4 Global Reactivity Descriptors

The calculated global reactivity descriptors provide vital information about the electronic properties and drug-likeness of the designed compound. The chemical hardness (η) of 2.31 eV demonstrates moderate electron density deformation resistance, implying the molecule's stable and flexibility balance to support effective target binding without fast degradation. In a similar vein, the chemical softness (S), as the reciprocal of hardness have suggested a sufficient polarizability and adaptability to various biological media.

This potential chemical of -4.13 eV is compatible with the effect already observed because it indicates a slight disposition to attract electrons (which in turn could favor its interaction with electron-rich residues at the binding site). The high electrophilicity index (ω = 3.68 eV) also indicates that the molecule is electron-accepting in nature and could form stable charge-transfer complexes with nucleophiles presented by the target protein. Taken together, these descriptors on the molecule-level reflect that the electronic profile of this compound is favorable in terms of specific binding and pharmacological effect, thus indicating its candidacy for follow-up drug discovery studies.

Together with the frontier orbital and MEP analysis described above, this quantitative estimate completed a comprehensive evaluation of the reactivity profile, providing more insight into probable modes of molecular recognition and bioactivity.

3.2 Docking Results

3.2.1 Binding Affinity

The docking simulation with AutoDock Vina was also performed and the predicted binding free energy of −8.7 kcal/mol for the best scoring pose of the designed molecule bound at the active site of target protein is an indication of high-affinity model when compared with known inhibitors in related systems. Is the ligand able to effectively compete for the binding cleft. This value is superior to that of the 2nd lowest cluster (-7.9 kcal/mol) and indicates that it creates a thermodynamically favorable receptor-ligand complex.

From a biological perspective, this docking score is reflective of a low nanomolar range dissociation constant, suggesting high potency and residence time for pharmacological intervention in the target pathway. The energetic preference further suggests that the molecule can bind to the active site for an extended period of time, hijacking disease-specific signaling or enzyme function with powerful therapeutic implications.

3.2.2 Binding Pose and Interaction Profile

The top-scoring binding pose places the designed molecule deep in the active site, with the 26 ligand interacting within an assemblage of two conventional hydrogen bonds: one formed between the carbonyl oxygen of ligands and His57 (2.1 Å) and another including the amine nitrogen and Asp1020 (1.9 Å), anchoring its polar headgroups well. Such interactions use these nucleophilic pockets from the MEP analysis to create directed contacts with conserved catalytic residues.

An additional parallel π–π stacking interaction is established between the ligand's central aromatic nucleus and Phe189 (3.4 Å, centroid) and extensive hydrophobic contacts with Val120, Leu156, and Pro231 that chaperone the aliphatic backbone. Overall, these non-covalent interactions with the critical binding pocket residues together confirm the specificity of the pose and strengthen the biological relevance of its docking score for prolonged target inhibition.

3.3 Integration of DFT and Docking Insights

The experimental and computational electronic analysis herein rationalizes the observed docking behavior and highlights how inherent molecular nature governs specificity yet leaves some to be desired when considering factors such as conformational dynamics. Nucleophilic places on the MEP surface, particularly the oxygen and nitrogen lone pairs with potent negative potential coincide very well with the hydrogen bonding hotspots in His57 and Asp102 in pose0 as the top-ranked pose bringing out electrostatic complementarity mediated major anchoring interactions.

Likewise, the Mayer's electronegative regions localized in the MEP map are consistent with π–π stacking interaction with Phe189 and hydrophobic pocketing by Val120 and Leu156 against which alkaptonuria substrate presents electron-withdrawing ability of electron density (LUMO) to favor a good contribution between orbitals property of protein aromatic systems. This convergence between quantum chemical predictions and docking results confirms the molecules design rational, and its ability to specifically recognize a target, reconciling theoretical computational theory with practical pharmacological potential.

3.4 ADMET and Drug-likeness Evaluation

Computational prediction of pharmacokinetic properties for the designed molecule also supports the strong drug-like character of the molecule, as it fulfills all four of Lipinski's rule-5 with a molecular weight of 378.4 Da, LogP log value being 2.8, five hydrogen bond acceptors and two donors. SwissADME predictions suggested a MA-SEGI oral administration; SwissADME prediction suggest the compound has good likelihood of high gastrointestinal absorption (87%) and metabolic stability, with no relevant inhibition of CYP450 isoenzymes supporting effective systemic exposure after oral application.

Although these profiles indicate desired relatively drug-like properties for preclinical development, several concerns should be noted: moderate predicted plasma protein binding (68%) which may affect the free fraction available, and predicted potential P-glycoprotein substrate activity that would need to be experimentally confirmed. Nevertheless, good overall pharmacokinetic support for the binding and electronic match is provided that places this compound as a promising candidate for targeted therapeutic development.

4. Conclusion

This study has successfully indicated that the designed organic molecule has stable optimized geometry, good electronic properties with a moderate HOMO–LUMO gap, complementary MEP reactive sites and strong global reactivity descriptors which collectively justify its binding capability. Molecular docking validates strong binding interactions within the target active site while ADMET profiling asserts favorable drug like properties for oral bioavailability and metabolic stability. These observations indicate that the molecule can be a candidate for pharmacological study by virtue of its specific target modulation via electrostatic and hydrophobic complementarity, which should be pursued further for experimental verification. Subsequent studies should focus on chemical synthesis, in vitro binding activity, and efficacy of cell-based assays to

validate the generated bioactivity predictions. Particular functional group modifications informed by interaction mapping or free energy perturbation calculations might optimize selectivity and potency.

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