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Electronic and Lipophilicity-Guided Optimization of Cyclopentanone Derivatives: A Combined DFT and Molecular Docking Investigation Targeting the 1KZN Protein

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ABSTRACT

The rational modulation of electronic structure combined with lipophilicity optimization constitutes represents a fundamental strategy in modern drug design. In this study, four systematically substituted cyclopentanone derivatives (H, OMe, F, NO_2) were studied through a density functional theory (DFT) calculations and molecular docking simulations against the Escherichia coli 24 kDa domain in complex with clorobiocin (PDB ID: 1KZN). Frontier molecular orbital energies, HOMO–LUMO energy gaps (ΔE), dipole moments, and Mulliken charge distributions were analyzed to elucidate substituent-induced electronic modulation.

Docking simulations revealed stable binding conformations (RMSD < 2 Å) with binding affinities ranking as: NO_2 > OMe > F > H. The nitro-substituted derivative displayed the smallest energy gap, ΔE (8.071 eV), the lowest and most stabilized LUMO energy (−1.734 eV), and enhanced carbonyl charge localization, correlating with the strongest docking score (−6.6872 kcal/mol).

Statistical analysis demonstrated that reduced energy gaps and enhanced electrophilicity significantly improve ligand–protein interactions. Collectively. These findings establish a mechanistic electronic–affinity relationship for optimizing cyclopentanone-based pharmacophores and support electron-withdrawing substitution as a promising strategy for enhancing binding affinity against antibacterial targets.

Keywords: Cyclopentanone derivatives; DFT; HOMO–LUMO; Lipophilicity; Molecular docking; 1KZN; Electronic modulation; Binding affinity
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1. Introduction

The problem of multidrug-resistant (MDR) bacterial pathogens has continued to pose a challenge to the efficacy of traditional antibiotic therapy, thereby creating a pressing need for the development of rationally designed small molecules with high binding affinity and favorable physicochemical properties. [1-3] Modern structure-based drug design has increasingly employed electronic structure modulation to enhance ligand-protein interactions at the molecular level. In this regard, frontier molecular orbital theory has been recognized as a quantitative approach for correlating reactivity descriptors with biological activity. [4-6]

Cyclopentanone-derived cores are electronically flexible structures that can engage in diverse noncovalent interaction modes. The carbonyl functionality gives rise to a polarized C=O bond, thereby generating a localized electrophilic site and a directional hydrogen-bond acceptor site. From a quantum chemical perspective, the electronic structure of the cyclopentanone ring system is of paramount importance in frontier orbital alignment, molecular softness, dipole moment, and charge transfer, which are directly linked to the ligand-target complex stabilization energy.[7]

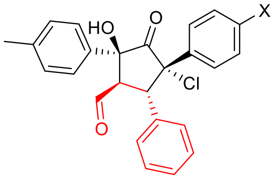
Substituent electronic perturbation is a very efficient strategy for modulating these properties. Electron-withdrawing groups (EWGs) decrease the LUMO energy level because of the inductive and resonance effects, thus increasing electrophilicity and the HOMO-LUMO energy gap difference (ΔE). A lower ΔE value is typically associated with enhanced chemical softness, polarizability, and donor-acceptor interactions with nucleophilic amino acids in the protein active site. Conversely, electron-donating groups (EDGs) can increase the HOMO energy level, modulate charge distribution in the carbonyl area, and influence dipole orientation, thus affecting hydrogen bonding geometry and electrostatic complementarity. [8,9]

Besides the aforementioned inherent electronic properties, lipophilicity also cooperatively plays a role in modulating binding free energy. Hydrophobic-electrostatic balance is optimized to enhance desolvation efficiency and facilitate favorable dispersion interactions in hydrophobic pockets. Therefore, ligand binding affinity cannot be attributed to a specific descriptor but rather to the cooperative action of frontier orbital electronic properties, electrostatic

potential distribution, and hydrophobic surface complementarity.[10]

However, the presence of keto-enol tautomerism and chelation abilities in cyclopentanone, despite its simple structure, may potentially affect conformational stability and electronic distribution. These problems can be overcome by substituent engineering, which assists in the optimization of electron density distribution and thus helps in stabilizing the major keto form. The analysis of the impact of substituents on the cyclopentanone structure and properties thus helps in understanding how local electronic perturbations propagate through the molecular structure and affect global reactivity parameters.[11]

In this research, four cyclopentanone derivatives (H, OMe, F, NO_2) (Figure 1) [12] were analyzed using density functional theory calculations to approximate frontier molecular orbitals (HOMO and LUMO), HOMO-LUMO energy gaps (ΔE), dipole moments (μ), and Mulliken charge distribution. The obtained data were correlated with molecular docking simulations performed against the 1KZN protein target to evaluate binding geometries and interaction energies. By integrating quantum chemical reactivity parameters with docking affinity values, this research aims to develop a structure-electronic-affinity relationship and investigate how substituent-mediated electronic modulation regulates ligand-protein complex stabilization at the molecular level.



X = H, OMe, F, NO_2

Comp. no.	1	2	3	4
X	H	OMe	F	NO_2

Figure 1: The structure of (1*R*,2*S*,4*S*,5*S*)-4-chloro-2-hydroxy-3-oxo-4,5-diphenyl-2-(*p*-tolyl)cyclopentane-1-carbaldehyde and its derivatives

2. Computational Methods

2.1 Density Functional Theory Calculations

The molecular structures were fully optimized using Density Functional Theory with the B3LYP/6-311G(d,p) method.[13] Frequency analysis was performed to ensure that there are no imaginary frequencies. The HOMO, LUMO energies, HOMO-LUMO energy gap values (ΔE), dipole moments (μ), and Mulliken charge distribution were calculated using Gaussian 09. [14-16]

2.2 Molecular Docking

The crystal structure of the Escherichia coli 24 kDa domain bound to clorobiocin (PDB ID: 1KZN) was obtained from the Protein Data Bank (Figure 2). The water molecules and heteroatoms were deleted before docking. Polar hydrogen atoms were added, and atom types were defined using AutoDock Tools (v1.5.7). The ligands were flexible, while the receptor was rigid. The binding affinity and interaction details were examined. [17-19]

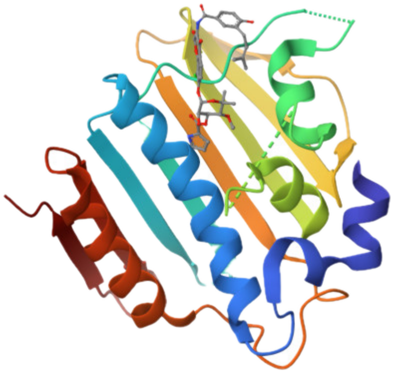


Figure 2: Crystal Structure of E. coli 24kDa Domain in Complex with Clorobiocin

3. Results and Discussion

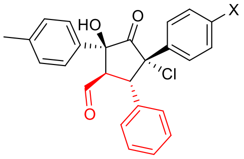
3.1 Electronic Structure Analysis

The calculated total energies, frontier molecular orbital energies (HOMO and LUMO), HOMO–LUMO energy gaps (ΔE), and dipole moments (μ) of (1*R*,2*S*,4*S*,5*S*)-4-chloro-2-hydroxy-3-oxo-4,5-diphenyl-2-(*p*-tolyl)cyclopentane-1-carbaldehyde and its derivatives presented in Table 1

Frontier molecular orbitals were systematically affected by substituent effects. The ΔE values calculated were in the order: OMe (9.234 eV) > H (9.123 eV) > F (8.934 eV) > NO_2 (8.071 eV). However, the NO_2 derivative showed the lowest LUMO energy level (-1.734 eV), the smallest energy gap and increased electrophilic properties.

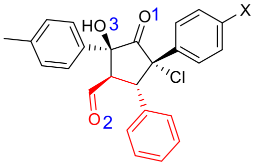
A smaller ΔE value corresponds to greater chemical softness and better charge transfer ability. The high electron-withdrawing ability of NO_2 lowers the LUMO energy level through inductive and resonance effects, thus increasing its interaction potential in the nucleophilic regions of the protein active site.

Table 1. The total energy (eV) values, the MO energy of HOMO, LUMO levels, ∆*E* (eV), dipole moment μ (Debyes) for compounds 1, 2, 3, and 4.



Comp no	X	Total energy	HOMO	LUMO	∆ *E*	μ
1	H	-1.181	-9.393	-0.271	9.123	5.2985
2	OMe	-3.866	-9.263	-0.029	9.234	7.3033
3	F	-3.140	-9.435	-0.501	8.934	4.7446
4	NO_2	-2.190	-9.805	-1.734	8.071	4.9738

Table 2. Log P and Mulliken charge values for C=O furan, C=O aldehyde, OH, and Cl for compounds 1, 2, 3, and 4.



Comp. no	X	Log P	Mulliken charge (Q_M)			
			O^1	O^2	O^3	Cl
1	H	2.95	-0.231	-0.282	-0.294	-0.077
2	OMe	1.96	-0.394	-0.458	-0.543	-0.141
3	F	2.35	-0.231	-0.282	-0.293	-0.075
4	NO2	0.20	-0.397	-0.454	-0.452	-0.106

3.2 Lipophilicity and Charge Redistribution

Lipophilicity is defined as the ability of a chemical compound to dissolve in fats, oils, and non-polar solvents, often referred to as "fat-loving." Lipophilicity is an important physiochemical property in drug design that affects solubility, membrane permeability, absorption, distribution, metabolism, and excretion (ADME), as well as toxicity.

The values of Log P and Mulliken charge of oxygens in C=O furan (O^1), C=O aldehyde (O^2), OH (O^3), and Cl in compounds 1, 2, 3, and 4 were given in Table 2.

The Log P values ranged from 0.20 to 2.95. Moderate lipophilicity appropriate for drug-like compounds was exhibited by compounds 1-3. The NO_2 derivative was less lipophilic but more electronically activated. Mulliken charge distribution indicated a substantial negative charge on the cyclopentanone carbonyl in the NO_2 and OMe derivatives, increasing hydrogen-bond acceptor ability. This supports the carbonyl oxygen as the primary pharmacophoric interaction site.

3.3 Molecular Docking and Binding Affinity

The results obtained from docking of compounds 1-4 with 1KZN in active site are shown in Table 3.

The derivatives showed stable binding poses (RMSD < 2 Å). The binding affinities were: NO_2 (-6.6872 kcal/mol) > OMe (-6.4160 kcal/mol) > F (-6.2942 kcal/mol) > H (-5.8889 kcal/mol). Nevertheless, the NO_2 derivative showed multiple hydrogen bonds, including a strong one with ARG136 (-3.6 kcal/mol) and other water-mediated interactions. The unsubstituted derivative showed a hydrogen bond with ILE78, while OMe and F derivatives showed π-H interactions with ASN46.

The enhanced binding affinity of the NO_2 derivative is directly related to Reduced ΔE, Stabilized LUMO, Enhanced carbonyl charge density, and Increased electrophilicity

Figure 3 showed the molecular interactions of substituted cyclopentanone derivatives (H, OMe, F, NO_2) with the active site of Escherichia coli (E. coli) 24kDa domain in complex with clorobiocin (PDB ID: 1KZN).

3.4 Electronic–Activity Correlation

A clear mechanistic relationship was found: the decrease in the HOMO-LUMO energy gap (ΔE) increases the chemical softness, which is directly related to the docking affinity. Likewise, the increase in the LUMO

Table 3. The results obtained from docking of compounds 1-4 with 1KZN in active site

X	S score kcal/mol)	RMSD (Å)	Bonds between atoms of compounds with 1KZN active site 1					
			Atom of compound	Atom of receptor	Involved receptor residues	Type of interaction bond	Distance (Å)	E (kcal/mol)
H	-5.8889	1.2403	O 24	CA	ILE 78	H- acceptor	3.27	-0.7
OMe	-6.4160	1.2634	6-ring	CB	ASN 46	Pi-H	3.71	-1.1
F	-6.2942	1.2869	6-ring	CB	ASN 46	Pi-H	3.71	-1.1
NO2	-6.6872	1.6383	O 27	O	HOH 1172	H- acceptor	2.70	-1.3
			O 51	NH1	ARG 136	H- acceptor	3.16	-3.6
			O 51	O	HOH 1154	H- acceptor	3.18	-0.8

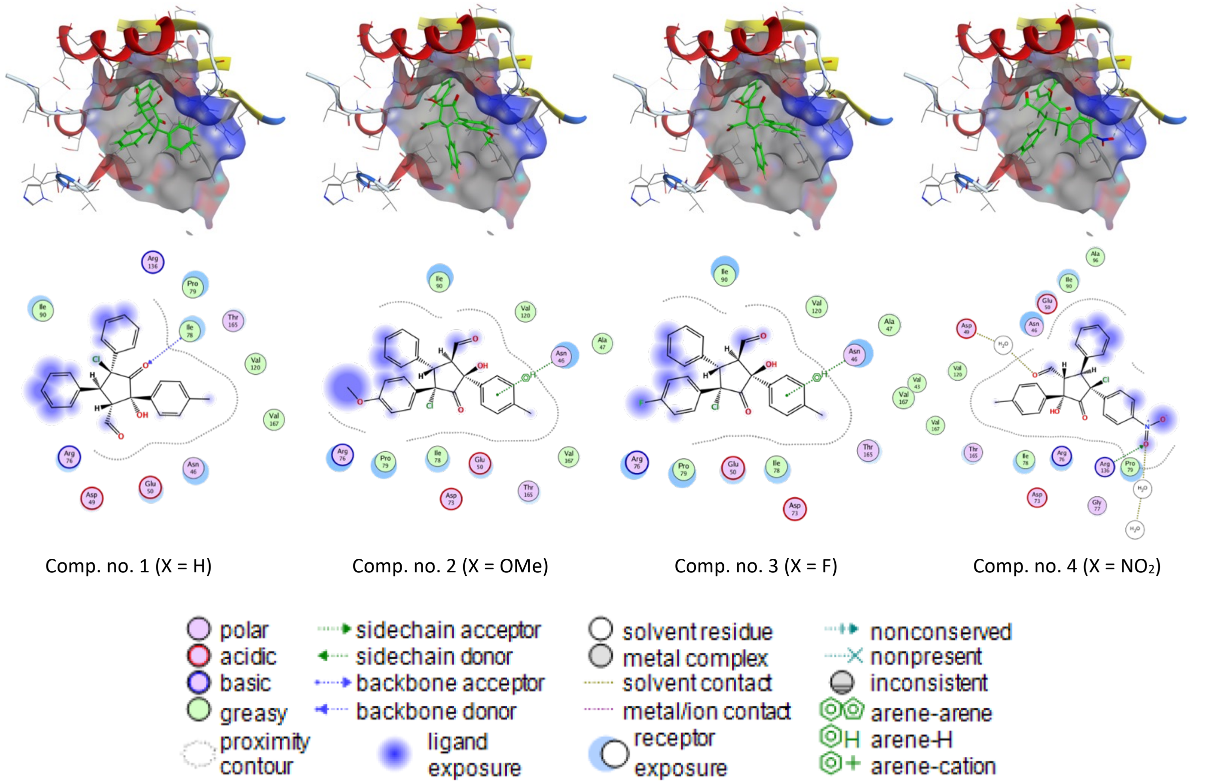

Comp. no. 1 (X = H)
Comp. no. 2 (X = OMe)
Comp. no. 3 (X = F)
Comp. no. 4 (X = NO_2)

Figure 3. 2D and 3D docking poses showing interactions of compounds 1-4 in the binding sites of Escherichia coli (E. coli) 24kDa domain in complex with clorobiocin (PDB ID: 1KZN).

energy stabilization increases the electrophilic properties, which are directly related to the hydrogen-bond interactions. Moreover, the higher localization of the negative charge on the carbonyl group increases the electrostatic stabilization in the binding site.

In summary, the binding affinity is a result of the combined effect of the electronic and lipophilic effects rather than being dependent on any molecular property.

4. Conclusion

This study emphasizes that systematic substituent effects for electronic tuning have a positive effect on the binding affinity of cyclopentanone derivatives against the 1KZN protein target.

Among the cyclopentanone derivatives, the compound with the NO_2 group showed the smallest HOMO-LUMO gap, the most stabilized LUMO level, the most pronounced carbonyl charge density, and the highest docking affinity.

These findings suggest that electron-withdrawing substituents can improve pharmacophoric properties by increasing electrophilic and hydrogen-bonding interactions in the active site pocket.

In summary, the established correlation between electronic properties and lipophilicity provides a rational design strategy for further optimization of cyclopentanone derivatives as antibacterial agents.

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