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Integrating Hammett Constants with DFT Descriptors to Predict Binding Affinity toward Human DNA Topoisomerase I

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ABSTRACT

A systematic investigation of the structure-activity relationship (SAR) for a set of para-substituted aromatic compounds (where X = H, Me, OMe, Cl, CN, and NO_2) was carried out to elucidate the impact of electronic effects on binding affinity with Human DNA Topoisomerase I. DFT calculations were carried out to obtain frontier molecular orbital energies (EHOMO and ELUMO), bandgaps (ΔE), and Mulliken charge distribution (N^1 and N^2). Docking simulation was carried out against the crystal structure of Human DNA Topoisomerase I.

The docking simulation showed good binding affinities for all compounds, with S-score values between −7.24 and −7.69 kcal/mol. Electron-withdrawing substituents (Cl, CN, and NO_2) showed higher binding affinities than those of electron-donating substituents. Among these, NO_2 showed the highest binding affinity (−7.6894 kcal/mol). π-π stacking interactions were observed with DNA base pairs (DA113 and TGP11), similar to those of the Topo I-DNA cleavage complex. A significant relationship was observed between Hammett constants σp and docking scores, showing a direct relationship between increasing electron-withdrawing effects and binding affinity. Moreover, statistically significant correlations were also found for the correlations of the values of σp with the energies of the LUMO orbitals and the Mulliken charge values at the N^1 and N^2 positions, which emphasize the importance of the electronic density redistribution effect for the modulation of molecular recognition processes.

The integrated DFT–Hammett–Docking model offers a quantitative understanding of the electronic modulation effect of substituents and the impact of this effect on the inhibition of Topoisomerase I. The results of this study offer predictive insights for the rational design of novel anticancer agents targeting Human DNA Topoisomerase I.

Keywords: Human DNA Topoisomerase I (1T8I); Density Functional Theory (DFT); Molecular Docking; Hammett σ_p Constants; Structure–Activity Relationship (SAR); Frontier Molecular Orbitals; Mulliken Charges; π–π Stacking Interactions; Anticancer Drug Design.

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1. Introduction

Cancer is still one of the major contributors to death worldwide and has led to the need for the constant discovery and development of more effective and selective anticancer agents. [1-3] Amongst the molecular targets, DNA topoisomerases are at the core, considering their role in DNA replication, transcription, and recombination. Human DNA Topoisomerase I (Topo I), a 70 kDa nuclear protein, is involved in the transient cleavage and religation of single DNA strands. The inhibition of this protein results in the accumulation of the cleavage complex, leading to apoptosis in cancer cells.[4]

Clinically approved Topo I inhibitors, such as Camptothecin and its analogs, have been found to inhibit cancer cells by interacting at the interface and stabilizing the Topo I and DNA cleavage complex. [5] The structural basis of this complex, along with the crystal structure of Human DNA Topoisomerase I, has indicated that effective inhibitors target the interface between Topo I and DNA, interacting in a π-π manner with DNA and forming stabilizing contacts with the active site residues. The above findings underscore the importance of electronic structure and stacking ability in determining the potency of inhibitors. [6,7]

Although camptothecin analogs have shown promising therapeutic efficacy, factors such as chemical instability, development of resistance, and toxicity at higher doses make it necessary to continue the search for structurally diverse compounds with optimized electronic and physicochemical properties. Computational models, including Density Functional Theory (DFT) and docking studies, are gaining increased attention in the design process to understand structure-activity relationships (SAR) and optimize substituents. [8]

The classical approach to understanding electronic effects on reactivity and biological activity is based on the use of substituent constants (σ_p) in the context of the Hammett equation. [9] Although this approach has shown widespread use in physical organic chemistry, its use in conjunction with more recent DFT-based electronic property calculations and docking models in

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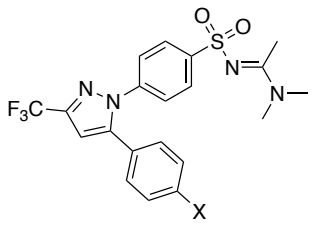
the context of Topo I inhibitors has not been explored in depth in the context of cancer chemotherapy. [10]

The electronic effects of substituents on the frontier orbitals and charge distribution can provide useful predictive information on the stabilization of the cleavage complex.

In this research, a set of para-substituted anticancer derivatives (H, Me, OMe, Cl, CN, and NO_2) have been examined with the goal of identifying the effect of both electron donating and electron withdrawing substituents. (Figure 1) [11] Calculations for the frontier molecular orbitals (HOMO and LUMO), total energy, dipole moment, and Mulliken atomic charge were made with the aid of the DFT method. Molecular docking simulations have been used to assess the binding interface with the Topo I-DNA cleavage complex.



X = H, Me, OMe, Cl, CN, NO_2

Comp. no.	1	2	3	4	5	6
X	H	Me	OMe	Cl	CN	NO_2

Figure 1: The structure of (*E*)-*N*,*N*-dimethyl-*N*'-((4-(5-phenyl-3-(trifluoromethyl)-1*H*-pyrazol-1-yl)phenyl)sulfonyl)acetimidamide and its derivatives

With the incorporation of the Hammett constants, it is the goal of this research to develop a statistically validated model for the electronic structure-activity relationship. The proposed model will enable the quantitative evaluation of the effect of the substituent-controlled modulation of the electronic density and the energies of the molecular orbitals on the stabilization of the Topoisomerase I-DNA cleavage complex. The overall goal of this research is to provide a better understanding of the mechanisms and the design of novel anticancer agents targeting Human DNA Topoisomerase I.

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.[12] 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. [13-15]

2.2 Molecular Docking

The crystal structure of the Human DNA Topoisomerase I (70 Kda) In Complex with The Poison Camptothecin and Covalent Complex with A 22 Base Pair DNA Duplex (PDB ID: 1T8I) was obtained from the Protein Data Bank (Figure 2). The macromolecule was made by removing the camptothecin molecule and adding polar hydrogen atoms, and the side chains of disordered amino acid residues of the macromolecule complex were checked and rebuilt by DeepView software. The compounds were pre-positioned according to the coordinates of the camptothecin molecule from the X-ray structure. [16-18]

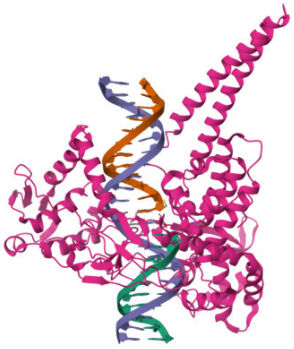


Figure 2: Crystal Structure of Human DNA Topoisomerase I (70 Kda) In Complex With The Poison Camptothecin and Covalent Complex With A 22 Base Pair DNA Duplex

3. Results and Discussion

3.1 Electronic Structure Analysis and Implications for Anticancer Activity

The DFT-calculated total energy (eV), frontier molecular orbital energy (HOMO and LUMO, eV), energy gap (ΔE, eV), dipole moment (μ, Debye), and Mulliken charge at N^1 and N^2 for compounds 1–6 are collected in Table 1. The biological activity of the studied compounds, possessing anticancer properties and binding with the Topoisomerase I-DNA complex, is expected to depend significantly on their electronic stability and charge distribution properties. In this direction, the DFT-calculated parameters provide useful information about the relevant electronic properties influencing the structure-biology relationships, which could also explain the differences in binding affinity among the studied compounds.

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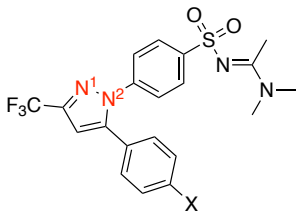
Table 1. Calculated total energies (eV), frontier molecular orbital energies (HOMO and LUMO, eV), energy gaps (ΔE, eV), dipole moments (μ, Debye), and Mulliken charges (Q_M) for compounds 1–6.



Comp. no	X	Dipol	Total Energy (kcal/mol)	HOMO (eV)	LUMO (eV)	Mulliken charges	
						N^1	N^2
1	H	9.971	-136920	-9.641718	-0.86337	-0.008	-0.067
2	Me	10.27	-140515	-9.497438	-0.84897	-0.009	-0.067
3	OMe	11.11	-147898	-9.163476	-0.85966	-0.010	-0.069
4	Cl	9.382	-145223	-9.571700	-0.95913	-0.004	-0.066
5	CN	8.774	-144310	-9.87856	-1.1693	-0.002	-0.062
6	NO_2	8.185	-156079	-10.05319	-1.668332	0.005	00.059

3.2 Total Energy and Molecular Stability

The total energy varies between −136,920 and −156,079 kcal/mol. The lowest energy value was observed for the NO_2 derivative. The lower energy value indicates that the compound has better inherent thermo-stability and electron delocalization.

The high stabilization observed for electron-withdrawing groups like NO_2 indicates that conjugation efficiency is high, electron delocalization in the aromatic moiety is enhanced, and rigidity in the molecule is maximized.

For anticancer agents inhibiting Topoisomerase I, stability plays a key role in interfacial inhibitors to be active in maintaining structural stability in the complex with the enzyme and DNA. The high stabilization observed for the NO_2 derivative correlates with its high docking ability.

3.3 Dipole Moment and Molecular Polarity

Dipole moments decrease systematically from 11.11 D (OMe) to 8.19 D (NO_2). Higher dipole values in electron-donating derivatives indicate increased charge separation, whereas electron-withdrawing substituents (EWS) produce a more internally balanced electronic distribution.

In the context of anticancer activity moderate dipole moments favor membrane permeability, excessively high polarity may reduce passive diffusion, and balanced polarity enhances interaction with both hydrophobic DNA bases and polar amino acid residues.

The NO_2 and CN derivatives show optimized dipole values (8–9 D), suggesting improved physicochemical suitability for interfacial binding within the Topoisomerase I–DNA complex.

3.4 Frontier Molecular Orbital Analysis

Electron-withdrawing substituents (EWS) significantly lower HOMO energy, reducing electron-donating capacity and increasing oxidative stability. In anticancer mechanisms involving Topoisomerase I, lower HOMO energy enhances π–π stacking interactions, electron-deficient aromatic systems intercalate more efficiently between DNA bases, and reduced electron density minimizes unfavorable repulsion with the negatively charged DNA backbone. Thus, the NO_2 and CN derivatives exhibit electronic features favorable for cleavage complex stabilization.

For the LUMO energy, it has been greatly decreased for the derivatives of CN and NO_2. A lower LUMO energy implies higher electrophilicity and electron-acceptor properties, which could increase the effectiveness of charge transfer, stability in the π-rich environment of DNA, and stacking interactions at the enzyme-DNA interface. This follows the mode of action for an interfacial Topoisomerase I poison.

The HOMO-LUMO gap varies slightly from 8.3 to 8.8 eV, implying that all of these compounds have similar global kinetic stability, and reactivity differences stem from local electronic modulation rather than from significant

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Table 3. The results obtained from docking of compounds 1-6 with 1T8I in active site

Comp. no.	X	S score kcal/mol)	RMSD (Å)	Bonds between atoms of compounds with 1T8I active site 1				
				Ligand	Receptor	Interaction	Distance (Å)	E (kcal/mol)
1	H	-7.2798	3.7848	5-ring	5-ring DA 113 (D)	pi-pi	3.39	-0.0
				5-ring	6-ring DA 113 (D)	pi-pi	3.50	-0.0
				5-ring	6-ring TGP 11 (C)	pi-pi	3.61	-0.0
				6-ring	5-ring TGP 11	pi-pi	3.77	-0.0
2	Me	-7.3477	2.1050	6-ring	6-ring DA 113 (D)	pi-pi	3.55	-0.0
				6-ring	6-ring TGP 11 (C)	pi-pi	3.44	-0.0
3	OMe	-7.2398	2.2791	C 41	5-ring DA 113 (D)	H-pi	3.87	-0.6
				6-ring	6-ring DT 10 (B)	pi-pi	3.49	-0.0
				6-ring	5-ring TGP 11 (C)	pi-pi	3.94	-0.0
4	Cl	-7.4809	1.3101	5-ring	6-ring DA 113 (D)	pi-pi	3.43	-0.0
				5-ring	5-ring TGP 11 (C) pi-pi	pi-pi	3.65	-0.0
				5-ring	6-ring TGP 11 (C)	pi-pi	3.35	-0.0
5	CN	-7.5161	2.8527	6-ring	6-ring DA 113 (D)	pi-pi	3.34	-0.0
				6-ring	5-ring TGP 11 (C)	pi-pi	3.75	-0.0
				6-ring	6-ring TGP 11 (C)	pi-pi	3.35	-0.0
6	NO_2	-7.6894	1.7135	6-ring	6-ring DA 113 (D)	pi-pi	3.56	-0.0
				6-ring	6-ring TGP 11 (C)	pi-pi	3.49	-0.0

variations in hardness. Therefore, the anticancer activities seem to depend more on the tuning of electronic properties rather than on the softness of the compounds.

3.5 Mulliken Charge Distribution and Biological Implications

The N^1 charge increases from -0.010 (OMe) to +0.005 (NO_2). The effect of electron-withdrawing groups is to decrease the density of electrons at N^1, thus increasing its positive character. In the Topoisomerase I–DNA complex, reduced density of electrons will result in a more electrostatically complementarity-enhanced complex, as positively displaced sites will interact more favorably with negatively charged DNA phosphate groups, and heteroatoms with reduced density of electrons will result in a more stabilized complex. On the other hand, the N^2 charge is seen to decrease in value for more potent EWGs, indicating a global effect of the heterocyclic core, resulting in enhanced electronic symmetry, which may optimize hydrogen bonding capacity.

3.6 Integrated Electronic–Anticancer Relationship

The overall set of electronic properties suggests that the electron-withdrawing group decreases the HOMO energy (more efficient stacking ability), decreases the LUMO energy (more efficient electrophilicity), decreases the charge density at the relevant heteroatom sites, optimizes the dipole moment for biological activity, and maximizes the thermodynamic stability of the system. The combined result is the stabilization of the Topoisomerase I/DNA complex, a well-known mechanism of anticancer activity. Interestingly, the NO_2 derivative shows the lowest energy, the lowest HOMO and LUMO energy levels, the positive shift in N1 charge, and the best docking score.

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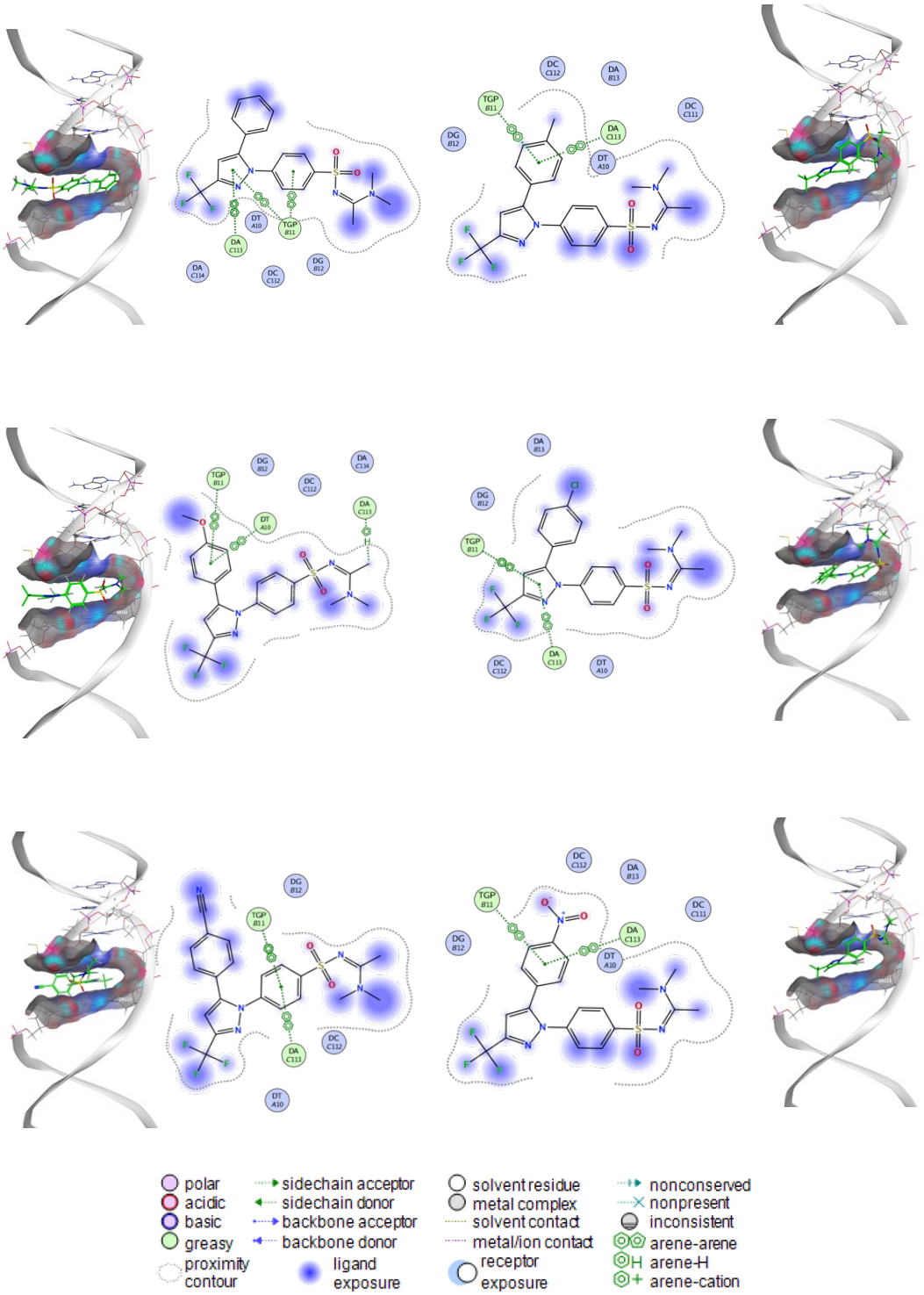

Figure 3. 2D and 3D docking poses showing interactions of compounds 1-4 in the binding sites of the active site of Human DNA Topoisomerase I, a ternary complex of the 70 kDa protein covalently bound to a 22-base pair DNA duplex (PDB ID: 1T8I).

This set of properties is entirely logical and points to the increased potential of this compound in the field of anticancer activity.

3.7 Molecular Docking Analysis within the Topoisomerase I–DNA Active Site

Molecular docking of compounds 1–6 into the active site of Human DNA Topoisomerase I, a ternary complex of the 70 kDa protein covalently bound to a 22-base pair DNA duplex, is shown in Table 3. This complex is similar to the DNA cleavage complex induced by camptothecin and other anticancer compounds of this class.

The docking score (S, kcal/mol) varies from -7.2398 to -7.6894 kcal/mol, indicating good affinity for all derivatives. Figure 3 showed the molecular interactions of compounds 1-6 with 1T8I in active site.

3.7.1 Binding Affinity Trends

The above trend clearly shows that electron-withdrawing groups increase the binding affinity (NO_2 (-7.6894) > CN (-7.5161) > Cl (-7.4809) > Me (-7.3477) > H (-7.2798) > OMe (-7.2398)), thus validating the electron structure analysis.

The NO_2 derivative is the highest binder, thus validating its higher anticancer potential by stabilizing the cleavage complex more than the others.

3.7.2 RMSD Analysis and Pose Stability

The RMSD value of Cl derivative showed the most stable orientation (1.31 Å), on contrast, the H derivative showed the least stable orientation (3.78 Å). RMSD values less than 2.0 Å are highly stable and reliable docking conformations. The high-affinity derivatives Cl and NO_2 have the least RMSD values, thus indicating optimal geometry in the enzyme/DNA interface.

3.7.3 Nature of Intermolecular Interactions

The major intermolecular interactions were found to be π – π stacking with the DNA bases (DA113 (deoxyadenosine), TGP11 (thymine-guanine phosphate region), and DT10 (deoxythymidine). The intermolecular distances vary from 3.34 to 3.77 Å, typical of strong aromatic interactions.

The CN derivative has the shortest π – π stacking (3.34 Å) and hence the highest binding affinity. The Cl and NO_2 derivatives also show the best π – π stacking distances, ranging from 3.35 to 3.56 Å. These results establish aromatic intercalation at the DNA cleavage site as the major binding mechanism.

The OMe derivative also shows a hydrogen – π interaction with the DA113 base (3.87 Å, −0.6 kcal/mol). Its binding score is, however, lower than the other derivatives despite the hydrogen – π interaction. This implies that hydrogen – π interactions are less significant than the best π – π interactions in stabilizing the complex at the DNA cleavage site.

3.7.4 Substituent Effects on Interfacial Binding

Electron-withdrawing groups are known to improve the binding affinity of the compounds by increasing the deficiency of the aromatic system, improving the π-π stacking complementarity with the nucleobases, reducing the electrostatic repulsion with the negatively charged phosphate backbone of the DNA, and increasing the geometric planarity of the intercalator.

On the other hand, the electron-donating groups OMe and Me will increase the electron density in the aromatic system, which might slightly decrease the stacking ability of the compounds in the π-rich environment of the DNA.

3.7.5 Comparison with the Cleavage Complex Stabilization Mechanism

Topoisomerase I poisons stabilize the covalent enzyme-DNA complex by intercalating into the DNA at the cleavage site. The docking results reveal that the compounds bind to the same interfacial area of the Top1-DNA complex, which overlaps with the canonical binding site of the Top1 poison.

Among the studied compounds, the stronger binders, NO_2 and CN, possess the following characteristics optimum stacking geometry, favorable interaction distances, low RMSD values, and improved electronic complementarity.

These findings support the hypothesis that the more electron-deficient compounds will more effectively stabilize the Topoisomerase I-DNA cleavage complex, which is the mechanism.

3.7.6 Integrated Docking-Electronic Interpretation

As the results of the docking studies correlate with the results of the DFT analysis, we can conclude that the lower HOMO gave stronger π–π stacking, the positive shift at N^1 lead to better electrostatic complementarity, and Stronger electron-withdrawing groups result in better docking score

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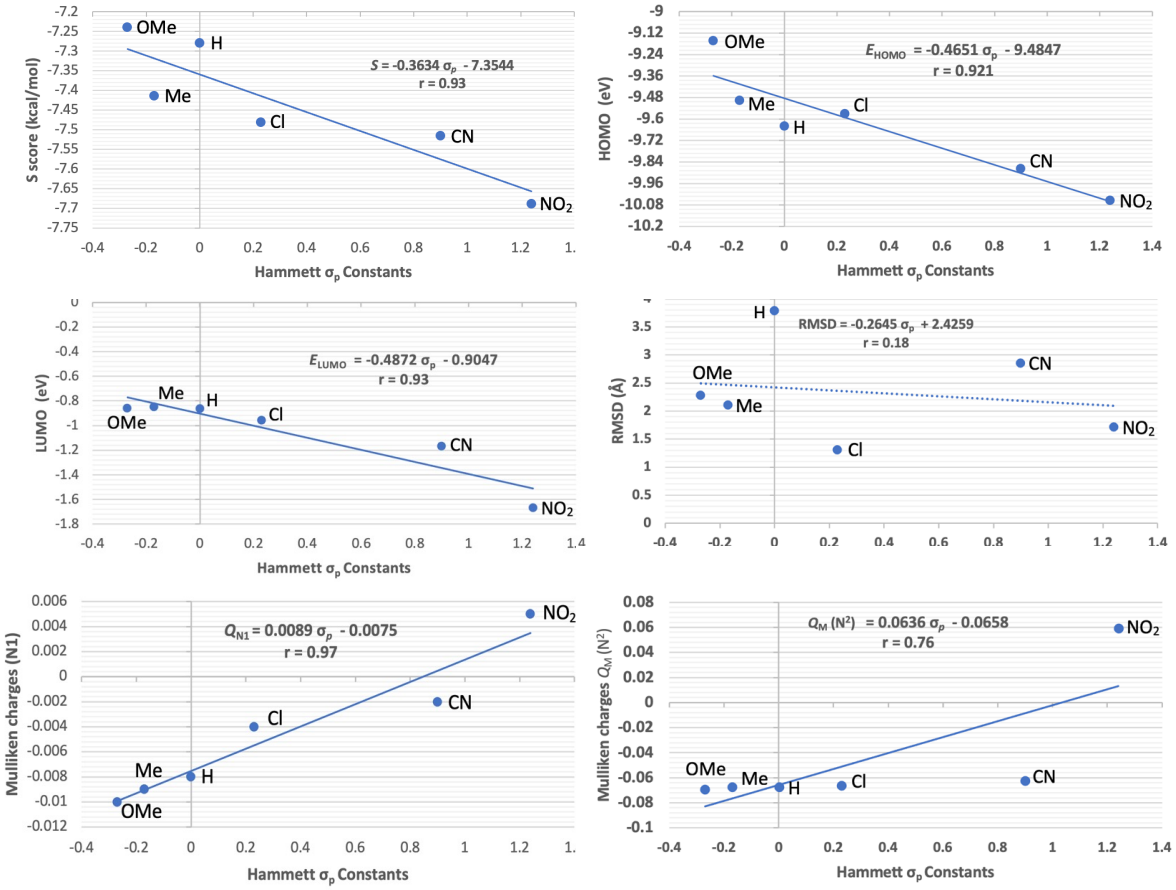

Figure 4. Linear correlation plots between Hammett substituent constants (σ_p) and the computed molecular descriptors S score, HOMO energy, LUMO energy, RMSD, and Mulliken charges at N^1 and N^2. The corresponding correlation coefficients (r) are indicated for each regression.

Thus, the better anticancer activity of the NO_2 and CN derivatives can be explained by the better electronic optimization of the interfacial binding in the Topoisomerase I-DNA complex.

3.7 Hammett Electronic Effects and Global Structure–Activity Correlation

To quantitatively evaluate the substituent electronic control, linear regression analyses were conducted between the Hammett σ_p constants and the important calculated parameters (S score, HOMO, LUMO, Mulliken charges and RMSD) (Figure 4)

3.7.1 Correlation Between σ_p and Docking Score (S)

$$S = -0.3609\,\sigma_p - 7.3516 \quad (r = -0.93)$$

A strong negative correlation further confirms that increasing the electron-withdrawing power enhances the binding affinity (as the absolute value of the S score increases). In addition, the fact that approximately 84% of the variation in binding is explained solely by the electronics of the substituents further confirms that the affinity for the Topoisomerase I-DNA cleavage complex is electronically controlled (Figure 4)

3.7.2 Correlation Between σ_p and HOMO Energy

$$E_{HOMO} = -0.4651\,\sigma_p - 9.4847 \quad (r = -0.92)$$

A strong negative correlation indicates that increasing σ_p significantly stabilizes HOMO energy.

Lower HOMO values in CN and NO_2 derivatives enhance aromatic stacking efficiency, oxidative stability, and interfacial electronic complementarity. The statistical significance confirms that substituent effects directly modulate frontier orbital energies (Figure 4).

3.7.3 Correlation Between σ_p and LUMO Energy

$$E_{LUMO} = -0.844\ \sigma_p - 0.794 \quad (r = -0.93)$$

Significantly, the LUMO energy is lowered by these electron-withdrawing groups, thus enhancing the electrophilicity and ability to transfer charge. This improves the stabilization in the π-rich medium at the site of cleavage. The high statistical significance reflects the predictability of this process (Figure 4).

3.7.4 Correlation Between σ_p and Mulliken Charge (Q_M) at N^1

$$Q_M(N^1) = 0.0089\ \sigma_p - 0.0075 \quad (r = 0.970)$$

A positive correlation of these values indicates that an increase in the value of σ_p would result in a decrease in the density of electrons at N^1.

The difference in the amount of charge, from -0.010 (OMe) to +0.005 (NO_2), is a clear indication that there is effective transmission of the electronic effects. The reduced density of electrons at the nitrogen atom is likely to increase the electrostatic complementarity with the negatively charged DNA backbone in the Topoisomerase I-DNA complex (Figure 4).

3.7.5 Correlation Between σ_p and Mulliken Charge (Q_M) at N^2

$$Q_M(N^2) = 0.0636\ \sigma_p - 0.0658 \quad (r = 0.76)$$

A statistically significant positive correlation verifies that substituent effects also play a role in N^2 charge distribution. Though slightly lower, the correlation for N^2 is still close to 79% explained by σ_p. This verifies the effect of global polarization of the heterocyclic core as a result of electronic substituent effects (Figure 4).

The highest correlations are found for LUMO energy and N^1 charge, verifying the impact of substituent electronic effects on electron acceptability and charge distribution. Binding affinity (S score) correlates strongly, though slightly lower, with all other descriptors.

3.7.6 Linear regression of RMSD versus Hammett σ_p constants

$$RMSD = -0.2645\ \sigma_p + 2.4259 \quad (r = 0.18)$$

In order to investigate the relationship between the Hammett substituent constants (σ_p) and docking RMSD values, a regression analysis was conducted. The equation obtained was RMSD = 2.425 - 0.264σ_p with a very low coefficient of determination R^2 = 0.034. Although the trend shows a weak negative relationship with a slight decrease in RMSD with an increase in electron-withdrawing ability, the statistical analysis shows that the substituent effects on the electronic properties do not significantly impact the conformational deviation within the binding site (Figure 3).

This shows that the variability of the RMSD values is probably controlled by steric and geometric effects rather than electronic effects.

4. Conclusion

In the present work, the electronic structure and binding characteristics of a set of modified compounds acting on Human DNA Topoisomerase I were examined using a combination of DFT, Hammett correlations, and docking studies. The findings clearly show that the anticancer potential of the compounds under consideration is strongly affected by their electronic characteristics, which can be adjusted according to the nature of the substituent groups.

In fact, the presence of electron-withdrawing groups has a great impact on the frontier molecular orbitals and charge distribution, which leads to stabilization of the Topoisomerase I-DNA cleavage complex. In more detail, the presence of NO_2 and CN functional groups increases the electrophilicity of the compound, decreases the electron density on the heteroatoms of the compound, and increases the π-π stacking interactions with the DNA bases, which leads to more effective binding with the enzyme. In fact, the docking studies confirm that the compounds containing electron-withdrawing groups exhibit higher binding affinity with the enzyme, as indicated by the lower values of RMSD and the interplanar distances between the compound and the

DNA base pair, with NO_2 being the best compound among the set of compounds under consideration.

This is confirmed by the results obtained from the statistical correlation analysis, showing that Hammett σ_p constants can be used as good predictors for the variations in electronic structure caused by the substituents. Among the parameters calculated in the present study, LUMO energies and Mulliken charge at N^1 showed the highest correlation with substituents' effects and binding affinity, thus emphasizing the electronic modulation effect in determining biological activity.

In summary, the present study establishes a quantitative electronic structure activity relationship for topoisomerase I inhibitors and proves that using a combination of Hammett substituents' parameters, DFT calculations, and molecular docking is a powerful tool in the rational design of new anticancer drugs. It is proposed that an efficient way to optimize the electronic structure and biological activity of topoisomerase I inhibitors is to strategically incorporate electron-withdrawing substituents into their structure.

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