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Theoretical Investigation of Some Substituted N-Phenylacetamides as Potential Inhibitors of the Biotin Carboxylase Enzyme: Thermodynamic Functions, Global Reactivity Descriptors and Molecular Docking Assessment

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Abstract: In the current work, the amine derivatives were evaluated with two computational programs with a total of six compounds. The former was Gaussian, which allowed the calculation of thermodynamic functions (ΔG , ΔH , and ΔS), chemical hardness (η), chemical potential (μ) and global electrophilicity index (ω). AutoDock Vina was the second program used, which was employed in molecular docking studies. Biotin Carboxylase (BC) (PDB ID: 3JZF), was chosen as the target protein. BC is a crucial part of the acetyl-CoA carboxylase (ACC) complex, which plays a vital role in bacterial fatty acid biosynthesis, by converting acetyl-CoA to malonyl-CoA, an intermediate product. This enzyme inhibitor can be used to inhibit the growth and proliferation of bacteria. The purpose of this research is to use molecular docking with AutoDock Vina to see if the studied compounds could bind to the active site of Biotin Carboxylase (BC) (PDB ID: 3JZF). Compounds S2 and S5 were the most promising compounds with the predicted binding affinity of -6.2 kcal/mol and S6 predicted binding affinity of -5.8 kcal/mol, respectively. In addition to π - π , π -alkyl, π - σ , cation- π , and van der Waals interactions, the results indicated the formation of hydrogen bonding between GLY165, GLY166, LYS159, HIS236, TYR82 and ASP382. The CF₃ group in compound S6 was involved in three hydrogen-bond interactions. In this study S2, S5, and S6 were the most promising compounds for enzyme inhibition. The predicted binding affinities of compounds S2 and S5 were found to be the most favorable and they also had the highest value in calculated thermodynamic parameters. The highest values were obtained for compound S5, with $\Delta G = 0.206713$, $\Delta H = 0.266856$, and $\Delta S = 126.583$. This was followed by compound S2, with thermodynamic function values of $\Delta G = 0.178726$, $\Delta H = 0.231667$, and $\Delta S = 111.424$. The results obtained by Gaussian and the results obtained by AutoDock Vina are seen to be correlated consistently with this result.

Keywords: amine derivatives, AutoDock Vina, Gaussian

Introduction

Amines are organic bases that contain one or more amino groups (NH_2) replaced by an R group, either an alkyl group or phenyl group[1], Amines are classified as primary amine, secondary amine or tertiary amine on the basis of the number of groups attached to the nitrogen atom. Medicinal and pharmaceutical chemistry is important with respect to [2] amines as a variety of drugs and biologically active compounds contain them in their structure. These are used in a variety of [3] pharmaceutical compounds such as analgesics, anesthetics, anti-depressants, anti-hypertensive, decongestants and antiallergic medications. They also participate in a number of biochemical pathways such as [4] amino acid synthesis and metabolism [5,6]

Recent developments in computational chemistry have made computational methods important tools for investigating the electronic structures and molecular properties of chemical compounds. A mathematical-based approach known as computational chemistry is utilized to calculate molecular properties and simulate molecular behavior that delivers valuable information to support experiments. Gaussian is one of the popular computational chemistry programs and can be employed to study the electronic properties and structures of molecules. With the help of [7,8](DFT), several molecular descriptors can be calculated: energies (HOMO) and (LUMO), electrophilicity(ω), chemical hardness(η), chemical potential(μ), and thermodynamic functions like ΔG , ΔS , and ΔH . DFT is a [9,10] quantum mechanical approach to the electronic structure of molecules that is based on density of electrons.

On the other hand, molecular docking has become an important computational approach in drug discovery and medicinal chemistry for investigating the potential interactions of chemical compounds with biological macromolecules. The molecular docking [11,12] technique is used to predict the binding mode of a molecule in the binding or active site of a target protein and to find a favorable docking orientation. It also can predict binding affinity and information about the intermolecular interactions between the ligand and the target protein such as hydrogen bonds, π -related interactions, electrostatic interactions, hydrophobic interactions and van der Waals interactions. For AutoDock Vina, the predicted binding affinity is shown in kcal/mol.

Materials and Methods

Computational chemistry [13] is a branch of chemistry that uses mathematical methods and computer-based simulations to calculate molecular properties and investigate molecular behavior. It provides theoretical and computational approaches for studying chemical systems and their structural, electronic, energetic, and thermodynamic properties.

The major applications of [14] computational chemistry include the investigation of intermolecular and intramolecular hydrogen bonding, calculation of vibrational frequencies, determination of potential energies, investigation of geometrical isomers and molecular conformations, calculation of electronic spectra, determination of molecular orbital energies such as [15] HOMO and LUMO, calculation of thermodynamic functions, determination of molecular dipole moments, and calculation of chemical shifts and coupling constants in NMR spectroscopy.

Computational chemistry methods can be broadly divided into two major categories:

1. Molecular Mechanics (MM) Calculations:

Molecular mechanics calculations are based on classical mechanics rather than quantum [16] mechanics. They use empirical potential-energy functions, commonly referred to as force fields, to describe molecular structures and energies. These force fields account for factors such as bond stretching, angle bending, torsional interactions, and nonbonded interactions, including van der Waals and electrostatic interactions.

2. Quantum Mechanical(QM) Calculations:

Quantum Mechanical [17] Calculation are based on the principles of quantum mechanics and the Schrödinger equation. They include several approaches that can be broadly classified as follows:

A. Semi-Empirical Methods, such as AM1, PM3, INDO, CNDO, PM3MM, PM6, and PDDG.

B. ab-initio and Density Functional Theory(DFT) Methods, including HF, MP2, MP4, and DFT. ab-initio quantum mechanical methods are based on the quantum-mechanical treatment of the electronic structure without empirical parameterization, whereas DFT describes the electronic structure in terms of the electron density.

Molecular Docking

Molecular docking [18,19] is a computational technique widely used in drug discovery , medicinal chemistry, biochemistry, and molecular biology. It aims to predict the interaction between two molecules, particularly the binding of a small molecule or ligand to a target protein or receptor.

The main purpose of molecular docking is to predict the preferred binding orientation of a ligand overlap the binding site of the target protein and to estimate the strength of the predicted interaction. Docking analysis can also provide information about the molecular interactions that contribute to ligand–protein recognition and stabilization, including hydrogen bonds, π – π interactions, π –alkyl interactions, cation– π interactions, electrostatic interactions, van der Waals interactions, hydrophobic interactions [20] AutoDock Vina reports the predicted binding affinity in kcal/mol.

Practical Section

Molecular docking modeling was performed using [21] AutoDock Vina, the protein structures were downloaded from the RCSB PDB (Protein Data Bank) website. Water molecules were removed from the protein structures, and polar hydrogens and Kollman charge were added . This process was performed using [22,23] AutoDock Tools 1.5.6. The docking results, including the 2D and 3D binding modes, were visualized and analyzed using Discovery Studio 2020 Client.

Gaussian09W Program

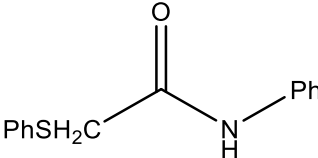
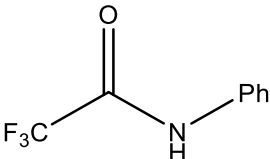
Theoretical Calculation Procedures for the Compounds Using

The molecular structures of the compounds were drawn using [24,25] ChemDraw. The drawn structures were then transferred from ChemDraw to Chem3D, where the compounds were saved as Input Files. Subsequently, the Gaussian View 6.0 program was opened, and the saved Input File was loaded. From the calculate menu, Gaussian Calculation Setup was selected. Under Job Type , Optimization was selected, followed by Minimum to obtain the lowest-energy structure, which corresponds to a more stable molecular structure and a more favorable spatial configuration.

Next, under Method, the theoretical method and basis set were selected. The calculation was then submitted by selecting Submit, after which the calculation was performed using the Gaussian 09W program. Upon completion of the calculations, the resulting data were saved using Notepad.

Table 1. Studied Compounds

Compound	Name	Structure
S1	<i>N</i> -phenylacetamide	
S2	<i>N</i> -phenylbenzamide	
S3	2-fluoro- <i>N</i> -phenylacetamide	
S4	2-methoxy- <i>N</i> -phenylacetamide	

Compound	Name	Structure
S5	<i>N</i> -phenyl-2-(phenylthio)acetamide	
S6	2,2,2-trifluoro- <i>N</i> -phenylacetamide	

Molecular Docking

Molecular docking was performed using the AutoDock Vina software suite, with the Biotin Carboxylase (BC) enzyme (PDB ID: 3JZF) selected as the target. Biotin Carboxylase is a key component of the acetyl-CoA carboxylase (ACC) enzyme complex, which is responsible for fatty acid synthesis in bacteria, and serves as a primary target for numerous drugs; its inhibition halts bacterial growth and replication.

The molecular docking protocol was investigated by re-docking the ligand bound to the Biotin Carboxylase enzyme (PDB ID: 3JZF). The grid box coordinates used were (X, Y, Z) = (-10.961, -28.6, 14.78), with box dimensions of (X, Y, Z) = (34, 20, 20). At a resolution of 1 Å, the resulting Root Mean Square Deviation (RMSD) was 0.158 Å. This value is well below the 2.5 Å threshold, indicating the validity of the molecular docking protocol, as shown in the images below.

Results

The molecular docking results obtained for the studied compounds are presented below.

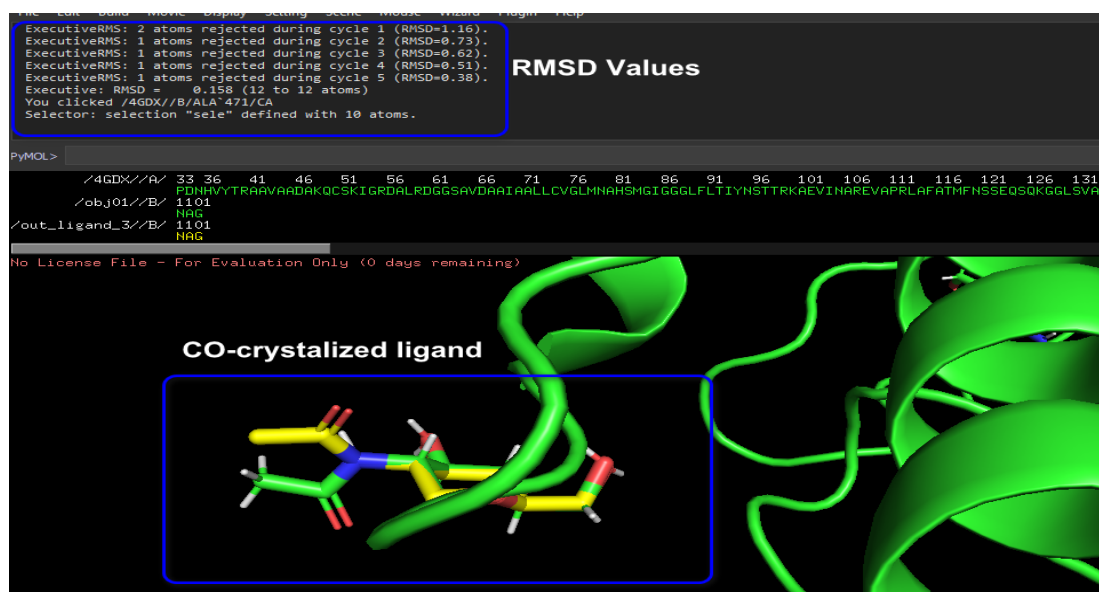


Figure 1. Validation of the molecular docking protocol between the ligand co-crystallized with the protein and the binding site of the enzyme (PDB ID: 3jzf).

Molecular docking Outcomes

Molecular docking was performed on selected compounds, a diverse group of amides, including:

Table 1. Molecular docking results of selected amides

Compound No.	S1	S2	S3	S4	S5	S6
PDB:ID	3jzf	3jzf	3jzf	3jzf	3jzf	3jzf
RMSD(A°)	3.185	1.561	6.316	3.410	2.108	1.709
Docking Score (kcal/mol)	-4.7	-6.2	-5.0	-4.7	-6.2	-5.8

Molecular docking images (Figure 1) show the binding of derivative S1 to the binding site of enzyme 3JZF, favorable value. The 2D and 3D visualizations show the presence of two hydrogen bonds: with a docking score of (-4.7Kcal/mol) and an(RMSD) value of 3.185 Å, a one between TYR:B:82 and the carbonyl group, and another between ASP:B:382 and the NH group.

Similarly, derivative S2 bound to the binding site of the same enzyme with a docking score of (6.2Kcal/mol) and an RMSD value of 1.561 Å(also a favorable value). The 2D and 3D images indicate significant interactions, such as van der Waals, Pi-Pi (T-shaped), (Pi-Sigma), and (Pi-Alkyl) interactions (Figure 2).

Derivative S3 bound to the binding site of enzyme 3JZF with a docking score of (5.0Kcal/mol) and an(RMSD) value of 3.41Å (Table 1). The results showed a single hydrogen bond between GLY:B:166 and the fluoride atom, alongside interactions such as van der Waals,(Pi-Alkyl),and(Pi-Sigma)interactions (Figure 2).

Derivative S4 exhibited a docking score of 4.7 kcal/mol \,a very low value indicating weak binding between the ligand molecule and the enzyme and an RMSD value of 3.410 Å, which is considered poor as it exceeds 2 Å. The results revealed a single hydrogen bond between GLU:B:276 and the NH group (see Figure 3).

Derivative S5 showed a docking score of (6.2Kcal/mol) and an RMSD value of 2.108Å, which is a reasonably good value. The interaction results demonstrated the presence of two hydrogen bonds between GLY:B:165 and HIS:B:236 and the NH group, in addition to significant interactions such as van der Waals , Pi-cation, and Pi-Pi T-shaped interactions (see Figure 3).

For compound S6, the docking score is -5.8 kcal/mol, with an excellent RMSD value of 1.709 Å. The results reveal the formation of three hydrogen bonds involving residues GLY:B:165, GLY:B:166, and LYS:B:159 with the terminal trifluoromethyl (CF₃) group, alongside interactions such as van der Waals,Pi-Sigma,and Pi-Alkyl contacts. In contrast, the molecular docking results for the other derivatives showed different docking scores, RMSD values, and interaction patterns with the active site of the Biotin Carboxylase enzyme (PDB ID: 3JZF), as presented in the corresponding figures and tables.

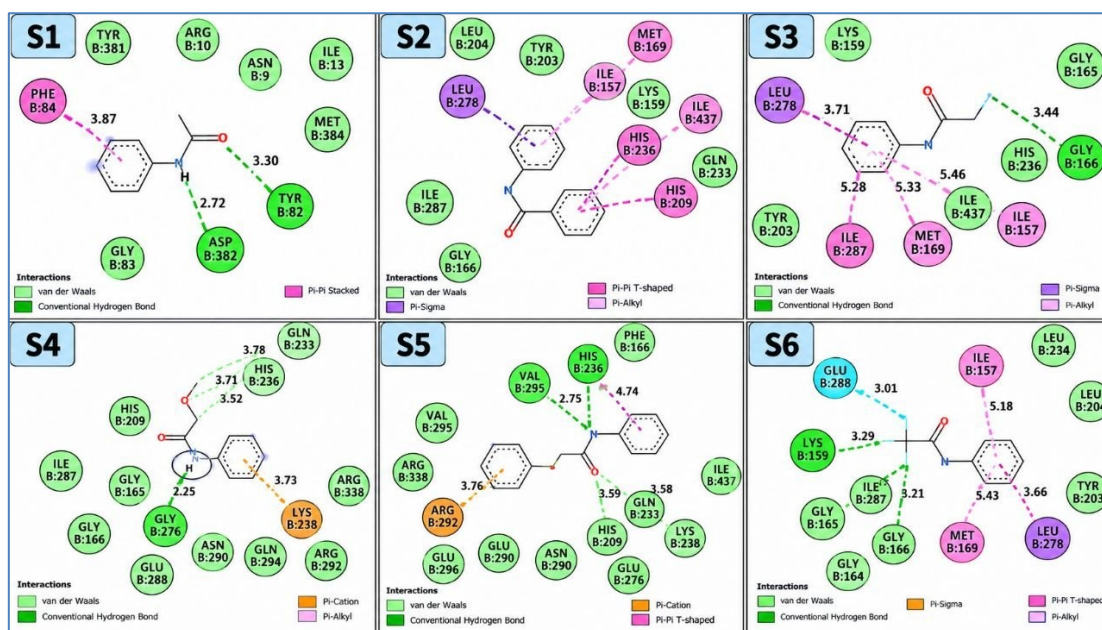


Figure 2. 2D structure of interaction of Amides(S1,S2,S3,S4,S5,S6) with binding site of Biotin Carboxylase enzyme (PDB ID: 3jzf).

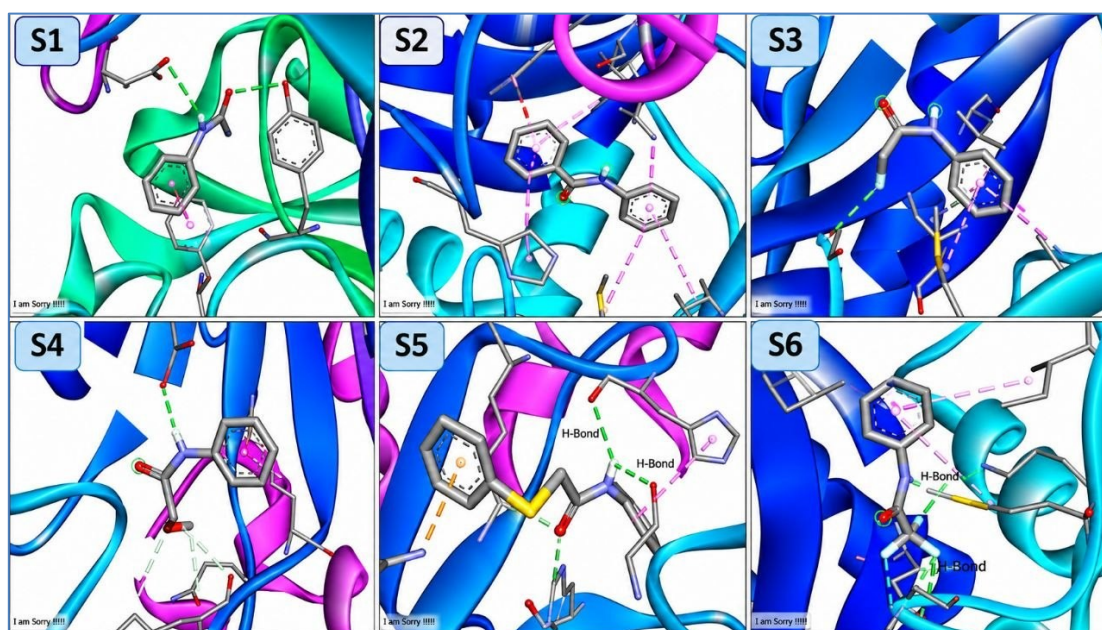


Figure 3. 3D structure of interaction of Amides(S1,S2,S3,S4,S5,S6) with binding site of Biotin Carboxylase enzyme (PDB ID: 3jzf).

Table 2. following table presents the calculated energy parameters obtained using : (DFT) with the basis set (6-31G).

Compounds	HOMO	LUMO	η	μ	ω
<i>N</i> -phenylacetamide	-0.12663	0.06570	0.096165	-0.03047	0.004826
<i>N</i> -phenylbenzamide	-0.12034	0.03644	0.07839	-0.04195	0.011225
2-fluoro- <i>N</i> -phenylacetamide	-0.13064	0.05608	0.09336	-0.03728	0.007443
2-methoxy- <i>N</i> -phenylacetamide	-0.12905	0.06214	0.095595	-0.03346	0.005854
<i>N</i> -phenyl-2-(phenylthio)acetamide	-0.13425	0.08411	0.10918	-0.02507	0.002878
2,2,2-trifluoro- <i>N</i> -phenylacetamide	-0.14467	0.06555	0.10511	-0.03956	0.007445

HOMO and LUMO values were theoretically calculated using the Gaussian program at the DFT level with the 6-31G basis set. The values of hardness, chemical potential⁽²⁶⁾, and global electrophilicity index were calculated from the (HOMO) and (LUMO) values using the following equations:

$$\eta = (E_{\text{LUMO}} - E_{\text{HOMO}})/2, \mu = (E_{\text{HOMO}} + E_{\text{LUMO}})/2, \omega = \mu^2/2\eta$$

Table 3. following table presents the results of the thermodynamic functions obtained using the (DFT) method with the basis set (6-31G).

COMP.	COMP. Name	ΔG	ΔH	ΔS
S1	<i>N</i> -phenylacetamide	0.129000	0.173880	94.459
S2	<i>N</i> -phenylbenzamide	0.178726	0.231667	111.424
S3	2-fluoro- <i>N</i> -phenylacetamide	0.117756	0.165293	100.049
S4	2-methoxy- <i>N</i> -phenylacetamide	0.158756	0.210638	109.194
S5	<i>N</i> -phenyl-2-(phenylthio)acetamide	0.206713	0.266856	126.583
S6	2,2,2-trifluoro- <i>N</i> -phenylacetamide	0.098281	0.148786	106.297

The thermodynamic function values were theoretically calculated using the Gaussian program at the (DFT) level with the (6-31G) basis set. Compound S5 exhibited the highest values of the thermodynamic functions, followed by compound S2, whereas compound S6 exhibited the lowest values for the thermodynamic functions, particularly ΔH and ΔG . This compound contains a CF_3 group.

Discussion

The computational results demonstrate that structural modification of the *N*-phenylacetamide scaffold substantially influences both its electronic characteristics and its predicted interaction with the active site of Biotin Carboxylase (BC). Among the six investigated derivatives, compounds S2 and S5 exhibited the most favorable docking scores, both reaching approximately -6.2 kcal/mol, whereas S6 also showed comparatively strong binding with a docking score of -5.8 kcal/mol. These values suggest that the presence of additional aromatic or sulfur-containing substituents may enhance ligand-protein stabilization through a combination of hydrophobic, π -related, and hydrogen-bonding interactions. The docking analysis further showed that the compounds interact with several residues within the BC binding pocket, including GLY165, GLY166, LYS159, HIS236, TYR82, ASP382, and GLU276.

The stronger predicted affinity of S2 can be associated with its additional phenyl group, which provides greater opportunity for π - π , π - σ , π -alkyl, and van der Waals interactions within the active site. The reported RMSD value of $1.561 \text{ \AA}$ for S2 also supports a relatively favorable binding pose. In contrast, S1 exhibited a weaker docking score of -4.7 kcal/mol and mainly formed hydrogen bonds with TYR82 and ASP382, suggesting that the unsubstituted *N*-phenylacetamide scaffold alone may provide less extensive stabilization inside the binding cavity. S3 and S4 also showed weaker binding behavior, while the relatively high RMSD values reported for some of these compounds indicate less favorable or less consistent docking orientations.

Compound S5 displayed particularly interesting behavior because it combined one of the best docking scores with two hydrogen bonds involving GLY165 and HIS236, together with van der Waals, cation- π , and π - π T-shaped interactions. This interaction pattern suggests that incorporation of the phenylthio substituent may increase the number and diversity of non-covalent contacts available for stabilizing the ligand within the enzyme pocket. The docking outcome is also consistent with the thermodynamic calculations, because S5 exhibited the highest calculated values of ΔG , ΔH , and ΔS among the studied compounds, with values of 0.206713, 0.266856, and 126.583, respectively. S2 ranked second in these thermodynamic parameters, further supporting the observation that these two structures possess distinctive calculated energetic characteristics compared with the other derivatives.

The S6 derivative provides another important structure–activity insight. Although its thermodynamic ΔG and ΔH values were the lowest among the studied compounds, S6 still demonstrated a relatively favorable docking score of -5.8 kcal/mol and an RMSD value of 1.709 Å. The trifluoromethyl group in S6 participated in three hydrogen-bond interactions involving GLY165, GLY166, and LYS159, in addition to van der Waals, π - σ , and π -alkyl contacts. This finding indicates that electron-withdrawing fluorinated substitution can alter the interaction profile substantially and may improve local complementarity with the binding site even when the corresponding bulk thermodynamic descriptors do not follow the same ranking.

The global reactivity descriptors also reveal meaningful electronic differences among the six compounds. The calculated HOMO, LUMO, chemical hardness, chemical potential, and electrophilicity values indicate that substitution changes the electron-donating and electron-accepting tendencies of the amide system. S5 displayed the highest hardness value, whereas S2 showed the lowest hardness among the investigated derivatives, implying differences in electronic stability and polarizability. At the same time, the electrophilicity values varied across the series, showing that each substituent modifies the ability of the molecule to participate in electron-transfer interactions. These electronic effects may contribute indirectly to differences in hydrogen bonding, electrostatic complementarity, and π -interactions observed during docking.

Taken together, the results indicate that there is no single molecular descriptor that completely explains the predicted inhibitory potential of these compounds. Instead, the docking behavior appears to arise from the combined influence of molecular geometry, substituent type, electronic distribution, thermodynamic characteristics, and the ability to form complementary non-covalent interactions in the Biotin Carboxylase active site. S2 and S5 emerge as the most promising candidates because they combine favorable docking scores with advantageous calculated energetic and interaction profiles, while S6 is noteworthy because of the contribution of its CF_3 group to multiple hydrogen-bond contacts. Nevertheless, these findings remain computational predictions. Experimental enzyme inhibition assays, molecular dynamics simulations, and further pharmacokinetic and toxicity evaluations would be necessary to confirm whether these compounds can function as effective Biotin Carboxylase inhibitors under biological conditions.

Conclusion

In summary, the current research has provided valuable theoretical insight concerning the properties such as structural, electronic, and molecular interaction of the studied amide derivatives. Through the calculations carried out, there was a difference in the theoretical properties of the molecules under study in terms of molecular interactions, electronic, and thermodynamics. The results have enhanced the understanding of the link between the chemical structure of the molecules and theoretical properties. However, computational prediction is not enough to prove biological activity or the mechanism of action. For this reason, more experimental studies should be carried out.

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