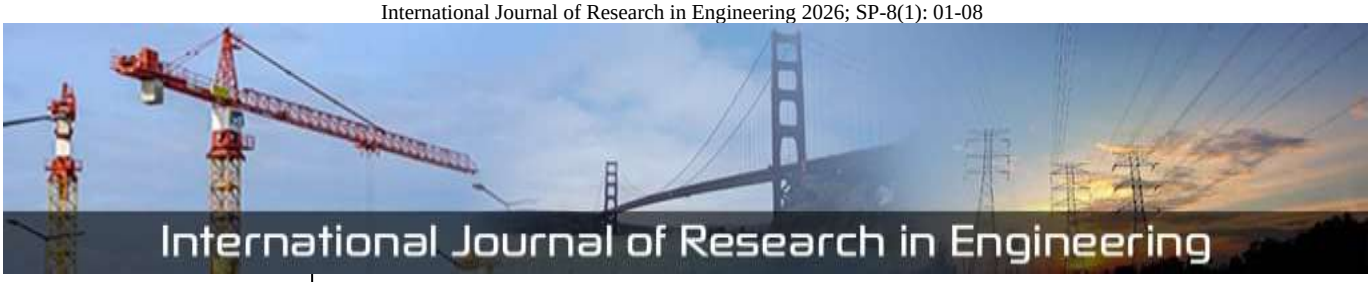

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A comprehensive study on the pharmacological potential of dibenzoxepine scaffolds

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Abstract
In the present work, molecular docking evaluation were conducted against a range of biologically significant targets to investigate the multitarget pharmacological potential of dibenzoxepine derivatives using the autodock software. Antibacterial activity was assessed using bacterial enzyme structures, including *Staphylococcus aureus* Gyrase B (PDB ID: 3G75, 2XCQ, 2P6F), and the DNA gyrase catalytic core (PDB ID: 2XCQ). Antifungal potential was examined through interactions with key fungal proteins such as *Saccharomyces cerevisiae* N-myristoyltransferase (2P6F). The docking analyses revealed strong binding affinities across all evaluated targets, suggesting that the dibenzoxepine scaffold exhibits a promising multitarget interaction profile that may account for its diverse pharmacological properties. Significant interactions with bacterial and fungal enzymes support its potential antimicrobial efficacy, while notable affinity for neurotransmitter transporters implies possible modulation of central nervous system pathways related to antidepressant effects. Overall, these findings provide meaningful structural insights that could guide the rational design and development of dibenzoxepine-based multifunctional therapeutic agents

Keywords: Dibenzoxepine; pharmacological; neurotransmitter; serotonin

Introduction
Dibenzoxepinone is a tricyclic organic scaffold composed of two fused benzene rings and a seven-membered oxepine ring. This structural framework underpins a variety of pharmacologically important derivatives with reported antitumor, antibacterial, antihistaminic, antidepressant, and anti-inflammatory activities [1–3]. A well-known derivative Doxepin, which is widely prescribed for depression and anxiety and is also used in the management of chronic dermatological conditions such as urticaria [4–5].

The structural versatility of the dibenzoxepinone core allows extensive chemical modification, making it an attractive scaffold in medicinal chemistry. In particular, its derivatives have demonstrated promising antibacterial potential, likely due to the unique tricyclic system that facilitates interactions with diverse bacterial targets [6]. Structural modifications of the dibenzoxepinone nucleus have led to enhanced activity against both Gram-positive and Gram-negative bacteria [7]. These compounds are reported to exert their effects through mechanisms such as disruption of bacterial cell wall integrity, inhibition of DNA replication, or interference with key bacterial enzymes.

Beyond antibacterial applications, several dibenzoxepinone derivatives are under investigation as potential anticancer agents [8]. Structural tailoring enables interaction with critical cellular pathways in cancer cells, leading to inhibition of cell proliferation, enzyme suppression, DNA interference, or induction of apoptosis. Their favorable physicochemical properties may also support efficient cellular uptake, further enhancing their therapeutic promise [9].

Motivated by the diverse biological significance of dibenzoxepinone and our ongoing research interest in heterocyclic compounds [10–14], we designed a series of novel derivatives by introducing amine substituents onto one of the aromatic rings through feasible synthetic routes.

Molecular docking studies were performed against selected antibacterial, antifungal, and ct-

DNA targets using the Protein Data Bank (PDB) entries 3G75, 2XCQ & 2P6F through AutoDock 4.2 [15–17]. These studies provided insights into binding energies, ligand–protein interactions, and the nature of intermolecular bonding.

In – Silico Study

Molecular Docking

Protein Preparation

The crystal structures of the target proteins—DNA gyrase (PDB ID: 3G75; antibacterial target), N-myristoyltransferase (PDB ID: 2P6F; antifungal target), and the DNA dodecamer (PDB ID: 2XCQ; ct-DNA activity)—were retrieved from the RCSB Protein Data Bank (www.pdb.org) [18–20]. Each structure contained multiple subunits; therefore, all chains except chain A were removed, along with water molecules and heteroatoms. Kollman charges and polar hydrogen atoms were subsequently added to chain A, including the relevant amino acid residues involved in ligand binding.

Binding Site

The binding site is the specific region of a target molecule—typically a protein—where a ligand interacts and binds. It generally consists of particular amino acid residues located on the protein surface or within a cavity, which engage with the ligand through various intermolecular forces. Table 1 lists the binding sites of different proteins, including clorobiocin-bound DNA gyrase, N-myristoyltransferase, and the DNA dodecamer.

Validation of Docking

The crystal structures of DNA gyrase and N-myristoyltransferase are complexed with ligands in chain A. The active sites were determined by referring to reported binding site data in the literature and visualized using Biovia Discovery Studio 2021 [21]. To validate the docking protocol, the co-crystallized ligands of DNA gyrase (3G75) and N-myristoyltransferase (2P6F) were extracted and re-docked into chain A of their respective proteins using the same grid coordinates. Docking performance was assessed based on the root mean square deviation (RMSD) values, which should ideally be below 2 Å. This validation step ensures the reliability and accuracy of the selected docking approach.

Docking procedure

The compounds were subjected to molecular docking using AutoDock 4.2. All the compounds and proteins were set in a cubic grid box having dimensions 60 Å (12.614x, 48.765y, -0.410z) for antifungal activity against *C. albicans* (PDB: 1D: 2P6F), 60 Å (19.587x, 19.118y, 45.257z) for antibacterial activity against *E.coli* (PDB: ID 3G75), and 120 Å (15.011x, 22.550y, 10.822z) for ct-DNA (PDB: ID 2XCQ) with a default spacing 0.675 Å. 10 conformations were obtained for every compound and a grid map was added using Autogrid 4.2. Docking calculation was performed by using AutoDock 4.2. The analysis of interactions between the protein and compounds was evaluated using Biovia Discovery Studio 2021.

ADME and Physicochemical (Drug Likeliness) Properties

An ADME (Absorption, Distribution, Metabolism, and Excretion) study evaluates the pharmacokinetic behavior of chemical compounds within a biological system. All pharmacokinetic parameters were calculated using the PreADMET online server. This analysis provides detailed insight into how compounds are absorbed, distributed, metabolized, and eliminated in the body. These properties are essential in drug development, as they influence therapeutic efficacy while minimizing potential side effects. Parameters such as blood–brain barrier (BBB) penetration, plasma protein binding (PPB), and skin permeability, among others, are commonly used to assess drug toxicity and safety profiles [22].

Physicochemical properties help predict whether a compound possesses characteristics suitable for drug candidacy. Parameters including LogP, polar surface area (PSA), molecular weight, and number of heavy atoms were calculated using the Molinspiration online server (www.molinspiration.com). These parameters serve as guidelines under Lipinski's rule of five to evaluate drug-likeness. Compounds with no more than one violation of Lipinski's criteria are generally considered suitable for oral activity [23].

Bioactivity scores such as those for GPCR ligands, kinase inhibitors, protease inhibitors, and ion channel modulators reflect the potential interaction between drugs and their biological targets. The Molinspiration online server was also used to estimate the bioactivity scores of the ligands. A compound is considered active if its bioactivity score is greater than 0.0, moderately active if it ranges between −5.0 and 0.0, and inactive if it is below −5.0 [24].

Result and Discussion

Molecular Docking

Active site of protein and validation of docking

The functionality of a protein is largely determined by the active binding site. To investigate and identify the active site residues involved in docking, the substrate chlorobiocin and N-myristoyl-transferase were utilized. This substrate was obtained from PDB:1D 3G75, 2XCQ, and 2P6F, accessed via the RCSB PDB database. The active binding site, comprising the amino acid residues listed in Table 1**,** was analyzed. The same docking methodology was applied for validation. The re-docked complex and the co-crystallized complex of the antibacterial protein and antifungal protein was superimposed using Biovia Discovery Studio 2021 (version 21.2). Root-mean-square (RMSD) values of 1.54 Å and 0.98 Å were obtained, as illustrated in Figures 1 and 2 demonstrating the high precision in the docking procedure.

Table 1: Amino acids present at the active binding site for antimicrobial activities.

PDB:ID	Amino acids at the active site
3G75	TYR119, TYR225, TYR107, TYR119, PHE339, PHE117, PHE240, PHE176, ILE111, ILE352, LEU451, LEU394, HIS227, CYS393, ASP110, ASN175, ASN392
2PF6	ARG76, ARG136, ARF186, ARG22, TYR26, TYR165, ILE90, ILE78, VAL71, ASP73, ASN46, PRO79, HIS95, GLU50, GLY77

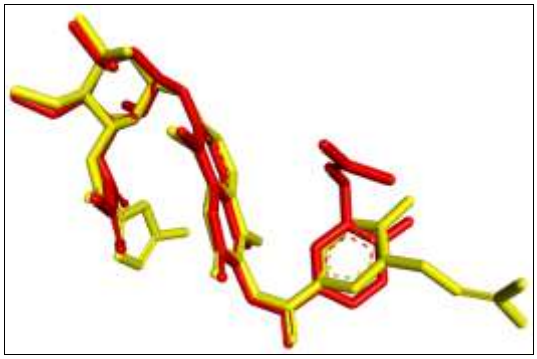


Fig 1: Validation of the Docking methodology by superimposing re-docked chlorobiocin (yellow color) with co-crystallized protein complex (red) with a RMSD: 1.54 Å.

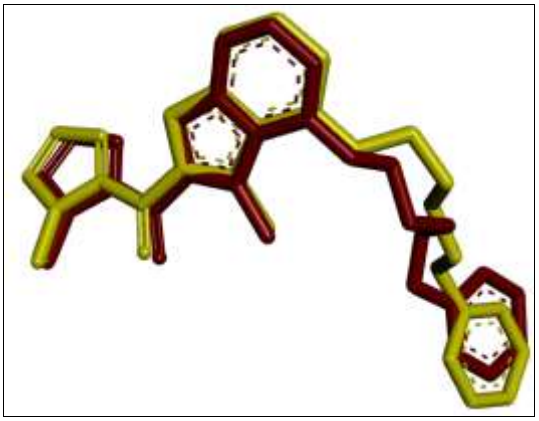


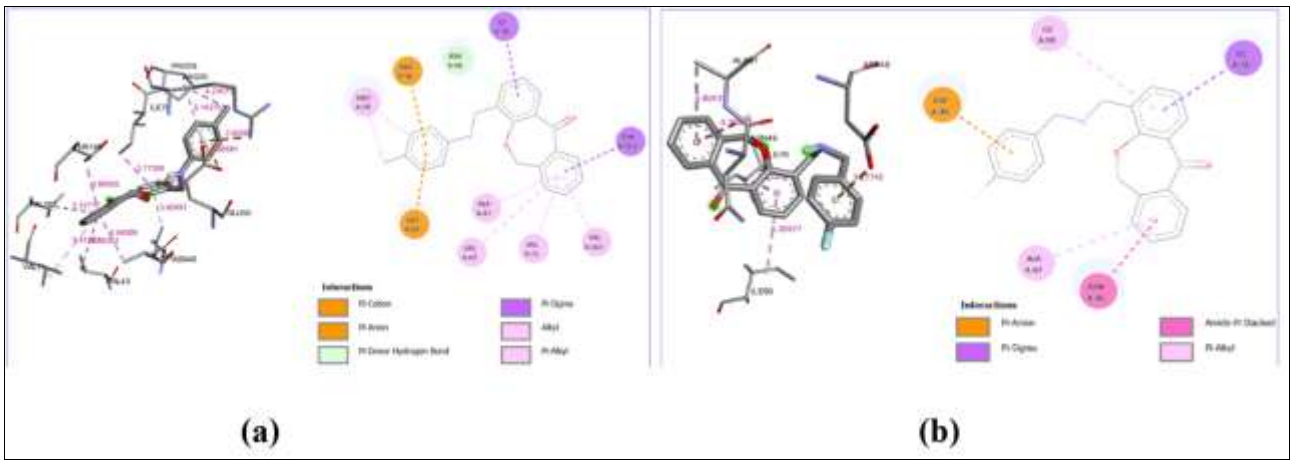
Fig 2: Validation of the Docking methodology by superimposing re-docked N-myristoyl transferase (yellow color) with co-crystallized protein complex (dark red) with a RMSD: 0.98 Å.

Antibacterial Molecular Docking

All the synthesized compounds 7(a–f) were subjected to molecular docking studies against the antibacterial target DNA gyrase from Staphylococcus aureus (PDB ID: 3G75) to investigate their interactions with the protein. DNA gyrase is an essential antibacterial target responsible for maintaining DNA supercoiling, a process crucial for replication, transcription, and other cellular activities.

Clorobiocin acts by binding to the ATP-binding pocket of the GyrB subunit of DNA gyrase, thereby inhibiting ATP hydrolysis, a key step required for the enzyme's catalytic function. As an aminocoumarin antibiotic, clorobiocin specifically targets the GyrB subunit of this essential type II topoisomerase.

The docking results indicated that all synthesized compounds exhibited favorable binding interactions with various amino acid residues in the active site through different types of bonding interactions. The calculated binding energies ranged from –7.0 to –10.0 kcal/mol. Among the tested compounds, compound 7a demonstrated the strongest binding affinity, with a binding energy of –10.2 kcal/mol (Table 2). It formed a π-donor hydrogen bond with ASN 46 and π–sigma interactions with ILE 78 and THR 165. Detailed binding interactions are illustrated in Figure 3.



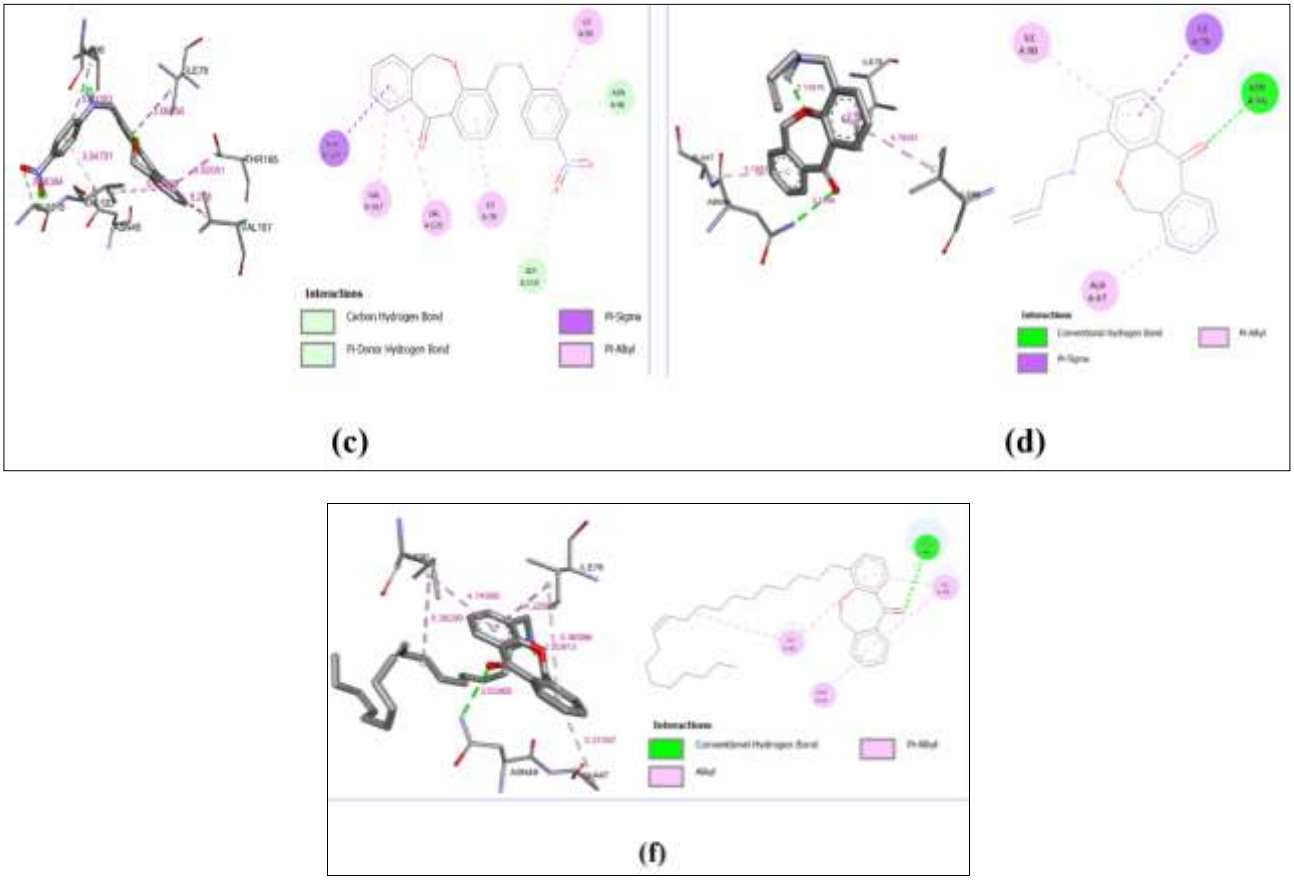


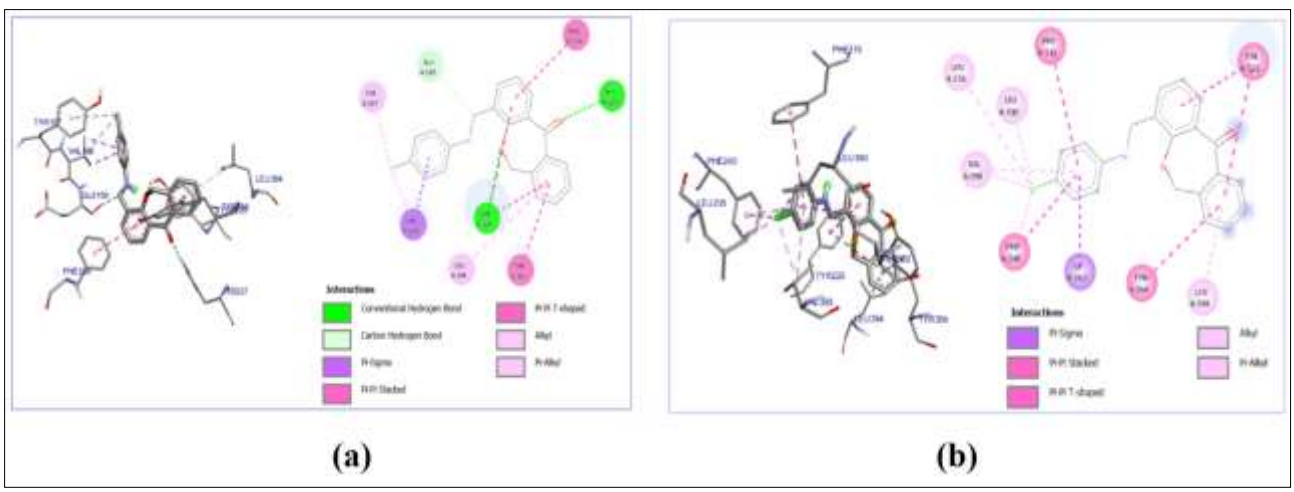
Fig 3: 3D and 2D interaction diagram of compound 7(a-f) with *S. aureus* bacterial protein (PDB ID: 3G75).

Antifungal Molecular Docking

Molecular docking studies of compounds 7(a–f) were carried out against N-myristoyl transferase from Saccharomyces cerevisiae (PDB ID: 2P6F). N-myristoyl transferase (NMT) is an essential single-subunit enzyme that catalyzes the covalent attachment of the 14-carbon fatty acid myristate to the N-terminal glycine residue of specific substrate proteins. This modification occurs in both co-translational and post-translational processes. The enzyme transfers myristate from myristoyl-CoA to various eukaryotic and viral proteins, thereby regulating their membrane localization and biological activity.

The crystal structure (PDB ID: 2P6F) represents NMT, a key enzyme involved in fungal survival and closely associated with ergosterol biosynthesis, an essential component of fungal cell membranes. Inhibition of this enzyme disrupts ergosterol formation, compromising membrane integrity and ultimately leading to fungal cell death.

The docking results showed that the binding energies of the tested compounds ranged from –8.3 to –11.8 kcal/mol (Table 2), indicating strong binding affinities toward the target protein. Among them, compound 7a exhibited the lowest binding energy (–11.8 kcal/mol), suggesting the highest affinity. It formed conventional hydrogen bonds with TYR 225 and HIS 227, a carbon–hydrogen bond with GLU 109, a π–sigma interaction with VAL 108, and alkyl and π–alkyl interactions with LEU 394 and TYR 107, as illustrated in Figure 4.



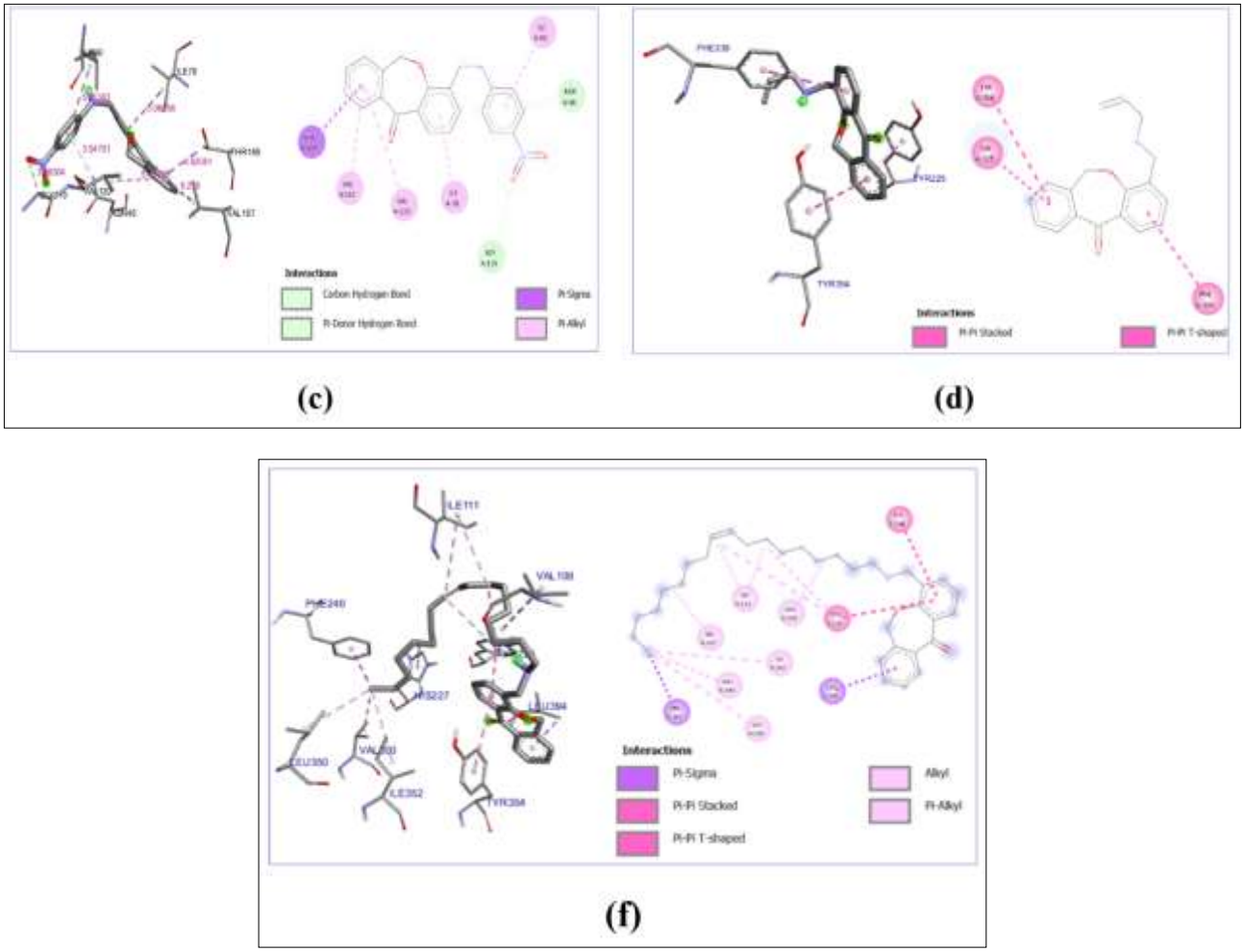
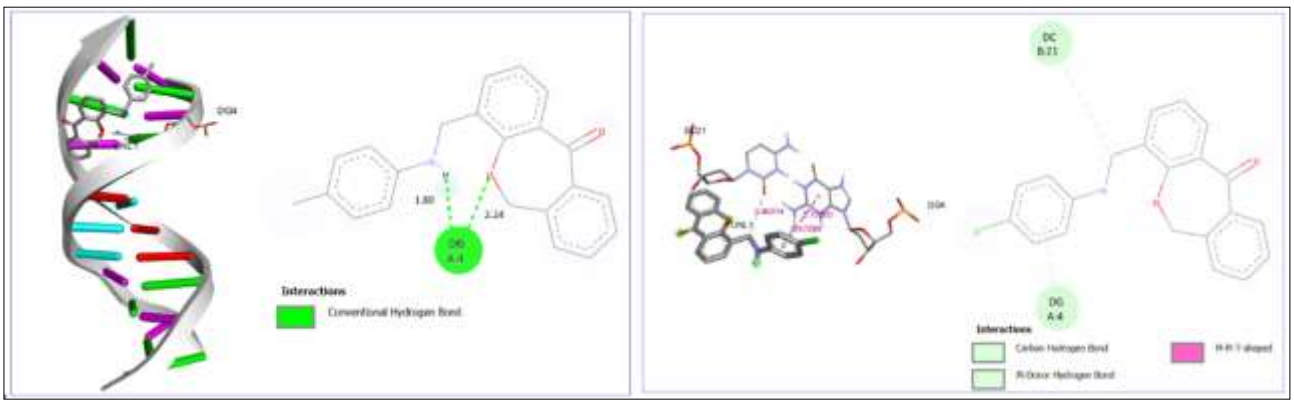


Fig 4: 3D and 2D interaction diagram of compound 7(a-f) with antifungal protein (PDB ID: 2P6F).

Molecular Docking with ct-DNA

The molecular docking results revealed that the synthesized derivative **7a** preferentially binds within the AT-rich minor groove of the DNA sequence rather than at the terminal G–C base pairs. A DNA dodecamer, consisting of 12 base pairs, is commonly used as a model system in structural and biochemical investigations of DNA. In this study, ligand 7a aligned well with the natural curvature of the DNA dodecamer and adopted a groove-binding mode, as illustrated in Figure 5.

Conventional hydrogen bonding played a crucial role in stabilizing the interaction between ligand 7a and DNA, with a minimum binding energy of –8.0 kcal/mol. Specifically, hydrogen bonds were formed between the carboxylic acid group of the ligand and the guanosine residue of the A strand (bond length: 2.24 Å), as well as between the NH group of the ligand and another guanosine residue of the A strand (bond length: 1.80 Å), as shown in the 2D interaction diagram.



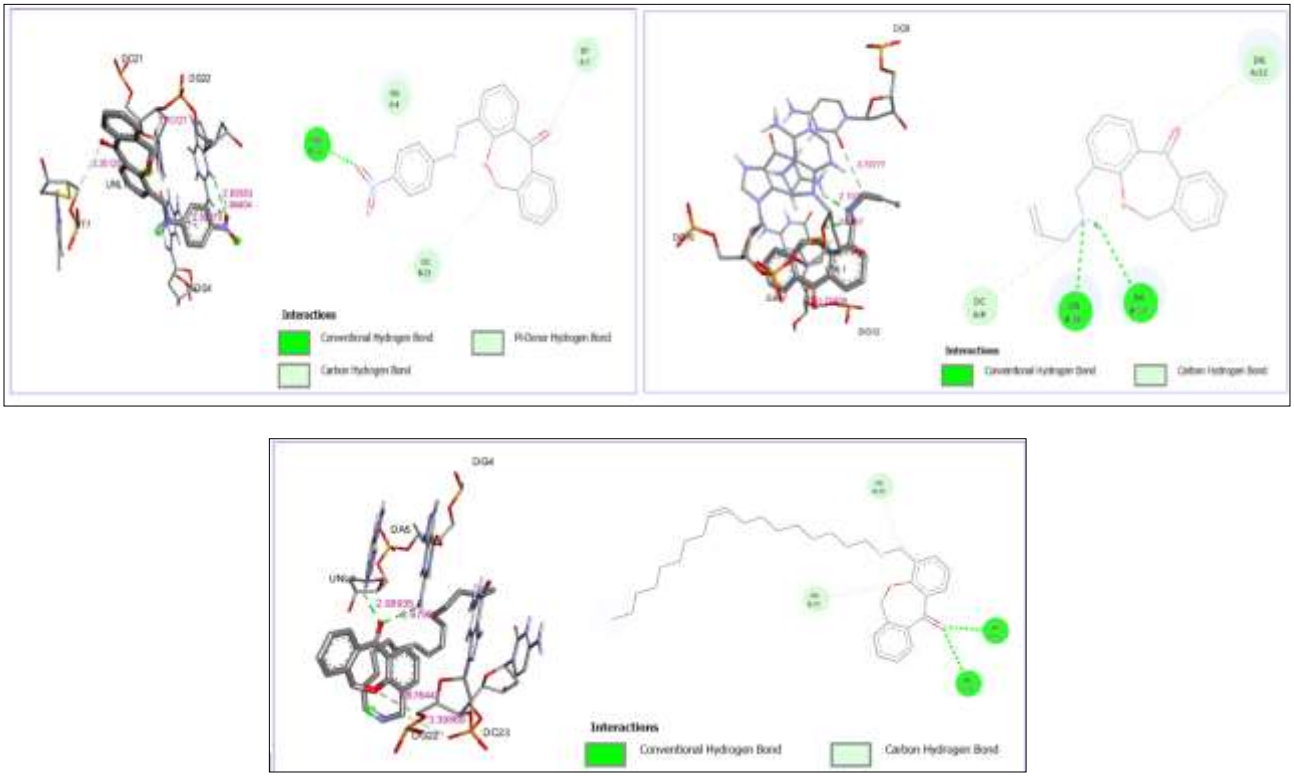
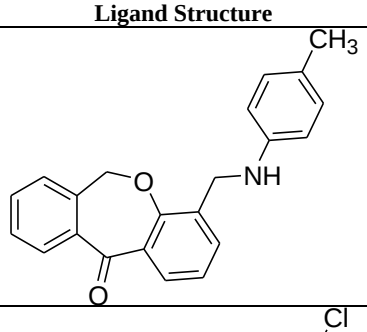
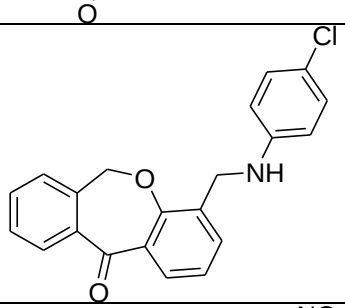
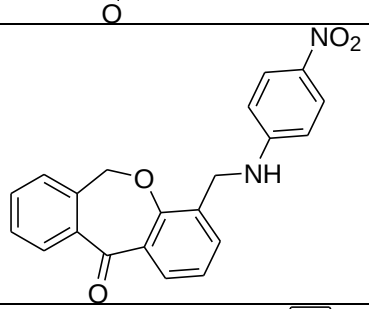
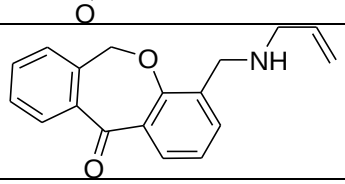
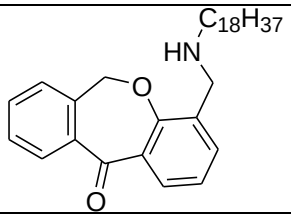


Fig 5: 3D and 2D interaction diagram of compound 7a with ct-DNA (PDB ID: 2XCQ).

Table 2: Details of Binding Energy (kcal/mol) and types of interactions between ligands and proteins

Ligands	Ligand Structure	3G75	2P6F	2XCQ
7a		-10.2	-11.8	-8.0
7b		-9.1	-11.0	-7.6
7c		-8.8	-10.0	-7.4
7d		-7.6	-8.9	-7.0

7e		-7.0	-8.3	-5.1

ADME and Physicochemical Parameters

For successful drug development, synthesized derivatives must exhibit favorable ADME (Absorption, Distribution, Metabolism, and Excretion) properties. According to Lipinski's Rule of Five, a compound is more likely to be orally active if it meets the following criteria: (i) molecular weight (MW) below 500 Da, (ii) fewer than 5 hydrogen bond donors, (iii) fewer than 10 hydrogen bond acceptors, (iv) logP value less than 5, and (v) total polar surface area (TPSA) not exceeding 140 Å². The presence of one violation is generally considered acceptable.

In this study, all synthesized molecules complied with Lipinski's criteria, except compounds 7b and 7e, each of which showed a single violation. Other important ADME parameters—including Blood–Brain Barrier (BBB) permeability, Caco-2 permeability, Human Intestinal Absorption (HIA), and plasma protein binding—were found to be within the acceptable range for active drugs (Table 3). These results suggest that compounds 7(a–f) possess characteristics consistent with orally active drug candidates.

Regarding bioactivity evaluation, a score below –5.0 indicates inactivity, a value between –5.0 and 0.0 reflects moderate activity, and a score above 0.0 suggests high biological activity. All designed derivatives fell within the active range and demonstrated favorable bioactivity scores, as presented in Table 4.

Table 3: ADME and Physicochemical parameters

Ligands	LogP	TPSA	nOH	nOHNH	Nvio.	Nrot	BBB	Caco2	HIA	MDCK	SP	PPB
7a	4.84	38.33	3	1	0	3	2.06	52.04	96.73	1.34	-2.54	97.34
7b	5.07	38.33	3	1	1	3	2.34	42.67	96.92	0.96	-2.66	100
7c	4.35	38.33	6	1	0	4	0.02	8.98	97.03	0.18	-2.68	98.99
7d	3.34	38.33	3	1	0	4	0.86	47.51	95.99	26.63	-2.89	84.47
7e	9.31	38.33	3	1	1	18	16.48	52.18	97.05	65.00	-1.03	97.92

Table 4: Bioactivity Score Parameters

Ligand	GPCR Ligand	Ion channel modulator	Kinase Inhibitor	Nuclear Receptor Ligand	Protease Inhibitor	Enzyme Inhibitor
7a	0.08	-0.31	0.08	0.11	-0.09	0.06
7b	0.12	-0.25	0.10	0.12	-0.07	0.08
7c	-0.02	-0.27	-0.04	0.04	-0.15	0.01
7d	0.11	-0.26	-0.12	0.00	-0.09	0.09
7e	0.21	-0.14	0.00	0.13	0.10	0.16

Conclusion

The designed derivatives 7(a–f) demonstrated strong potential as drug candidates based on multiple computational analyses. Molecular docking studies showed that the compounds exhibit favorable binding affinities with key antibacterial and antifungal targets, including Staphylococcus aureus DNA gyrase (PDB ID: 3G75) and Saccharomyces cerevisiae N-myristoyl transferase (PDB ID: 2P6F), as well as effective groove binding to DNA. Compound 7a consistently displayed the highest binding affinities in all docking studies.

ADME analysis indicated that most derivatives comply with Lipinski's Rule of Five, suggesting good oral bioavailability, while other pharmacokinetic parameters, including BBB permeability, Caco-2 absorption, HIA, and plasma protein binding, were within acceptable ranges. Bioactivity predictions further supported their potential, with all compounds showing favorable activity scores.

Overall, these findings highlight compounds 7(a–f) as promising leads for further experimental evaluation as orally active antibacterial, antifungal, and DNA-targeting agents.

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