Advanced Journal of Scientific Research
www.advjsr.edu.iq

Electronic Structure–Binding Affinity Correlation of Sulfur/Selenium-Modified AZT Derivatives Targeting HIV-1 M184V Reverse Transcriptase

Manar M. Al-Ahmed [a], Hasan Y. Al-Buzayd[b]

[a]Department of Anesthesia Techniques, Alsharq College of Specialized Technical Sciences, Basrah, Iraq
[b]Department of Radiology Techniques, Alsharq College of Specialized Technical Sciences, Basrah, Iraq
Email: manar.mahmoud@shau.edu.iq

ABSTRACT

The emergence of drug resistance caused by mutations in HIV-1 reverse transcriptase (RT), particularly M184V, significantly compromises the clinical efficacy of nucleoside reverse transcriptase inhibitors such as azidothymidine (AZT). In this study, sulfur- and selenium-modified AZT derivatives were rationally designed to enhance electronic properties and improve binding performance against the HIV-1 M184V RT–DNA complex (PDB ID: 6UIR). A combined density functional theory (DFT) and molecular docking approach was employed to elucidate structure–activity relationships and identify key electronic determinants governing target recognition.

Frontier molecular orbital analysis reveals that compound 1 stands out with the smallest HOMO-LUMO gap, which means it's the most reactive of the group. Its strong docking score and solid hydrogen bonding with the mutated active site back this up. Compound 3, on the other hand, has a bigger HOMO-LUMO gap. So, it's more kinetically stable but doesn't bind as well. What's interesting is compound 2—a much higher dipole moment gives it better electrostatic complementarity and stronger stabilizing interactions with the M184V RT enzyme.

All in all, these results make it clear: electronic reactivity and molecular polarity matter a lot when you're looking at how ligands interact with reverse transcriptase in drug-resistant variants. Knowing this gives researchers a smarter way to design second-generation AZT inhibitors that actually work against resistant forms of HIV.

Keywords: 3'-Azido-3'-Deoxythymidine (AZT), HIV-1 reverse transcriptase (RT), density functional theory (DFT), molecular docking,
Received: 15/11/2025 Accepted: 04/01/2026 Published: 31/03/2026

1. Introduction

Zidovudine or 3'-azido-3'-deoxythymidine (AZT) has been widely used in the treatment of HIV/AIDS, and was a well- accepted nucleoside reverse transcriptase inhibitor (NRTI).[1,2] AZT works by selectively inhibiting the HIV-1 reverse transcriptase (RT) enzyme, the enzyme that the virus uses to make a DNA copy of its RNA and terminating viral DNA chain elongation. Its antiviral efficacy depends on intracellular phosphorylation by host cellular kinases to form the active metabolite AZT-5'-triphosphate (AZT-TP), which competes with the natural substrate deoxythymidine triphosphate (dTTP) for incorporation by HIV-1 reverse transcriptase; owing to the absence of a 3'-hydroxyl group, AZT-TP acts as an obligate chain terminator, a mechanism that underpins its interaction profile and binding behavior explored in the present computational study.[3,4]

Despite its clinical relevance, zidovudine is associated with both common and severe adverse effects, including gastrointestinal symptoms, bone marrow suppression, mitochondrial toxicity, and lipodystrophy following long-term therapy. These limitations constrain its therapeutic applicability and motivate the rational design of improved nucleoside analogues, as explored in this computational study. [5-8]

Structural modification of the AZT (Figure 1) scaffold offers a rational approach to overcoming its limitations. The tetrahydrofuran (THF) ring, a nucleoside moiety of AZT plays a critical for molecular recognition and binding within the reverse transcriptase (RT) active site.

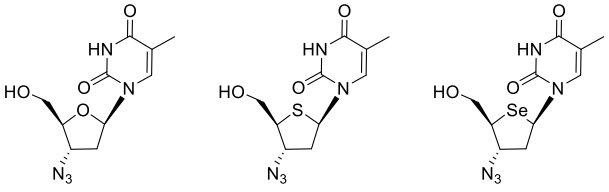

Figure 1: The structure of 3'-azido-3'-deoxythymidine (AZT) derivative

Substituting the oxygen atom with sulfur or selenium within the THF ring is expected to alter modulate

molecular polarity, polarizability, and electronic distribution. Sulfur and selenium have larger atomic radii as compared with oxygen, so we expect enhanced polarizability, which may strengthen non-covalent interactions—including hydrogen bonding, electrostatic interactions, and van der Waals forces—thereby improving binding affinity and stability within the enzyme active site. [9,10]

The major challenge of chemists in HIV therapy is remain drug resistance. The most clinically significant mutations affecting the efficacy of nucleoside reverse transcriptase inhibitors with the M184V mutation is HIV-1 reverse transcriptase This mutation alters both the geometry and electrostatic environment of the RT active site, leading to reduced susceptibility to several nucleoside analogues. To investigate the binding behavior of AZT derivatives against this resistant form of the enzyme, molecular docking studies were conducted using the HIV-1 M184V reverse transcriptase–DNA complex bound to the FTC-TP subunit (PDB ID: 6UIR), which provides a biologically relevant crystallographic model for evaluating ligand–enzyme interactions in the context of drug resistance. [11]

In the present study, AZT and two novel derivatives incorporating sulfur and selenium atoms into the tetrahydrofuran ring were investigated using a combination of density functional theory (DFT) and molecular docking approaches. DFT calculations have been used to examine frontier molecular orbitals (HOMO–LUMO), Δ*E* (eV), and dipole moment (μ), providing understanding of molecular stability and interaction capability. These electronic parameters were subsequently connected with molecular docking results, showing that compounds exhibiting lower HOMO–LUMO energy gaps and enhanced molecular polarity tended to display stronger binding affinities and more favorable interaction patterns within the RT active site. Molecular docking simulations further elucidated binding modes, binding affinities, inhibition constants (Ki), and root mean square deviation (RMSD) values, while key intermolecular interactions—including hydrogen bonds, π-anion, π-alkyl, π-cation interactions, and salt bridges—were analyzed using both two- and three-dimensional visualizations. Collectively, this integrated computational strategy provides a comprehensive structure–activity relationship and supports the rational design of improved AZT-based NRTIs with potential efficacy against resistant HIV-1 strains.

2. Molecular docking

Molecular docking was employed to investigate the binding affinity of selected synthesized compounds toward the human immunodeficiency virus type 1 (HIV-1) M184V reverse transcriptase–DNA complex bound to the FTC-TP subunit (PDB ID: 6UIR). The crystal structure of the HIV-1 M184V reverse transcriptase–DNA complex with (−)-FTC-TP was retrieved from the Protein Data Bank. [12,13]

3. Preparation of Ligand and Receptor

The binding site of the HIV-1 M184V reverse transcriptase–DNA complex co-crystallized with (−)-FTC-TP (PDB ID: 6UIR) was selected as the receptor and retrieved from the Protein Data Bank. All heteroatoms and crystallographic water molecules were removed prior to docking. The receptor structure was refined by checking for missing atoms and correcting structural inconsistencies and then the hydrogen atoms were added. AutoDock Tools (version 1.5.7) was employed to assign atom types, add polar hydrogens, and define the receptor as rigid while allowing full flexibility of the ligands.[12]

4. Computational methods

4.1 Density functional theory

The molecular structures of compounds 1–3 were optimized using density functional theory (DFT) at the B3LYP/6-311G(d,p) level to obtain their most stable conformations. All quantum chemical calculations, including the evaluation of global reactivity descriptors, were performed using the Gaussian 09 software package.[14]

5. Results and discussion

5.1 Density functional theory

The calculated total energies, frontier molecular orbital energies (HOMO and LUMO), HOMO–LUMO energy gaps (ΔE), and dipole moments (μ) of compounds 1–3 are presented in Table 1

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

Comp no.	Total energy (eV)	HOMO	LUMO	Δ *E*	μ
1	-25446.6037	-0.12428	0.01515	0.13943	3.7877
2	-34143.8403	-0.13382	0.02105	0.15487	3.9497
3	-88051.9075	-0.14177	0.01933	0.16110	3.6989

The total energy values indicate that compound 3 possesses the highest thermodynamic stability, as evidenced by its most negative total energy (−88051.9075 eV), whereas compound 1 exhibits the lowest stability among the investigated compounds.

A gradual decrease in HOMO energy is observed from compound 1 (−0.12428 eV) to compound 3 (−0.14177 eV), suggesting a reduced electron-donating capability with increasing compound index. In contrast, the LUMO energy values show only minor variations, reflecting comparable electron-accepting tendencies across the studied molecules. The HOMO–LUMO energy gap increases in the order of compound 1 (0.13943 eV) < compound 2 (0.15487 eV) < compound 3 (0.16110 eV). This trend indicates that compound 1 is expected to exhibit higher chemical reactivity, while compound 3 demonstrates enhanced kinetic stability and lower reactivity.

The calculated dipole moments further differentiate the electronic properties of the compounds. Compound 2 displays the highest dipole moment (3.9497 D), indicating increased molecular polarity, which may favor stronger electrostatic interactions with polar environments or biological targets. Overall, the frontier molecular orbital analysis reveals a clear relationship between electronic structure, stability, and reactivity, providing valuable insight into the physicochemical behavior of the investigated compounds.

5.2 Molecular Docking Study

Molecular docking simulations were performed using the Molecular Operating Environment (MOE, 2015) to investigate the binding sites and interaction patterns of the examined ligands within the largest active site of the HIV-1 M184V reverse transcriptase–DNA complex (PDB ID: 6UIR), as identified by the Site Finder module. The crystal structure, resolved at 2.64 Å, is provides sufficient resolution for reliable structure-based docking studies.

An induced-fit docking protocol was applied, allowing flexibility of both the ligands and key amino acid residues of the protein. Each ligand was permitted to form up to five interactions with active site residues (Figure 2). Protein structures with resolutions around 2.0–3.0 Å are widely used in molecular docking studies, and RMSD values close to or below 2.5 Å and binding energies ≤ −7.0 kcal/mol are generally considered indicative of reliable docking poses. The binding poses and key interactions of the three compounds (1–3) are illustrated in Figure 2, whereas docking scores, hydrogen bond interactions, participating atoms, and corresponding binding energies for all studied compounds are summarized in Table 2.

5.3 Structure–Activity Relationship Based on DFT and Molecular Docking

The correlating of frontier molecular orbital (FMO) descriptors obtained from DFT calculations with the molecular docking behavior within the active site of HIV-1 M184V reverse transcriptase (PDB ID: 6UIR) was used to elucidate the structure–activity relationship of compounds 1–3. The analysis of combined results provides mechanistic insight into how electronic properties govern ligand–protein interactions.

Compound 1 showed highest chemical reactivity among the studied compounds as we can see from the smallest HOMO–LUMO energy gap (ΔE = 0.13943 eV), This enhanced reactivity is compatible with its most favorable docking score (−5.2098 kcal/mol), Pointing strong affinity toward the active site.

Table 2. The results obtained from docking of compounds 1-3 with 6UIR in active site

Comp. no.	S score kcal/mol)	RMSD (Å)	Bonds between atoms of compounds and residues of active site 1 of 1R42					
			Atom of compound	Atom of receptor	Involved receptor residues	Type of interaction bond	Distance (Å)	E (kcal/mol)
Comp 1	-5.2098	2.2975	O 15	O	HOH 717	H-donor	2.94	-1.2
			C 18	OD2	ASP 67	H-donor	3.32	-1.3
			N 32	O	HOH 718	H-acceptor	3.22	-2.3
Comp 2	-4.7494	2.1253	O 15	OE1	GLN 242	H- donor	2.99	-0.7
			O 15	N	GLY 231	H-acceptor	3.01	-2.2
Comp 3	-4.9815	1.8715	SE 17	OD2	ASP 67	H-donor	3.41	-0.1
			O 3	NZ	LYS 220	H-acceptor	2.99	-4.4
			O 7	NH2	ARG 72	H-acceptor	3.33	-3.5
			N 32	NE2	GLN 222	H-acceptor	3.21	-5.7

The higher value of HOMO energy facilitates electron donation, encouraging of formation effective hydrogen bond with both active site residues (ASP67) and structural water molecules (HOH 717 and HOH 718). Despite of a slightly higher RMSD value, these interactions participate to stabilizing the ligand within the binding pocket, reflecting moderate conformational flexibility.

On the other hand, compound 3 showed the largest HOMO–LUMO energy gap (ΔE = 0.16110 eV), revealing of greater kinetic stability along with reduced chemical reactivity. This electronic stabilization is reflected in its comparatively weaker docking performance, suggesting a lower predilection to engage in strong intermolecular interactions with 6UIR in active site. Moreover, the lower HOMO energy of compound 3 limits its electron-donating ability, reducing the strength and number of hydrogen bonding interactions within the active site of the HIV-1 M184V reverse transcriptase–DNA complex.

The highest dipole moment (μ = 3.9497 D) of compound 2 and intermediate ΔE energy value (0.15487 eV), reflecting increased molecular polarity. This electronic feature is strongly connected to its docking behavior. However, compound 3 formed multiple hydrogen bond interactions (ligand–protein interactions) with polar and charged amino acids such as LYS220, ARG72, and GLN222. Conspicuously, several interactions displayed high binding energies (up to −5.7 kcal/mol) and short interaction distances, accompanied by the lowest RMSD value (1.8715 Å) among the studied compounds. These findings suggest that molecular polarity, rather than maximum reactivity alone, plays an important role in the stability of ligand – protein (active site of HIV-1 M184V reverse transcriptase) complexes via electrostatic and hydrogen bonding interactions.

Overall, the combined DFT and molecular docking analyses reveal that smaller HOMO–LUMO energy gaps contribute to improve binding affinity by increasing molecular reactivity, while higher dipole moments (μ) enhance binding stability via stronger electrostatic interactions. This combined interaction accounts for the favorable docking performance of compounds 1 and 2 and emphasize the necessity of optimizing both electronic reactivity and molecular polarity in the rational design of potent HIV-1 reverse transcriptase inhibitors.

6. Conclusion

This work presents a comprehensive computational evaluation of zidovudine (AZT) and two sulfur- and selenium-modified AZT derivatives targeting the drug-resistant HIV-1 M184V reverse transcriptase–DNA complex (PDB ID: 6UIR). By integrating density functional theory (DFT) calculations with molecular docking analyses, clear correlations between electronic structure, binding affinity, and interaction stability were established.

According to DFT results, compound 1 showed the smallest HOMO–LUMO energy gap, indicative of enhanced chemical reactivity, which translated into the most favorable docking score and strong hydrogen-bond interactions within the 6UIR in active site. On the other hand, high kinetic stability in compound 3 reduced overall binding affinity, despite forming multiple

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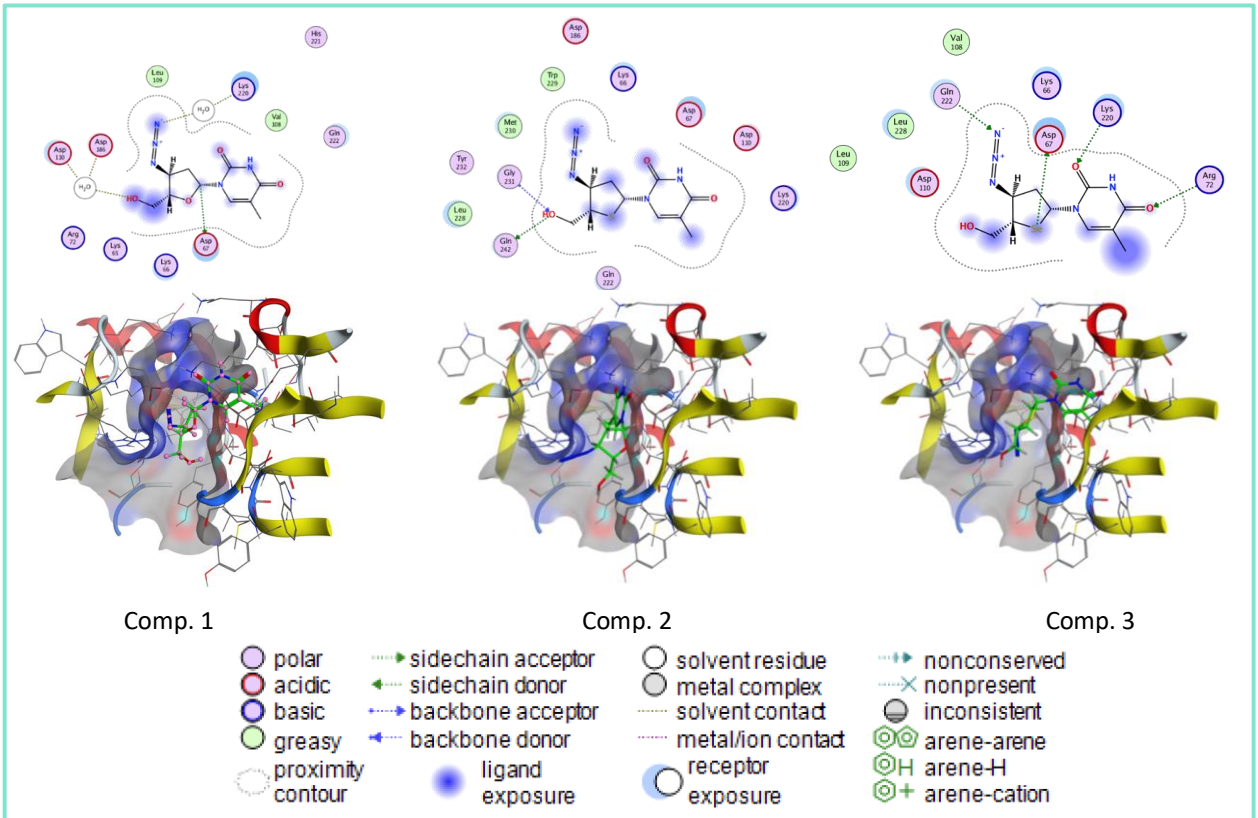

Figure 2: 2D and 3D Binding interaction of compound 1-3 in the active site 1 of 6UIR.

stabilizing interactions, that's mean the reactivity alone does not govern binding behavior. Importantly, compound 2, with the highest dipole moment (3.7877 D) showed that the increasing in molecular polarity significantly enhances electrostatic and hydrogen-bond interactions, resulting in stable ligand–protein complexes with low RMSD values.

Collectively, these findings demonstrate that optimal inhibition of HIV-1 reverse transcriptase requires a balanced interplay between electronic reactivity and molecular polarity rather than reliance on a single descriptor. The sulfur and selenium-modified AZT scaffolds investigated herein exhibit improved binding characteristics relative to the parent ligand and provide a rational framework for the development of next-generation nucleoside reverse transcriptase inhibitors with potential efficacy against resistant HIV-1 variants. This study underscores the utility of integrated DFT–docking strategies in guiding the rational design of antiviral agents targeting clinically relevant resistance mutations.

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