

Synthesis, Antioxidant and Antibacterial Potentials of Schiff Base Derivatives Containing Hydroxy Groups: Molecular Docking and ADME Approaches

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ABSTRACT

In this study, hydroxyl-containing Schiff base derivatives (**7-11**) were synthesized and confirmed by detailed spectroscopic analyses. The antioxidant and antibacterial potentials of the synthesised compounds were evaluated. In Fe³⁺ and Cu²⁺ reduction assays, compound **7** showed the highest Fe³⁺ reducing capacity, while compound **8** exhibited the strongest Cu²⁺ reduction. In the DPPH assay, compound **8** was the most potent, with the lowest IC₅₀ value (12.24 µg/mL). In ABTS, compound **7** showed greater reducing activity than Trolox. Antibacterial results indicated clear differences between Gram-positive and Gram-negative bacteria; notably, compound **10** was highly active against *Acinetobacter baumannii*, exceeding gentamicin (GN) and ciprofloxacin (CIP). Molecular docking and ADME analyses further supported the findings by showing strong binding to target proteins and good drug-like properties. Overall, the derivatives demonstrated remarkable biological potential, especially antioxidant and antimicrobial activities.

Keywords: Hydroxyl groups, Schiff Base, Antioxidant, Antibacterial, Molecular docking, ADME.

1. INTRODUCTION

Schiff bases are formed by the nucleophilic addition of amines to a carbonyl compound; water is subsequently eliminated, resulting in the characteristic C=N (carbon–nitrogen double bond). Schiff bases are frequently preferred due to advantages such as ease of preparation, structural diversity, various synthetic options and good solubility. Furthermore, Schiff bases and the complexes derived from them have a wide range of applications in the development of certain drugs, dye production, the electronics and plastics industries, agriculture, cosmetic and pharmaceutical applications, polymer production, analytical chemistry, liquid crystal technology, corrosion prevention and the

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electronics sector [1]. Schiff bases are attracting considerable interest in scientific research due to their versatile biological properties. Numerous studies in the literature demonstrate that these compounds can be effective in various therapeutic areas, such as anti-cancer, anti-ulcer, antifungal, anti-inflammatory, antibacterial and antiviral applications [2, 3]

The antimicrobial, antioxidant and cytotoxic effects of certain Schiff derivatives, **1–2**, on MCF-7 breast cancer cells were reported in the study by Erturk et al. (2020); these findings have been detailed in the literature (**Figure 1**) [4]. Pyrazole- **3–4** and pyrimidine-based **5** Schiff bases have also been reported to exhibit antidiabetic, anti-Alzheimer, anti-arthritic, and strong antioxidant properties (**Figure 1**) [2, 5]. Furthermore, phenol-containing Schiff bases **6** show antiproliferative effects against MCF-7, HCT-116, and A549 cells, along with moderate antibacterial activity [6].

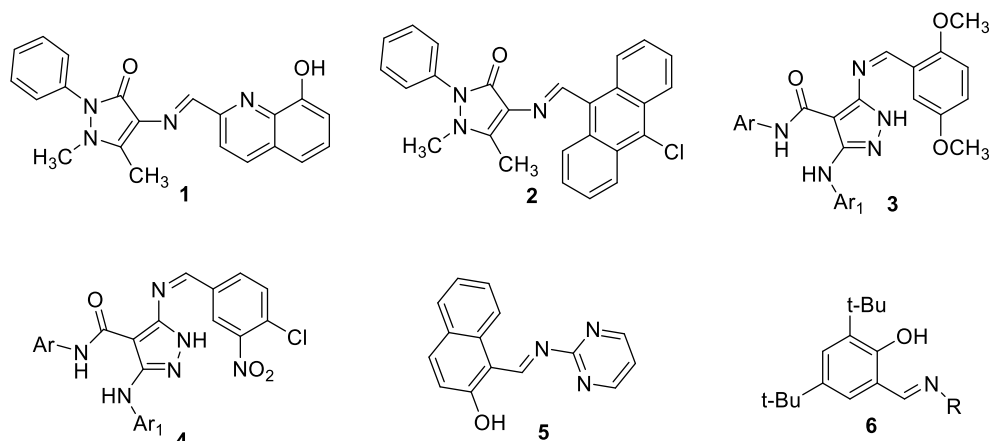


Figure 1. Schiff bases **SB1-SB6** are bioactive compounds with diverse biological properties [2, 4-6].

In addition to all these findings, some pharmaceutical agents in clinical use are also known to be based on Schiff base structure. For example, drugs such as nifuroxazide (an antibacterial agent used in the treatment of gastrointestinal infections), tiacetazone (a drug used in the treatment of tuberculosis) and dantrolene (an agent used as a skeletal muscle relaxant) are associated with chemical structures containing Schiff bases (**Figure 2**) [7].

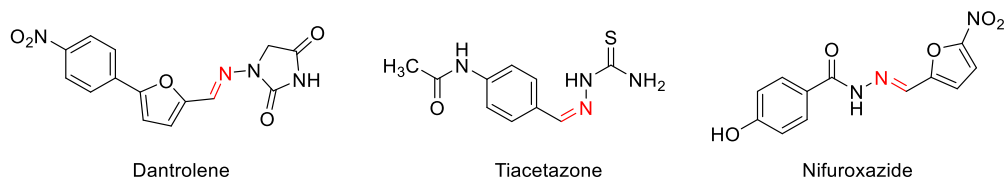


Figure 2. Examples of clinically used drugs based on Schiff base derivatives [7].

Free radicals play a critical role in vital biological processes by enabling energy transfer to cells, tissues, and organs. They are constantly generated and neutralized in the human body to preserve homeostasis. While normally beneficial defending against pathogens such as fungi and bacteria an imbalance resulting in excess radicals can lead to cellular damage and contribute to diseases like Alzheimer's disease [8], Parkinson's disease [9], chronic kidney disease[10], cancer [11] and other diseases.

Such compounds reduce oxidative stress within cells by directly scavenging free radicals, thereby preventing potential damage to cells. These agents can be obtained from natural sources or produced through chemical synthesis. Numerous derivatives have been reported in the literature for their high antioxidant capacity; however, elucidating the reaction mechanisms of these compounds in detail and designing 'safer/improved' analogues is a critical issue in current research. In this context, especially Schiff base ligands attract attention. These compounds, which can exhibit both antioxidant and biologically active properties in a wide range of areas thanks to the imine group in their structures, can further increase their activity by forming complexes with metal ions. It is seen that coordination compounds based on Schiff bases stand out not only in the reduction of oxidative stress, but also with their antimicrobial potential [12, 13]. Therefore, Schiff bases are among the promising candidates for the development of potent antioxidant and antipathogenic agents.

Numerous different synthetic routes for the preparation of certain Schiff derivatives have been comprehensively reported in the literature. However, a significant proportion of traditional methods are not sufficiently efficient due to serious limitations such as low chemical yield, difficult-to-implement and laborious process steps, long reaction times, and the frequent need to use large amounts of catalyst. For this reason, there is a need to develop new methods for the synthesis of certain compounds that are more effective, simpler, more economical and more environmentally friendly [14]. Traditionally, Schiff bases are synthesised by combining amines with carbonyl compounds under reflux conditions. Solvents such as 1,2-dichloroethane, tetrahydrofuran (THF), methanol or ethanol are typically used in this process. This process typically employs acidic catalysts, and water molecules are released during the reaction [15]. Microwave-assisted techniques offer a highly advantageous method for synthesis. This approach significantly reduces reaction times whilst simultaneously increasing product yield, enhancing process stability and improving experimental reproducibility. Under certain conditions, this method yields remarkable results in terms of chemo-, stereo- and zonal selectivity, thereby accelerating the shift from traditional thermal processes to microwave heating. Furthermore, in materials synthesis, it enables more precise control over macroscopic morphology, phase homogeneity and particle size distribution [16, 17].

In this study, two new Schiff base derivatives containing hydroxyl groups, which were not previously reported in the literature, were obtained for the first time by microwave-assisted synthesis method. Three of the five compounds synthesized were previously reported in

the literature in different ways, and their synthesis was carried out for the first time in our study by microwave-assisted synthesis. Structural characterizations of all compounds obtained were carried out by ^1H -NMR, ^{13}C -NMR and elemental analysis or high-resolution mass spectrometry (HR-MS) techniques. According to literature findings, compound **7** was previously synthesized only as an intermediate step, but was transferred to the next reaction step without purification or structural analysis [18, 19]. Compound **9** was reported in the literature to have been synthesized by classical methods, which took a long time, and its antifungal activity was evaluated by Sidhu and colleagues [20, 21]. In addition, it is reported that Compound **10** was synthesized at high temperatures to form complex structures [22]. In this study, the biological potential of newly synthesised or resynthesised compounds was assessed by examining their ABTS and DPPH• radical scavenging capacities and their ability to reduce Fe^{3+} and Cu^{2+} ions; in this way, their antioxidant properties were determined. In addition, the antimicrobial effects of these compounds against some Gram-positive and Gram-negative bacterial species were investigated and their biological activities were comprehensively demonstrated.

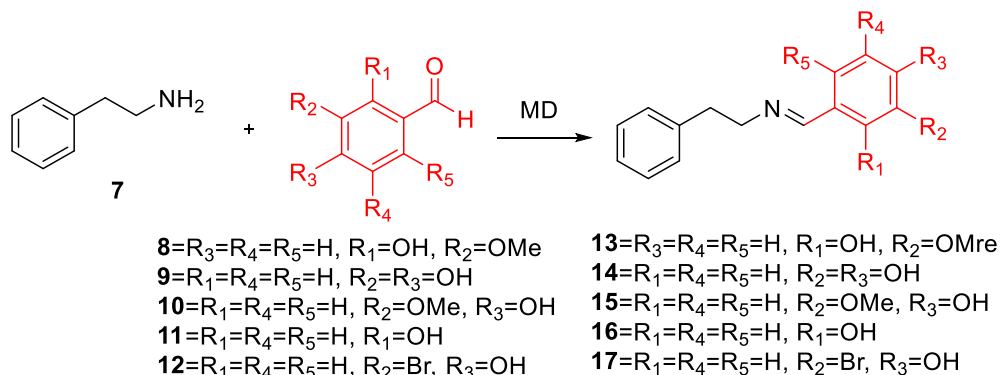
2. MATERIALS AND METHODS

2.1. Chemicals and Apparatus

All reagents and analytical solvents used in the experiments were commercially available from Merck and Sigma-Aldrich. Radical scavenging assays were performed using ABTS and DPPH reagents, while neocuproine and trolox were employed for antioxidant analyses. No further purification steps were carried out prior to experimental use. The melting behavior of the synthesized compounds was measured using a Gallenkamp melting point apparatus. Structural confirmation was carried out using ^1H and ^{13}C NMR analyses performed on Bruker and Varian instruments operating at 400 MHz and 100 MHz; additionally, elemental composition measurements were carried out using a Leco CHNS-932 analyser.

2.2. General Procedure for Microwave-Induced Synthesis of Schiff Bases

The synthesis of certain derivatives of the compound (**7–11**) was carried out in accordance with methods previously reported in the literature [1, 23]. Structurally, 2-phenylethylamine (**1**) (1 mmol) was mixed with various aromatic aldehydes (**2–6**); the resulting reaction mixture was then irradiated under a microwave set to 900 W for a total of 5 minutes (**Scheme 1**). The progress of the reaction was monitored at regular intervals using TLC plates. The formation of a single, pure product corresponding to the target compound was confirmed by ^1H and ^{13}C NMR data.



Scheme 1. Synthesis plan of the imine compounds to be synthesized.

2.3. Evaluation of Reducing Capacities

The reducing capacities of hydroxy-substituted Schiff base derivatives (**7-11**) toward Fe³⁺ and Cu²⁺ ions were investigated at concentrations ranging from 50–100 µg/mL.

To evaluate the Fe³⁺ reduction capacity, the sample solutions were mixed with a reagent containing potassium ferricyanide in 0.2 M phosphate buffer (pH 6.6) to form a homogeneous mixture. The mixture was incubated at 50 °C for 20 minutes. Trichloroacetic acid was then added to stop the reaction.

The supernatant was separated from the sample, then diluted with distilled water, and finally a FeCl₃ solution was added. To calculate the reduction yield, the spectrophotometric absorbance values of the samples at a wavelength of 700 nm were carefully measured [1].

The reducing capacity of Cu²⁺ was analysed in a reaction medium containing CuCl₂, neocuproin and ammonium acetate buffer. Samples were completed to a total volume of 4.1 mL with distilled water, vortexed, and left to stand at room temperature for 1 hour. Subsequently, spectrophotometric measurements were performed in the UV–Vis range against an appropriate blank, and absorbance values were determined at 450 nm [24]. The results obtained were interpreted to comparatively evaluate the reduction performance of certain hydroxyl-containing Schiff compounds with respect to Fe³⁺ and Cu²⁺.

2.4. Radical Scavenging Capabilities

The DPPH• scavenging activity of certain hydroxyl-containing Schiff compounds (**7-11**) was determined using the Blois method [25]. In summary, 1 mL of a stock solution prepared from an ethanol-based DPPH• stock solution (0.1 mM) which has a characteristic purple colour was added simultaneously to the reference samples along with different concentrations of the synthesised compounds.

Afterwards, the samples were incubated in the dark at room temperature for 30 minutes. To assess the colour change associated with antioxidant activity, absorbance (optical density) values were determined by spectrophotometric measurement at 517 nm.

To assess the ABTS^{•+} radical cation scavenging capacity, an aqueous solution of ABTS (7.0 mM) was first reacted with K₂S₂O₈ (2.5 mM) to form the active chromophore [26]. Before proceeding to sample analysis, this stock solution was appropriately diluted in 0.1 M phosphate buffer (pH 7.4). This yielded a stable absorbance at 734 nm for the blank control (0.80 ± 0.05).

Subsequently, for each sample, 1 mL of the prepared ABTS^{•+} working solution was mixed with 3 mL of the synthesised compounds or reference standards; the mixture was adjusted to be homogeneous and left to stand in complete darkness for 30 minutes. Following incubation, absorbance measurements were taken at 734 nm, and IC₅₀ values were calculated from the corresponding dose-response curves.

2.5. Antimicrobial Evaluation and Minimum Inhibitory Concentration Profiling

Anti-bacterial activities of synthesized compounds were tested using the in vitro agar well diffusion method in accordance with NCCLS guidelines [27]. In the screening studies, the following pathogenic microorganisms of critical importance to human health were used: *S. aureus* (ATCC 25213), *B. cereus* (709 Roma), *E. faecalis* (ATCC 29212), *L. monocytogenes* (ATCC 43251), *A. baumannii* (ATCC 02026), *K. pneumoniae* (ATCC 10031), *E. coli* (ATCC 25922), and *P. aeruginosa* (ATCC 43288). Bacterial stocks were first propagated by incubating them in culture medium at 37 °C for 24 hours. The cell density of the resulting cultures was then adjusted to exactly 1×10^6 CFU/mL using sterile saline solution. On agar plates inoculated with the standardised suspensions, wells of uniform size, each 6 mm in diameter, were prepared using a sterile punch. The compounds under investigation were dissolved in 10% aqueous DMSO to a concentration of 10 mg/mL and added to the wells in the specified volumes, and the plates were incubated again at 37 °C for 24 hours. At the end of the incubation period, the inhibition zones formed around the wells were measured in millimetres (mm) using a calibrated antibacterial activity scale. Gentamicin (GN) and Ciprofloxacin (CIP) were used as positive controls (reference standards), whilst a 10% DMSO solution was used as the negative control.

2.6. Molecular Docking Analysis

Molecular docking is widely used in drug discovery to predict ligand–protein interactions and potential binding conformations. In this study, compounds **7–11** were subjected to in silico docking analysis against selected target proteins using AutoDock Tools.

Specifically, human peroxiredoxin 5 (PDB ID: 1HD2) was used for antioxidant modelling, whilst DNA gyrase B (PDB ID: 4URO) was used as a reference for antimicrobial evaluations. Both crystal files were obtained directly from the RCSB Protein Data Bank database [28, 29]. Protein preparation was performed according to standard procedures [30, 31]. Co-crystallized ligands, unnecessary water molecules, and cofactors were removed

prior to docking studies. Protein structures were prepared using AutoDock 4.2 with MGL Tools 1.5.7, while ligand structures (7–11) were geometry-optimized using Avogadro and saved in PDB format. Polar hydrogens, Kollman charges, and torsional parameters were assigned before conversion to PDBQT format.

Docking studies were conducted using the Lamarckian Genetic Algorithm (LGA). To ensure that the active binding sites were fully encompassed, a grid box measuring $60 \times 60 \times 60 \text{ Å}^3$ with a grid spacing of 0.553 Å was defined. The grid centres were positioned at the following coordinates: For the peroxiredoxin 5 model: $x = 9.0657$, $y = 37.1454$, $z = 24.2268$. For the DNA gyrase B structure: $x = -2.6331$, $y = -1.3091$, $z = -12.0716$. Following the simulations, the ligand-receptor interaction patterns and relative binding energies were evaluated in detail; the resulting docking scores were organised and presented in Tables 5 and 7.

2.7. ADMET Prediction

The computer-assisted ADMET prediction methods are widely used in the early stages of drug discovery to evaluate the pharmacokinetic behaviour and drug-like properties of biologically active compounds. In this study, ADMETlab 2.0 was used to determine the ADMET profiles of all the synthesised compounds[32].

The molecular properties of compounds 7–11, including parameters related to oral bioavailability and drug-likeness, were further estimated using SwissADME [33]. This predictive model provides comprehensive data on the physicochemical properties, pharmacokinetic behaviour and ADMET parameters of compounds. Such computer-based (in silico) screening is extremely useful for predicting in advance whether synthesised molecules meet the bioavailability, efficacy and safety thresholds required to be safe and effective drug candidates [34].

3. RESULTS AND DISCUSSION

3.1. Chemical Results

The structures of compounds 7–11 were confirmed using ^1H NMR, ^{13}C NMR and elemental analysis results. Schiff base derivatives were synthesized from 2-phenylethylamine (7) (1 mmol) and various aromatic aldehydes (2–6) (1 mmol). Although the synthesis of Schiff bases has previously been described in the literature (7, 9, 10), the present study employed microwave-assisted solvent-free conditions. This approach provided rapid and efficient synthesis with high product yields (96%). In the ^1H NMR spectra, characteristic azomethine ($\text{H}-\text{C}=\text{N}$) proton signals were observed in the 8.04–8.22 ppm range.

3.2. Physical Properties and Spectral Data of Synthesized Compounds (7–11)

2-methoxy-6-((phenethylimino)methyl)phenol (7): It was isolated as a yellow solid with a chemical yield of 99%; its melting point (m.p.) is 84–85 °C.

^1H NMR (400 MHz, CDCl_3): δ 13.88 (s, 1H), 8.16 (s, 1H), 7.35–7.14 (m, 5H), 6.89 (d, J = 6.6 Hz, 1H), 6.83–6.70 (m, 2H), 3.89 (s, 3H), 3.83 (t, J = 5.1 Hz, 2H), 2.99 (t, J = 6.9 Hz, 2H, CH_2).

^{13}C NMR (100 MHz, CDCl_3): δ 165.22, 151.99, 148.47, 139.16, 128.95, 128.54, 126.39, 122.85, 118.46, 117.78, 113.72, 60.67, 56.06, 37.36. **HRMS** (ESI): m/z ; Calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{16}\text{H}_{17}\text{NO}_2$: 256.3170, Found: 256.1332.

4-((phenethylimino)methyl)benzene-1,2-diol (8): It was obtained in a 94% yield as a black solid. ^1H NMR (300 MHz, CDCl_3) δ 8.22 (s, 1H), 7.29 – 7.22 (m, 2H), 7.21 – 7.11 (m, 3H), 6.98 (s, 1H), 6.90 (s, 1H), 6.63 (s, 1H), 3.81 – 3.71 (m, 3H), 3.64 (s, 1H), 3.00 – 2.90 (m, 2H). **HRMS**: (ESI), m/z : Calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{15}\text{H}_{15}\text{NO}_2$: 242.11; Found: 242.11

2-methoxy-4-((phenethylimino)methyl)phenol (9): It was obtained in a 97% yield as a brown solid. m.p:115-116 °C. (m.p:110-113 °C). ^1H NMR (400 MHz, CDCl_3) δ 8.04 (s, 1H), 7.44 (d, J = 1.8 Hz, 1H), 7.33 – 7.17 (m, 5H), 7.03 (dd, J = 8.1, 1.8 Hz, 1H), 6.90 (d, J = 8.1 Hz, 1H), 3.91 – 3.76 (m, 5H), 3.02 (t, J = 7.6 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 162.16, 149.36, 147.79, 139.98, 129.23, 129.10, 128.60, 126.38, 124.46, 114.66, 108.76, 62.89, 55.98, 37.74. **HRMS**: (ESI), m/z : Calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{16}\text{H}_{17}\text{NO}_2$: 256.3170; Found: 256.1326

2-((phenethylimino)methyl)phenol (10): It was obtained in a 97% yield as a yellow solid. m.p:51-52 °C. ^1H NMR (400 MHz, CDCl_3) δ 13.46 (s, 1H, -OH), 8.20 (s, 1H), 7.33 – 7.25 (m, 3H), 7.24 – 7.14 (m, 4H), 6.95 (d, J = 8.1 Hz, 1H), 6.87 – 6.80 (m, 1H), 3.91 – 3.74 (m, 2H), 2.99 (t, J = 7.1 Hz, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 165.11, 161.18, 139.29, 132.18, 131.24, 128.96, 128.54, 126.41, 118.76, 118.52, 117.02, 61.10, 37.45. **HRMS**: (ESI), m/z : Calculated for $[\text{M}+\text{H}]^+$ $\text{C}_{15}\text{H}_{15}\text{NO}$: 226.1154; Found: 226.1225

2-bromo-4-((phenethylimino)methyl)phenol (11): It was obtained in a 94-95% yield. ^1H NMR (400 MHz, CDCl_3) δ 8.40 (brs, 1H, OH), 7.85 (s, 1H), 7.76 (s, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.33 – 7.13 (m, 5H), 6.82 (d, J = 8.5 Hz, 1H), 3.79 (t, J = 7.2 Hz, 2H), 3.10 – 2.87 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3) δ 159.99, 139.97, 139.27, 132.66, 129.23, 129.05, 128.82, 128.58, 126.65, 126.37, 116.71, 62.92, 37.72. Elemental analysis calcd. for $\text{C}_{15}\text{H}_{14}\text{BrNO}$, C, 59.23; H, 4.64; N, 4.60; found C, 59.28; H, 4.60; N, 4.63.

3.3. Reducing Ability Assays

Free radicals, generated as natural byproducts of metabolic processes, are highly reactive species due to their unpaired electrons. The uncontrolled increase in free radicals directly threatens cellular structure by entering into destructive interactions with vital macromolecules within the cell, and accelerates the development of various degenerative diseases.

Antioxidant compounds, on the other hand, provide vital protection to the cell by neutralising reactive oxygen species (ROS) and halting radical chain reactions, even at very low concentrations. Consequently, the observed inhibitory effect acts as a protective shield that preserves cellular integrity under physiological conditions. At the same time, it supports product stability by preventing oxidative deterioration in food products [35]. The key factor determining the antioxidant activity of certain synthetic shikimic acid derivatives is the hydroxyl groups present on the molecules. As these groups are prone to donating electrons or hydrogen radicals, they help to neutralise and balance the harmful reactions caused by free radicals. Thus, these compounds contribute to the preservation of cellular integrity and the prevention of oxidative damage by reducing the harmful processes triggered by free radicals [36].

Various methods exist for determining the antioxidant activity of synthesised molecules. In this study, selected methods were employed to evaluate the compounds' ABTS•+ and DPPH• radical scavenging activities, as well as their Fe³⁺ and Cu²⁺ reduction capacities.

The reducing potentials of Schiff base derivatives containing hydroxyl groups (**7–11**) were analysed using two different reduction assays. To systematically evaluate the reducing power of these newly synthesised derivatives, both Fe³⁺ reduction capacity and CUPRAC analyses were carried out. The primary mechanism underlying these antioxidant tests is the reduction of Cu²⁺ or Fe³⁺ (ferricyanide) complexes in the medium to Cu¹⁺ and Fe²⁺ forms, respectively, via antioxidant compounds. Upon examination of the experimental data presented in **Table 1** and **Figure 3**, it can be seen that the Fe³⁺ reduction capacities of the tested molecules (**7–11**) and the reference standard are ranked from highest to lowest as follows: **10** (0.025 ± 0.001 ; r^2 : 0.9992) < **11** (0.076 ± 0.001 ; r^2 : 0.9504) < **8** (0.225 ± 0.004 ; r^2 : 0.9994) < **9** (0.225 ± 0.004 ; r^2 : 0.9614) < **7** (0.648 ± 0.012 ; r^2 : 0.9790) < **Trolox** (1.095 ± 0.053 ; r^2 : 0.9807), respectively.

According to the CUPRAC assay, which measures the ability of the synthesised target compounds (**7–11**) to reduce Cu²⁺ ions to the Cu¹⁺ form (**Table 1** and **Figure 3**), the copper-reducing powers of both the reference standard and the molecules under investigation followed this order from highest to lowest: **10** (0.067 ± 0.001 ; r^2 : 0.9956) < **11** (0.115 ± 0.003 ; r^2 : 0.9905) < **7** (0.699 ± 0.1023 ; r^2 : 0.9896) < **Trolox** (0.929 ± 0.051 ; r^2 : 0.9924) < **8** (0.976 ± 0.038 ; r^2 : 0.9973). Compound **8** (0.976) has higher Cu⁺² reduction capacity than **Trolox** (0.929), while other compounds have lower Cu⁺² reduction capacity.

Table 1. Reduction effects of Schiff base compounds (7-11) containing 50 µg/mL hydroxy group with Fe³⁺ and Cu²⁺ reduction methods.

Compounds	Fe ³⁺ Reducing		Cu ²⁺ Reducing	
	λ ₇₀₀ *	R ²	λ ₄₅₀ *	R ²
7	0.648 ± 0.012	0.9790	0.699 ± 0,023	0.9896
8	0.225 ± 0.004	0.9994	0.976 ± 0.038	0.9973
9	0.225 ± 0.004	0.9614	0.601 ± 0.019	0.9863
10	0.025 ± 0.001	0.9992	0.067 ± 0.001	0.9956
11	0.076 ± 0.001	0.9504	0.115 ± 0.003	0.9905
Trolox	1.095 ±0.053	0.9807	0.929 ± 0.051	0.9924

* expressed as absorbance values.

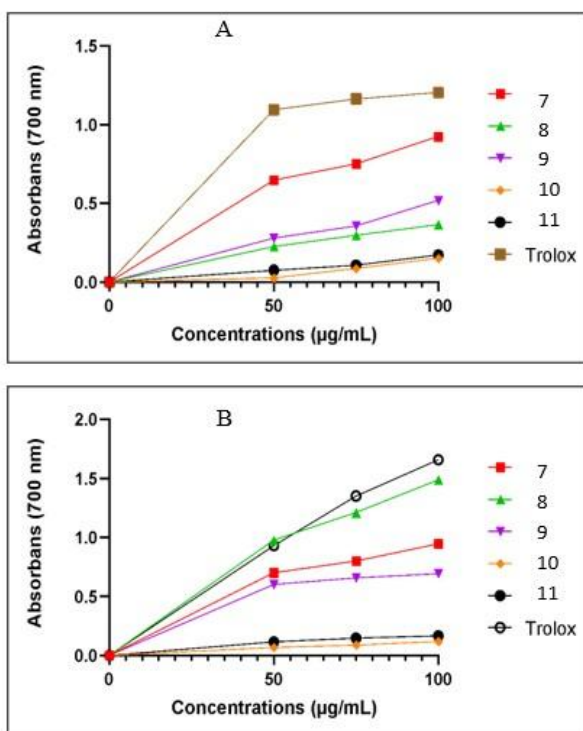


Figure 3. Reducing ability of Schiff base compounds (7-11) containing hydroxy group at 50-100 µg/mL and trolox used as standard. a. Fe³⁺ reducing effect, b. Cu²⁺ reducing effect.

Various radical scavenging protocols can be employed to thoroughly assess the antioxidant potential of the synthesised derivatives and reference standards from different perspectives. To this end, DPPH• and ABTS•⁺ radical scavenging capacity assays, whose reliability is widely accepted in the literature, were systematically applied. The results are shown in **Table 2** and **Figure 4**, showing a significant increase in DPPH radical scavenging activities with increasing concentrations of Schiff bases (7-11). The half maximum removal concentration (IC₅₀) values of Schiff bases (7-11) and their comparison with standard trolox were determined as follows, respectively: **11** (IC₅₀: 339.30 µg/mL; r²: 0.9885) > **7** (IC₅₀: 253.34 µg/mL; r²: 0.9871) > **10** (IC₅₀: 251.53 µg/mL; r²: 0.9639) > **9** (IC₅₀: 70.98 µg/mL; r²: 0.9794) > **8** (IC₅₀: 12.24 µg/mL; r²: 0.9432) > **Trolox** (IC₅₀: 7.74). According to the generated datasets, compound **8** exhibited the maximum DPPH radical trapping activity, demonstrating a performance nearly on par with that of the positive control, Trolox.

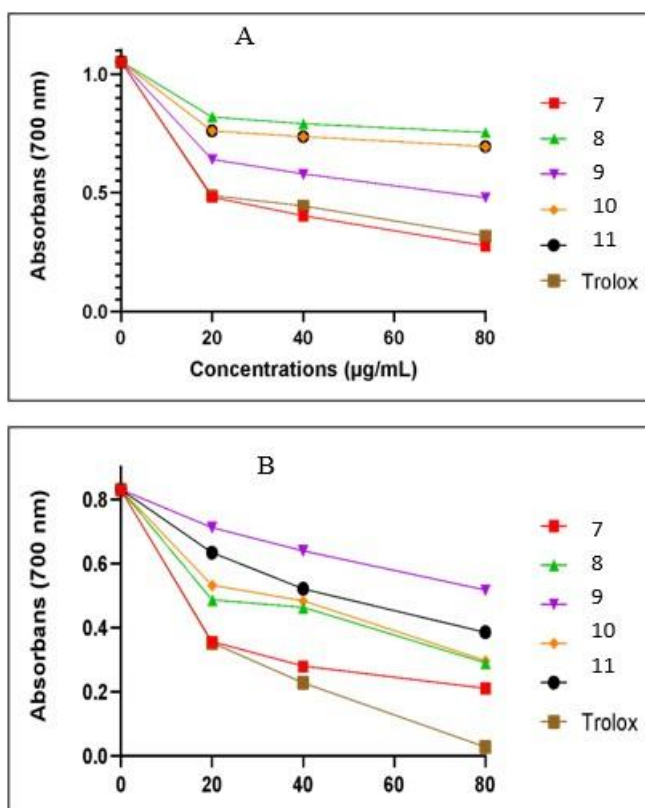


Figure 4. Reducing ability of Schiff base compounds (7-11) and Trolox used as standard at 20-80 µg/mL A. DPPH• removal effect, B. ABTS•⁺ removal effect.

Table 2. IC₅₀ (μg/mL) values for DPPH• and ABTS^{•+} scavenging abilities of Schiff base compounds (7-11).

Compounds	DPPH• Scavenging		ABTS ^{•+} Scavenging	
	IC ₅₀	R ²	IC ₅₀	R ²
7	253.34	0.9871	1.77	0.9723
8	12.24	0.9432	50.21	0.9892
9	70.98	0.9794	121.53	0.9988
10	251.53	0.9639	63.15	0.9712
11	339.30	0.9885	81.94	0.9835
Trolox	7.74	0.9950	6.94	0.9912

ABTS^{•+} scavenging test was also applied to determine the radical scavenging capacity of the compounds. Data presented in **Figure 4** and **Table 2** revealed that ABTS^{•+} scavenging efficiency increased with increasing concentrations. The results are ranked based on IC₅₀ of the compounds as follows: **9** (IC₅₀: 121.53 μg/mL; r²: 0.9988) > **11** (IC₅₀: 81.94 μg/mL; r²: 0.9835) > **10** (IC₅₀: 63.15 μg/mL; r²: 0.9712) > **8** (IC₅₀: 50.21 μg/mL; r²: 0.9892) > **7** (IC₅₀: 1.77 μg/mL; r²: 0.97233) > **Trolox** (IC₅₀: 6.94 μg/mL; r²: 0.9912). Especially, compound **7** attracted attention with the lowest IC₅₀ value of 1.77 μg/mL and showed the strongest radical scavenging capacity with a lower IC₅₀ value than **Trolox** (IC₅₀: 6.94 μg/mL). These results indicate that Schiff bases (**7-11**) have a remarkable potential in terms of antioxidant activity.

It has been determined that the synthesised Schiff bases (**7-11**) exhibited significantly greater efficacy in scavenging ABTS^{•+} cation radicals compared to DPPH radicals. Obtaining such differing results in laboratory (in vitro) antioxidant tests is a common occurrence in the literature and is generally attributed to the microenvironments in which the analyses are conducted. The main reasons for this can be explained as follows: Solvent Differences: Whilst the DPPH method is carried out in a hydroalcoholic system containing 50% ethanol/water, ABTS measurements are performed in a completely aqueous phase; this difference fundamentally affects the radical scavenging dynamics. Radical Structure and Kinetics: Whilst the ABTS assay utilises a charged cation radical, the DPPH protocol is based entirely on free radical reduction kinetics [33]. Solubility Effect: The solubility levels of the molecules under investigation in these different solvent systems are a highly critical factor. If compounds do not dissolve completely in the medium, this can mask or obscure the true biological potential of a molecule that is, in fact, highly active.

3.4. Antimicrobial Activity

Pathogenic microorganisms that develop resistance to existing antibiotics pose a serious threat to public health. This has shifted the focus of medicinal chemistry and pharmaceutical research towards the discovery and development of new and effective

antibacterial agents [37]. In this context, Schiff bases stand out as an important research topic. The sp^2 hybridised nitrogen atom contained in the azomethine ($-C=N-$) group in their structure interacts with biological systems and prepares the ground for various pharmacological effects. The lone electron pair of nitrogen increases the capacity of these compounds to bond with biological targets and contributes to their potential therapeutic efficacy. The antimicrobial effects of Schiff bases are usually based on structural disruptions on the cell membrane or wall of microorganisms. These compounds disrupt the integrity of the cell membrane, upset the ion balance and inhibit cellular functions. Many studies have shown that Schiff bases and especially metal complexes target microbial cell membranes, increasing membrane permeability, causing ion leakage and consequently stopping cellular metabolism [38-40]. In addition, some studies show that the addition of a hydroxy group to the structure of Schiff bases can increase antimicrobial activity. In particular, derivatives with more than one hydroxy group have been reported to exhibit higher biological activity by interacting more strongly with bacterial cells [41]. Based on these strong findings in the literature, this study investigated the antibacterial potential of newly synthesised Schiff base derivatives (**7–11**) containing a hydroxyl group in their structure. This series of synthesised compounds was systematically tested against a broad panel of bacteria representing both Gram-positive and Gram-negative pathogens (*S. aureus*, *B. cereus*, *E. faecalis*, *L. monocytogenes*, *A. baumannii*, *K. pneumoniae*, *E. coli* and *P. Aeruginosa*). Biological analyses conducted using the agar well diffusion method were performed under exactly the same experimental conditions as those for the commercial reference antibiotics GN and CIP, to allow for direct comparison of the results. The results obtained are summarised in **Table 3**. When the data are evaluated overall, it was determined that the synthesised Schiff bases (**7–11**) exhibited an inhibitory effect on both groups of bacteria to varying degrees, and that the diameters of the resulting net inhibition zones ranged from 12 to 22 mm (**Table 3**).

The tested compounds showed wider inhibition zones against *E. faecalis* (13-16 mm), *L. monocytogenes* (12-16 mm; no inhibition was observed for compound **9**), *K. pneumoniae* (11-16 mm) and *E. coli* (12-15 mm) strains compared to standard antibiotics such as GN and CIP). Compound No. **10**, in particular, exhibited stronger antibacterial activity against the Gram-negative bacterium *P. aeruginosa*, with an inhibition zone of 20 mm compared to the standard antibiotic GN (17 mm). The same compound also exhibited higher antibacterial activity against *A. baumannii* than both GN (21 mm) and CIP (20 mm) with a zone diameter of 22 mm.

All the synthesised compounds exhibited an inhibitory effect on *A. baumannii* comparable to or greater than that of standard test antibiotics; inhibition zones measured between 16 and 22 mm. These findings revealed that all tested compounds showed remarkable antibacterial activity on *A. baumannii* with inhibition zones ranging from 16-22 mm. This Gram-negative pathogen, which is of increasing clinical importance, is isolated especially in intensive care and invasive medical device-associated infections and causes serious treatment difficulties due to multidrug resistance, especially carbapenem resistance[42].

Similarly, *P. aeruginosa* is an opportunistic Gram-negative bacterium known for its low outer membrane permeability, multiple efflux pump systems and broad resistance mechanisms [43].

The high inhibitory activity of the Schiff base derivatives evaluated in this study against resistant pathogens such as *A. baumannii* and *P. aeruginosa* indicates that these compounds can be evaluated as alternative antimicrobial agents. In particular, compound **10** demonstrated its therapeutic potential by outperforming reference antibiotics against these two clinically problematic bacteria. Similarly, compound **11** showed high binding affinity with the DNA gyrase B enzyme due to the synergistic effect of para-hydroxyl and meta-bromo groups in its structure and was another remarkable candidate in terms of antibacterial activity. This potent biological activity is largely attributed to the ability of the hydroxyl and azomethine groups in the molecule structure to form hydrogen bonds with microbial cell components [41]. It has been shown that an increase in the number of hydroxyl groups significantly enhances the antimicrobial activity of certain derivatives and strengthens their interaction with cell membranes [44]. In conclusion, the structural features of compound **10** make it a promising antimicrobial candidate against resistant bacteria.

Table 3. Inhibition zones in mm diameter for the synthesized compounds.

Microorganisms	7	8	9	10	11	GN	CIP
<i>S. aureus</i>	16	14	14	15	12	18	22
<i>B. cereus</i>	14	15	14	14	17	21	19
<i>E. faecalis</i>	13	14	16	15	16	n.d	20
<i>L. monocytogenes</i>	16	12	n.d	13	15	n.d.	n.d.
<i>A.baumannii</i>	20	16	20	22	18	21	20
<i>K. pneumoniae</i>	14	11	12	16	13	18	21
<i>E. coli</i>	12	14	13	15	14	19	22
<i>P. aeruginosa</i>	n.d	n.d	13	20	n.d	17	27

GN: Gentamisin, CIP: Ciprofloxacin. ^[b] n.d: Not detected.

3.5. Molecular Docking Results

In the docking study, Human peroxiredoxin 5 (PDB ID: 1HD2) was used to study the antioxidant effects of small molecule compounds and DNA gyrase B (PDB ID: 4URO) was used to study their mode of action as antimicrobial agents.

In molecular docking calculations performed with human peroxiredoxin 5 (PDB ID: 1HD2) enzyme, binding energy values of -6.26, -7.29, -6.98, -6.27 and -6.91 kcal/mol were obtained for **7**, **8**, **9**, **10** and **11** ligands, respectively. According to these values, the ligand showing the strongest binding was determined as **8**, and the ligand showing the weakest binding was determined as **7**. Binding models showing the molecular interactions between

compounds synthesized with human peroxiredoxin 5 (PDB ID: 1HD2) enzyme are presented in **Figures 5-9**.

Figure 5 shows the two-dimensional (2D) and three-dimensional (3D) structures of the complex between the human peroxiredoxin 5 (PDB ID: 1HD2) and compound **7**, with detailed binding interactions on the protein surface. Compound **7** exhibited conventional hydrogen bond interaction with GLU16 (2.19 Å) and LEU96 (2.04 Å), C–H bond interaction with LEU96 (2.93 Å), an alkyl interaction with LEU96 (4.55 Å), and π -alkyl interactions with ARG86 (5.41 Å), ALA90 (5.10 Å), and LEU96 (4.98 Å).

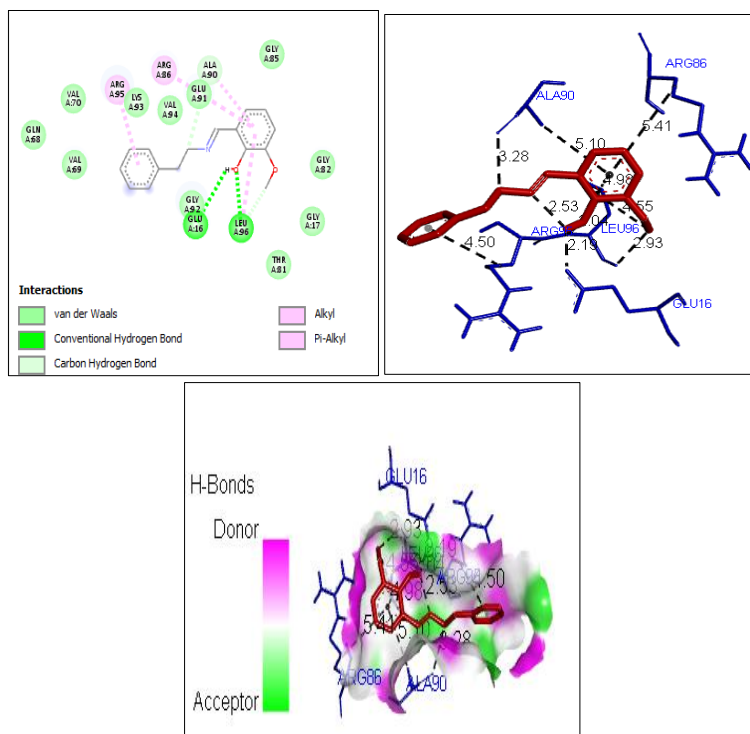


Figure 5. 2D and 3D receptor interactions and the surfaces around ligand (3D) for compound **7**.

Figure 6 shows the two-dimensional (2D) and three-dimensional (3D) structures of the complex between the human peroxiredoxin 5 (PDB ID: 1HD2) and compound **8**, with detailed binding interactions on the protein surface. Compound **8** exhibited C–H bonding with ASP81 (3.44 Å), a π -cation interaction with ARG84 (4.26 Å), and a π -anion interaction with GLU58 (3.48 Å). Additionally, a π -sigma interactions with ILE175 (3.71 Å) and π -alkyl interactions were observed between ARG84 (4.77 Å) and PRO87 (5.06 Å).

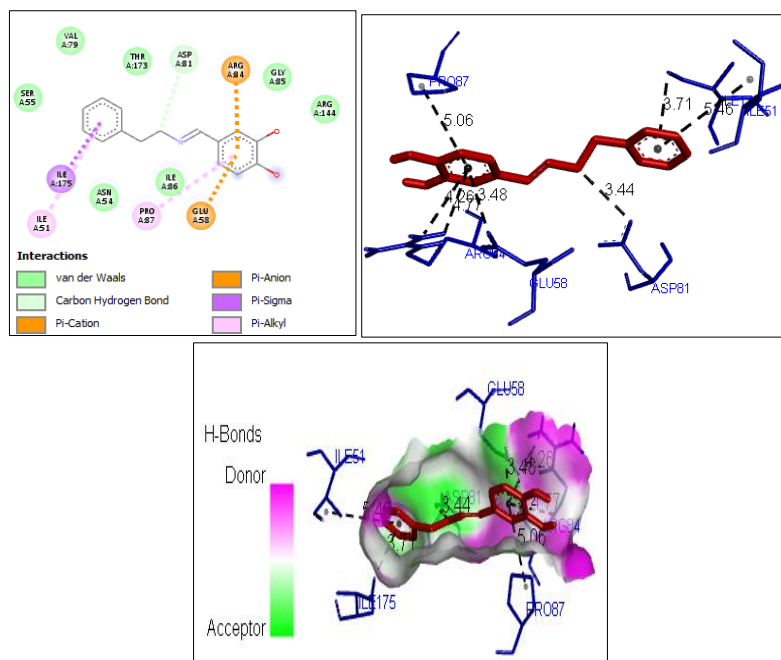


Figure 6. 2D and 3D receptor interactions and the surfaces around ligand (3D) for compound **8**.

Figure 7 shows the two-dimensional (2D) and three-dimensional (3D) structures of the complex between the human peroxiredoxin 5 (PDB ID: 1HD2) enzyme and compound **9**, as well as the binding interactions on the protein surface. Compound **9** exhibited a conventional hydrogen bond with GLN68 (2.00 Å), an amide- π stacked interaction with GLY92 (3.95 Å), and an alkyl interaction with VAL70 (3.91 Å). A π -sigma interaction was observed with LEU96 (3.69 Å), and π -alkyl interactions were observed with ALA90 (4.81 Å) and ARG95 (4.83 Å).

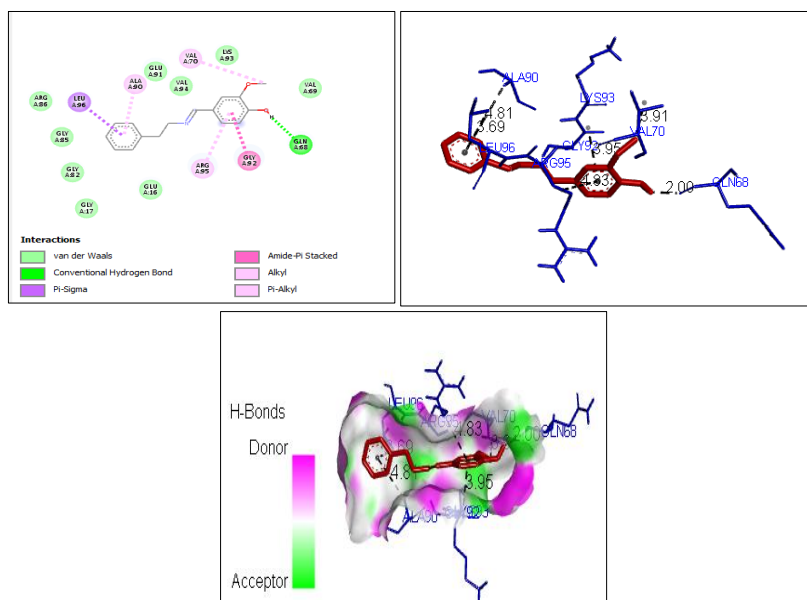


Figure 7. 2D and 3D receptor interactions and the surfaces around ligand (3D) for compound **9**.

Figure 8 shows two-dimensional (2D) and three-dimensional (3D) views of the complex between the human peroxiredoxin 5 (PDB ID: 1HD2) enzyme and compound **10**, as well as detailed binding interactions on the protein surface. Compound **10** exhibited conventional hydrogen bonding with GLU16 (2.01 Å) and LEU96 (2.06 Å), as well as a C-H bonding with ARG95 (3.65 Å). Additionally, π -alkyl interactions were observed between **10** and ARG95 (4.24 Å), ALA90 (4.62 Å) and LEU96 (4.62 Å).

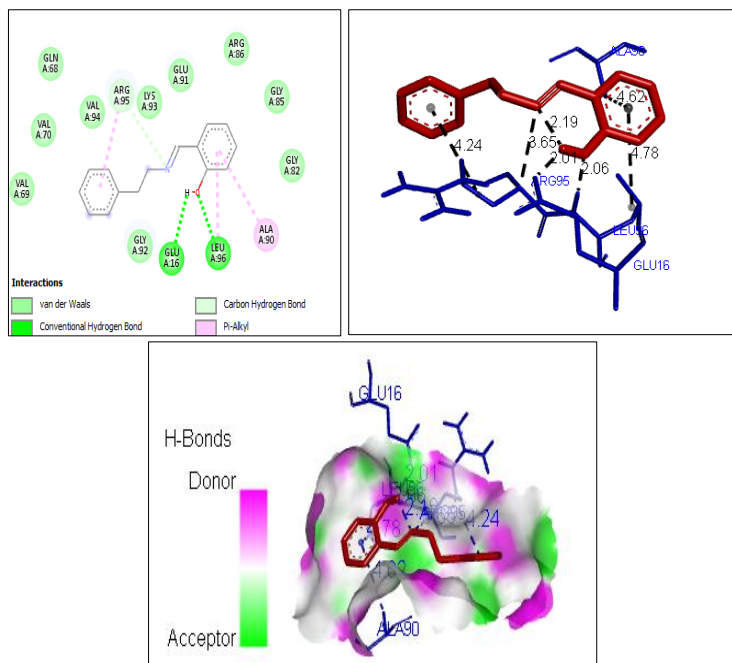


Figure 8. 2D and 3D receptor interactions and the surfaces around ligand (3D) for compound **10**.

Figure 9 shows the two-dimensional (2D) and three-dimensional (3D) structures of the complex between the human peroxiredoxin 5 (PDB ID: 1HD2) enzyme and compound **11**, as well as the detailed binding interactions on the protein surface. Compound **11** exhibited conventional hydrogen bonding with GLY92 (2.08 Å) and GLN68 (2.26 Å), and a π -donor hydrogen bond interaction with LEU96 (3.20Å). An amide- π stacked interaction was observed with GLY92 (3.57Å) and a π -sigma interaction with LEU96 (3.70 Å). Additionally, π -alkyl interactions were observed between **11** and ARG95 (4.96 Å) and ALA90 (4.86 Å).

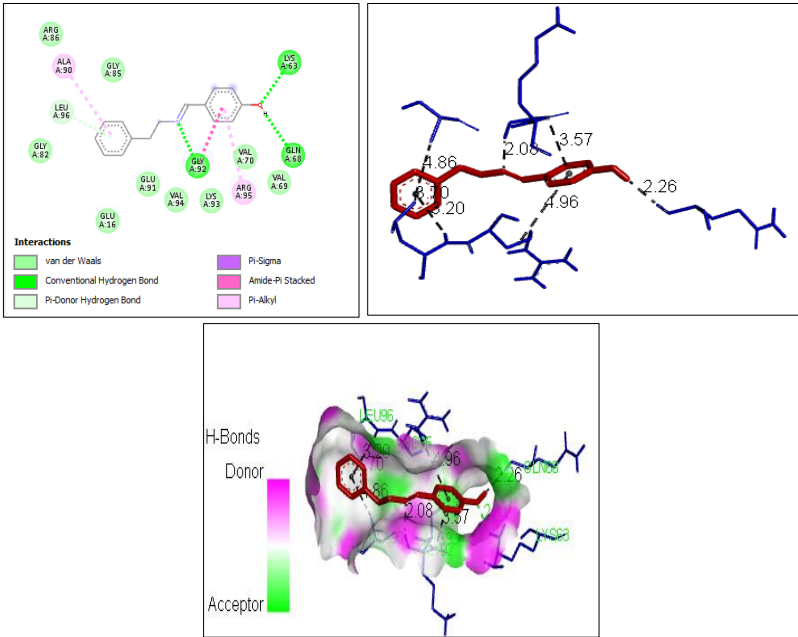


Figure 9. 2D and 3D receptor interactions and the surfaces around ligand (3D) for compound **11**.

A comprehensive compilation of the calculated docking scores, encompassing specific ligand–receptor binding affinities and spatial interaction profiles, is organized in **Table 4**.

Table 4. Docking results with (PDB ID:1HD2): Binding affinities and interaction profiles.

Bond Types / Interaction		Compound 7	Compound 8	Compound 9	Compound 10	Compound 11
Hydrogen Bonds	Conventional H-bond	GLU16 (2.19 Å) LEU96 (2.04 Å)	–	GLY92 (2.08 Å) GLN68 (2.26 Å)	GLU16 (2.01 Å) LEU96 (2.06 Å)	GLN68 (2.00 Å)
	C–H Bond	LEU96 (2.93 Å)	ASP81 (3.44 Å)	–	ARG95 (3.65 Å)	–

	π -Donor H Bond	–	–	LEU96 (3.20 Å)	–	–
Electrostatic	π -Cation	–	ARG84 (4.26 Å)		–	–
	π -Anion	–	GLU58 (3.48 Å)		–	–
	Amide-Pi Stacked	–	–	GLY92 (3.57 Å)	–	GLY92 (3.95 Å)
Hydrophobic	Alkyl	LEU96 (4.55 Å)	–	–	–	VAL70 (3.91 Å)
	π -Sigma	–	ILE175 (3.71 Å)	LEU96 (3.70 Å)		LEU96 (3.69 Å)
	π -Alkyl	ARG86 (5.41 Å) ALA90 (5.10 Å) LEU96 (4.98 Å)	ARG84 (4.77 Å) PRO87 (5.06 Å)	ARG95 (4.96 Å) ALA90 (4.86 Å)	ARG95 (4.24 Å) ALA90 (4.62 Å) LEU96 (4.78 Å)	ALA90 (4.81 Å) ARG95 (4.83 Å)

Table 5 presents a comparative overview of the lowest binding energies, reference RMSD values and estimated inhibition constants (K_i) for compounds **7–11**, based on molecular docking studies conducted with human peroxiredoxin 5 (PDB ID: 1HD2). Compound **8** stands out as the compound with the strongest binding potential to the target protein by showing the lowest binding energy with -7.29 kcal/mol. At the same time, the calculated K_i value for this compound is 4.54 μ M, which is one of the lowest inhibition constants, indicating high inhibitory activity. Compounds **9** and **11** also show remarkable inhibitory potential with binding energies of -6.98 and -6.91 kcal/mol, respectively, and low K_i values (7.69 and 8.57 μ M). In contrast, the binding energies of compounds **7** and **10** (-6.26 and -6.27 kcal/mol) are higher and their K_i values are also larger (25.65 and 25.43 μ M, respectively), which means lower efficiency in terms of binding and inhibition. It is observed that the reference RMSD values are close to each other for all compounds and the system maintains its stability.

Table 5. Docking results of compounds **7–11**.

Compounds	Lowest binding energy	Reference RMDS	Estimated inhibition constant, K_i (μ M)
7	-6.26	46.16	25.65
8	-7.29	44.52	4.54
9	-6.98	44.63	7.69
10	-6.27	46.77	25.43
11	-6.91	44.88	8.57

In molecular docking calculations performed with **DNA gyrase B (PDB ID: 4URO) enzyme**, binding energy values of -5.58, -5.76, -5.75, -5.34, and -6.05 kcal/mol were obtained for **7**, **8**, **9**, **10** and **11** ligands, respectively. According to these values, the ligand showing the strongest binding was determined as **11**, and the ligand showing the weakest binding was determined as **10**. Binding models showing the molecular interactions between compounds synthesized with DNA gyrase B (PDB ID: 4URO) enzyme are presented in **Figures 10-14**.

Figure 10 shows the two-dimensional (2D) and three-dimensional (3D) structures of the complex between the DNA gyrase B (PDB ID: 4URO) and compound **7**, with detailed binding interactions on the protein surface. Compound **7** exhibited conventional hydrogen bond with GLU58 (1.72 Å), a C–H bond interaction with ASP81 (3.55 Å), and π -cation interactions with ARG84 (4.98 Å). An amide- π stacking interaction was observed with ASN54 (4.18 Å), along with an alkyl interaction with PRO87 (4.73 Å). Additionally, π -alkyl interactions were observed with ILE175 (5.28 Å), PRO87 (4.59 Å), and ILE86 (5.24 Å).

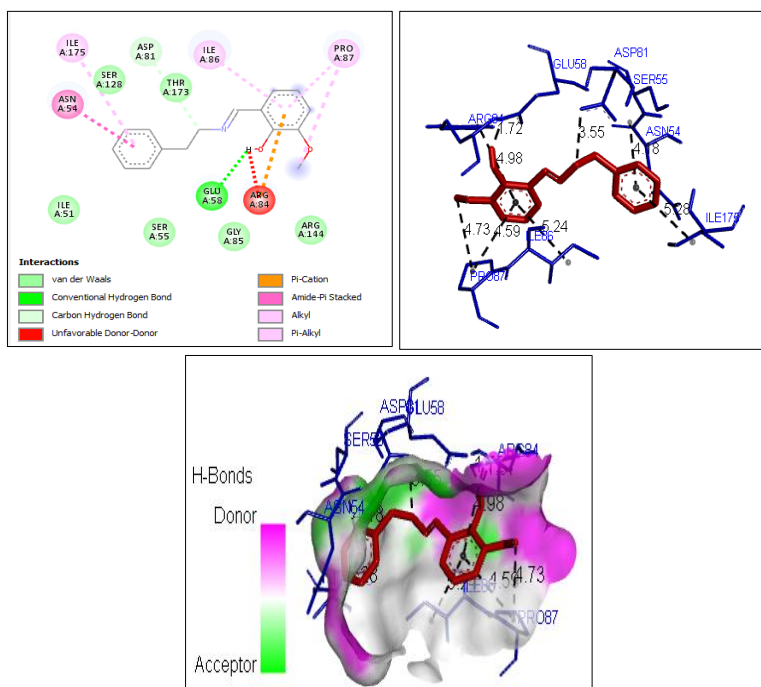


Figure 10. 2D and 3D receptor interactions and the surfaces around ligand (3D) for compound **7**.

Figure 11 shows the two-dimensional (2D) and three-dimensional (3D) structures of the complex between the DNA gyrase B (PDB ID: 4URO) and compound **8**, with detailed binding interactions on the protein surface. Compound **8** exhibited a carbon hydrogen bond with ASP81 (3.44 Å), π -cation interactions with ARG84 (4.26 Å), a π -anion with GLU (3.48 Å), a π -sigma with ILE175 (3.71 Å). Additionally, π -alkyl interactions between ILE51 (5.46 Å), PRO87 (5.06 Å), and ARG84 (4.77 Å).

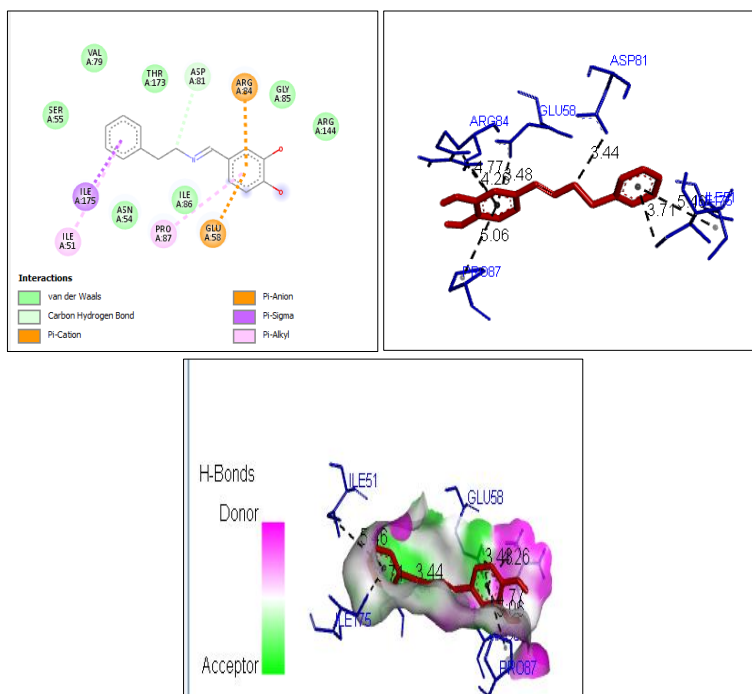


Figure 11. 2D and 3D receptor interactions and the surfaces around ligand (3D) for compound **8**.

Figure 12 shows the two-dimensional (2D) and three-dimensional (3D) structures of the complex between the DNA gyrase B (PDB ID: 4URO) and compound **9**, with detailed binding interactions on the protein surface. Compound **9** forms a conventional hydrogen bond with ARG144 (2.06 Å), a π -cation interaction with ARG84 (4.06 Å), a π -anion interaction with GLU58 (3.75 Å), and an amide- π stacking interaction with ASN54 (4.16 Å). In addition, alkyl interactions were observed with ARG84 (4.24 Å) and PRO87 (4.89 Å) and π -alkyl interactions involving PRO87 (4.78 Å), ARG84 (4.95 Å), and ILE175 (5.29 Å) were observed.

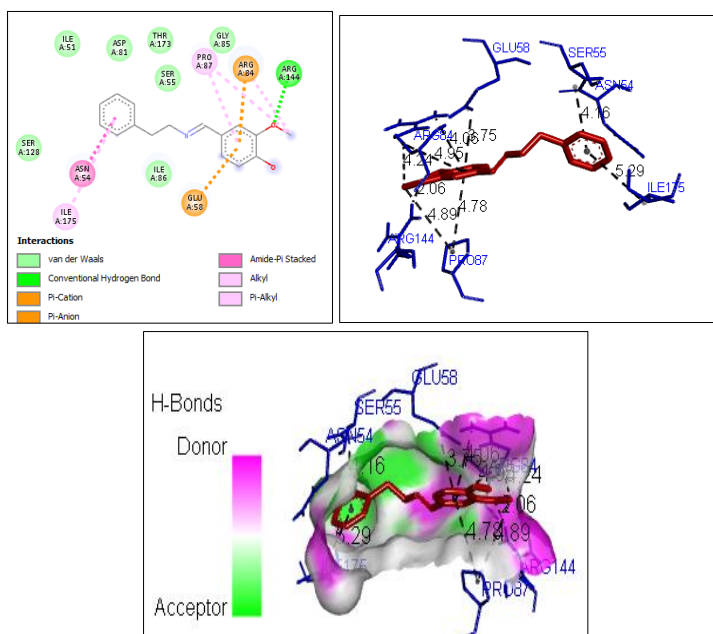


Figure 12. 2D and 3D receptor interactions and the surfaces around ligand (3D) for compound **9**.

Figure 13 shows the two-dimensional (2D) and three-dimensional (3D) structures of the complex between the DNA gyrase B (PDB ID: 4URO) and compound **10**, with detailed binding interactions on the protein surface. Compound **10** observed a conventional hydrogen bond with GLU58 (2.07 Å), a C–H bond with ASP81 (3.51 Å), a π -cation interaction with ARG84 (4.59 Å), a π -anion interaction with GLU58 (4.32 Å), and π -sigma interactions with ILE86 (3.88 Å). Also π -alkyl interaction was also observed with PRO87 (4.37 Å).

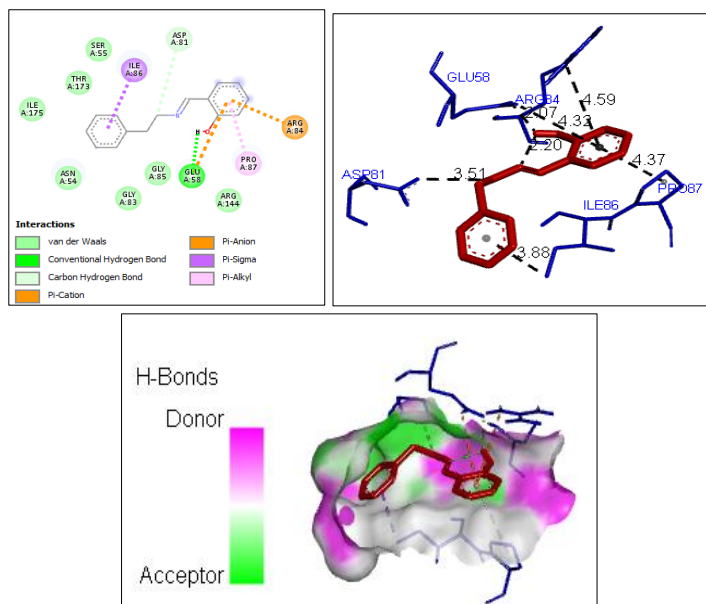


Figure 13. 2D and 3D receptor interactions and the surfaces around ligand (3D) for compound **10**.

Figure 14 shows the two-dimensional (2D) and three-dimensional (3D) structures of the complex between the DNA gyrase B (PDB ID: 4URO) and compound **11**, with detailed binding interactions on the protein surface. Compound **11** exhibited π -cation interactions with ARG84 (4.41 Å), π -anion interactions with GLU58 (4.39 Å), and amide- π stacked interactions with ASN54 (4.40 Å). A π -sigma interaction was also observed with ILE175 (3.98 Å), along with π -alkyl interactions between ILE86 (5.29 Å), PRO87 (4.15 Å), and ARG84 (4.82 Å).

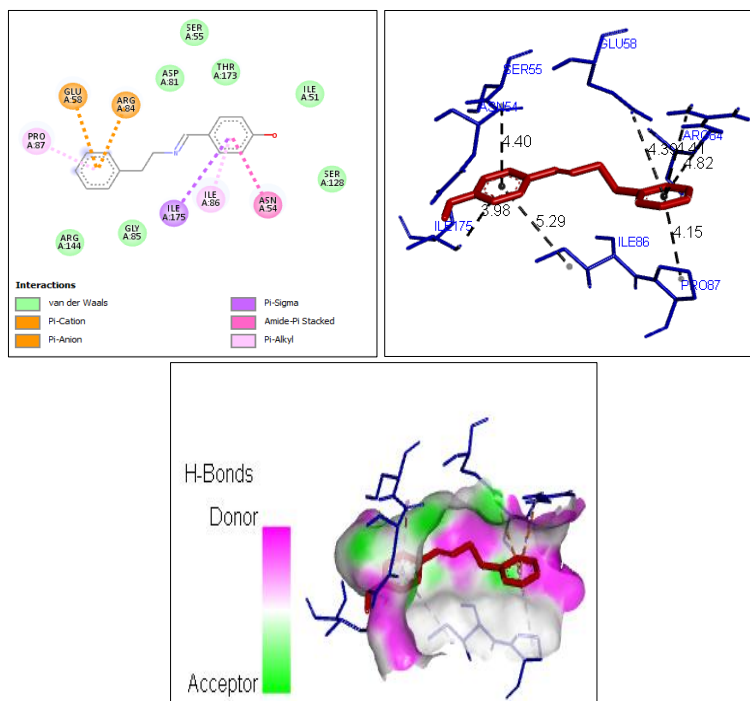


Figure 14. 2D and 3D receptor interactions and the surfaces around ligand (3D) for compound **11**.

The docking results, including binding affinities and interaction profiles, are comprehensively summarized in **Table 5**.

Table 6. Docking results with (PDB ID: 4URO) : Binding affinities and interaction profiles.

Bond Type	Interaction	Compound 7	Compound 8	Compound 9	Compound 10	Compound 11
HYDROGEN BONDS	Convention al H-bond	GLU58 (1.72 Å)	–	ARG144 (2.06 Å)	GLU58 (2.07 Å)	–
	C–H Bond	ASP81 (3.55 Å)	ASP81 (3.44 Å)	–	ASP81 (3.51 Å)	–
ELECTROSTATIC	π -Cation	ARG84 (4.98 Å)	ARG84 (4.26 Å)	ARG84 (4.06 Å)	ARG84 (4.59 Å)	ARG84 (4.41 Å)
	π -Anion	–	GLU58 (3.48 Å)	GLU58 (3.75 Å)	GLU58 (4.32 Å)	GLU58 (4.39 Å)
	Amide- π Stacked	ASN54 (4.18 Å)	–	ASN54 (4.16 Å)	–	ASN54 (4.40 Å)
HYDROPHOBIC	Alkyl	PRO87 (4.73 Å)	–	ARG84 (4.24 Å) PRO87 (4.89 Å)	–	–
	π -Sigma	–	ILE175 (3.71 Å)	–	ILE86 (3.88 Å)	ILE175 (3.98 Å)
	π -Alkyl	ILE175 (5.28 Å) PRO87 (4.59 Å) ILE86 (5.24 Å)	ILE51 (5.46 Å) PRO87 (5.06 Å) ARG84 (4.77 Å)	PRO87 (4.78 Å) ARG84 (4.95 Å) ILE175 (5.29 Å)	PRO87 (4.37 Å)	PRO87 (4.15 Å) ARG84 (4.82 Å) ILE86 (5.29 Å)

The moststable (lowest-energy) binding configurations obtained from the molecular docking studies conducted on the DNA gyrase B enzyme (PDB ID: 4URO), along with their corresponding reference RMSD values and estimated inhibition constants (K_i), are presented in a comparative table in **Table 6**. Based on these computational modeling datasets, compound **11** emerged as the most energetically favorable architecture among the tested series, displaying the lowest binding energy at -6.05 kcal/mol. This result reveals that compound **11** has a high affinity for the target protein and exhibits a strong binding tendency. In addition, the estimated inhibition constant (K_i) calculated for this compound is 36.64 μ M, indicating that it has a higher inhibitory potential compared to other compounds. However, the reference RMSD value of compound **11** was determined as 12.05 Å, which may indicate flexibility or instability of the binding position.

Similarly, compounds **8** and **9** have close values with binding energies of -5.76 kcal/mol and -5.75 kcal/mol, respectively. The K_i values of these compounds were determined as 59.81 μ M and 60.92 μ M, respectively, and are thought to exhibit moderate inhibitory properties. However, the high RMSD values of these compounds, 11.86 Å and 11.90 Å, respectively, indicate that the stability of the binding positions should be questioned. Compound **7** exhibits lower inhibitory activity with a binding energy of -5.58 kcal/mol and a K_i value of 81.30 μ M. The RMSD value was determined as 11.44 Å. On the other hand, compound **10** has the weakest binding energy of -5.34 kcal/mol and the highest inhibition constant of 122.57 μ M. These findings clearly reveal that compound **10** has the lowest inhibitory potential against the target protein. The RMSD value of compound **10** is 11.29 Å, which is similar to the other compounds.

When the overall evaluation is made, compound **11** stands out as one of the most potent inhibitor candidates in terms of target protein with both the lowest binding energy and the lowest K_i value. However, the fact that the reference RMSD values of all compounds are 11 Å above the reference RMSD values raises questions about the stability of the binding positions (**Table 7**). Therefore, it is recommended to perform advanced analyses such as molecular dynamics simulations in order to interpret the molecular docking findings more accurately and to verify the binding behaviors of the candidate compounds.

Table 7. Docking results of compounds 7-11.

Compounds	Lowest binding energy	Reference RMSD	Estimated inhibition constant, K_i (μM)
7	-5.58	11.44	81.30
8	-5.76	11.86	59.81
9	-5.75	11.90	60.92
10	-5.34	11.29	122.57
11	-6.05	12.05	36.64

3.6. ADME prediction results

For a compound to be considered a drug candidate, it must demonstrate good pharmacological activity and fall within acceptable ranges in terms of absorption, distribution, metabolism and excretion (ADME); it must also comply with Lipinski's Five Rules [45, 46]. The ADME properties of compounds **7–11** synthesised in this study were evaluated using the SwissADME tool, and the results are summarised in **Table 8**.

Table 8. Predicted drug similarity parameters of Schiff bases obtained from ADME analysis with the SwissADME program.

	Physicochemical Properties				
	7	8	9	10	11
Formula	$C_{16}H_{17}NO_2$	$C_{15}H_{15}NO_2$	$C_{16}H_{17}NO_2$	$C_{15}H_{15}NO$	$C_{15}H_{14}BrNO$
Molecular weight (g/mol)	255.31	241.29	255.31	225.29	304.18
Num. heavy atoms	19	18	19	17	18
Num. arom. heavy atoms	12	12	12	12	12
Fraction CSP3	0.19	0.13	0.19	0.13	0.13
Num. rotatable bonds	5	4	5	4	4
Num. h-bond acceptors	3	3	3	2	2
Num. h-bond donors	1	2	1	1	1
Molar refractivity	77.71	73.24	77.71	71.22	78.92
TPSA	41.82 Å ²	52.82 Å ²	41.82 Å ²	32.59 Å ²	32.59 Å ²

Lipophilicity					
LOG P _{o/w} (iLOGP)	2.72	2.10	3.04	2.59	3.11
LOG P _{o/w} (XLOGP3)	2.89	3.16	3.28	3.10	3.90
LOG P _{o/w} (WLOGP)	3.06	2.76	3.06	3.05	3.82
LOG P _{o/w} (MLOGP)	2.49	2.24	2.49	2.86	3.50
LOG P _{o/w} (SILICOS-IT)	4.12	3.60	4.12	4.09	4.76
Consensus LOG P _{o/w}	3.06	2.77	3.20	3.14	3.82
Water Solubility					
LOG S (ESOL)	-3.38	-3.56	-3.63	-3.45	-4.41
Solubility	1.06e-01 mg/ml ; 4.16e-04 mol/l	6.71e-02 mg/ml ; 2.78e-04 mol/l	6.03e-02 mg/ml ; 2.36e-04 mol/l	8.03e-02 mg/ml ; 3.56e-04 mol/l	1.18e-02 mg/ml ; 3.87e-05 mol/l
CLASS	Soluble	Soluble	Soluble	Soluble	Moderately soluble
Pharmacokinetics					
GI Absorption	High	High	High	High	High
BBB Permeant	Yes	Yes	Yes	Yes	Yes
P-GP Substrate	No	No	No	No	No
CYP1A2 Inhibitor	Yes	Yes	Yes	Yes	Yes
CYP2C19 Inhibitor	Yes	No	Yes	Yes	Yes
CYP2C9 Inhibitor	No	No	No	No	Yes
CYP2D6 Inhibitor	Yes	Yes	Yes	Yes	Yes
CYP3A4 Inhibitor	No	No	No	No	No
LOG K _p (Skin permeation) CM/s	-5.81 cm/s	-5.53 cm/s	-5.53 cm/s	-5.47 cm/s	-5.39 cm/s
Druglikeness					
Lipinski	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation	Yes; 0 violation
Ghose	Yes	Yes	Yes	Yes	Yes
Veber	Yes	Yes	Yes	Yes	Yes
Egan	Yes	Yes	Yes	Yes	Yes
Muegge	Yes	Yes	Yes	Yes	Yes
Biavailability Score	0.55	0.55	0.55	0.55	0.55
Medicinal Chemistry					
PAINS	0 alert	1 alert: catechol_A	0 alert	0 alert	0 alert
Brenk	1 alert: imine	2 alerts: catechol, imine	1 alert: imine	1 alert: imine	1 alert: imine
Leadlikeness	Yes	No; 1 violation: MW<250	Yes	No; 1 violation: MW<250	No; 1 violation: XLOGP3>3.5
Synthetic accessibility	2.48	2.25	2.36	2.23	2.33

Computer-aided screening protocols were applied to predict the pharmacokinetic behaviour, oral drug-likeness potential and key ADME properties of compounds **7–11**. Within the framework of a rational drug design approach, a detailed evaluation of the physicochemical descriptors and pharmacokinetic profiles of lead compounds is of critical importance for ensuring the highest possible levels of systemic bioavailability, therapeutic efficacy and safety margins [47]. In this study, the basic molecular properties of compounds

(7–11) were compared and their drug development potentials were discussed. Estimating drug-likeness fundamentally centers on forecasting a molecule's oral bioavailability potential, thereby determining its structural suitability as an orally active therapeutic agent [33]. The assessment of a compound's ADME properties is based on its physicochemical properties, which are critical to the design and development process.

The molecular weights of the compounds ranged from 225.29–304.18 g/mol. The lowest molecular weight was observed in compound **10** (225.29 g/mol), while the highest value was observed in bromine-containing compound **11** (304.18 g/mol). When the Csp³ carbon ratios are examined, it is seen that compounds **7** and **9** (0.19) have a more saturated character, while other compounds contain more aromatic and planar structures.

TPSA (total polar surface area) values reflect the hydrophilicity degrees of the molecules. While compound **8** has the highest TPSA value with 52.82 Å², the TPSA value of compounds **10** and **11** was calculated as 32.59 Å². The fact that TPSA is below 90 Å² shows that all compounds are suitable for absorption by passive diffusion in the gastrointestinal tract.

Lipinski's "rule of five" is widely accepted in the literature as a fundamental criterion for assessing the oral bioavailability potential of chemical compounds. According to this approach, for a molecule to exhibit "drug-like" properties, it must not exceed certain structural limits: (i) a maximum of 10 hydrogen bond acceptors, (ii) a maximum of 5 hydrogen bond donors, (iii) a molecular weight below 500 Da, and (iv) a lipophilicity with a log P value of less than 5 [48]. In this context, the Lipinski parameters were calculated in detail for all the synthesised derivatives (7–11); the detailed findings are presented in **Table 8**. In particular, it was observed that all the ligands examined fully complied with these rules, a finding that supports the structural suitability of these compounds as potential drug candidates for oral administration.

Molecular lipophilicity, indicated by LogP values, is a key determinant of membrane permeability [49]. All compounds showed LogP values below 5, in line with Lipinski's criteria, indicating favorable membrane permeability. Consensus Log Po/w values reflect the lipophilicity levels of the compounds. In this respect, the most lipophilic compound is **11** (Log Po/w = 3.82), followed by compounds **9** (3.20) and **10** (3.14). The lowest lipophilicity belongs to compound **8** (2.77). According to Log S (ESOL) values, all compounds are in the water-soluble class; however, compound **11** (-4.41) is separated from the others by being only in the "moderately soluble" category.

Based on the predictive ADME screening, all synthesized compounds are anticipated to possess excellent gastrointestinal absorption profiles and exhibit the capacity to successfully permeate the blood–brain barrier. These compounds, which are not P-glycoprotein substrates, are advantageous in terms of absorption and bioavailability. However, their potential interaction with cytochrome P450 enzymes should be taken into consideration. All compounds are inhibitors of CYP1A2 and CYP2D6 enzymes. In

addition, compounds **7**, **9**, **10** and **11** inhibit CYP2C19; only compound **11** also inhibits the CYP2C9 enzyme. All compounds successfully passed the Lipinski, Ghose, Veber, Egan, and Muegge rules, and their bioavailability scores were calculated as 0.55.

Finally, all compounds are considered to be easily synthesized molecules with synthetic accessibility scores ranging from 2.23–2.48. This increases the applicability of structural modifications in potential optimization processes.

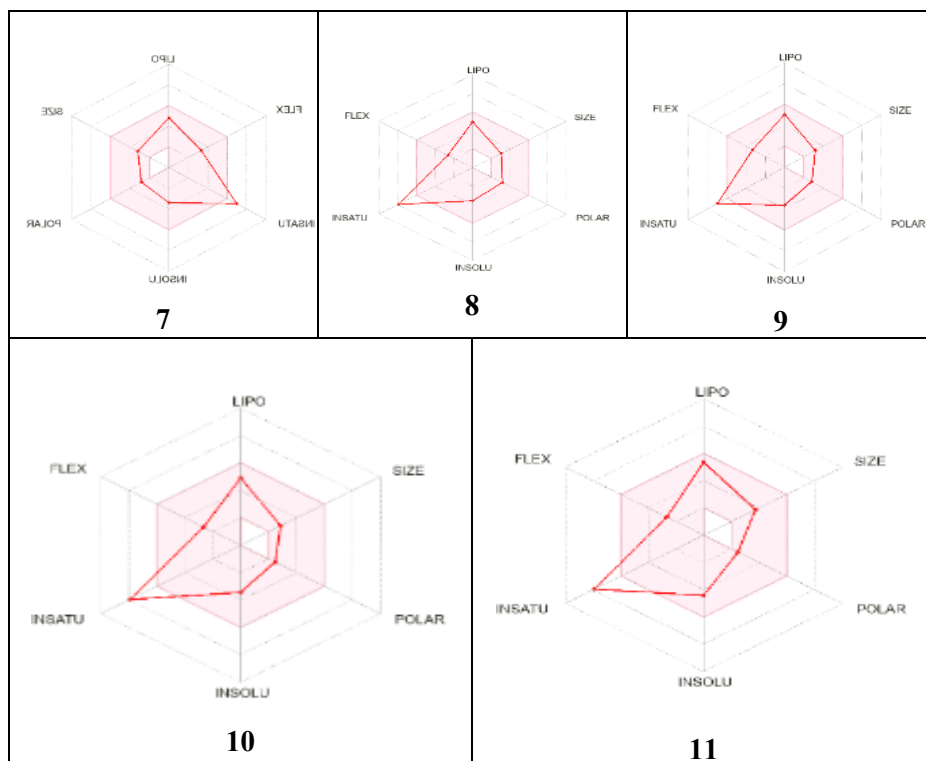


Figure 15. Bioavailability radars of all synthesized compounds (7-11).

Figure 15 shows the bioavailability radar plots for the synthesised Schiff bases (**7–11**). The pink area of this graph shows the ideal limits determined for six critical parameters: lipophilicity (Lipo), molecular weight (Size), topological polar surface area (Polar), water insolubility (Insolu), degree of unsaturation (Insatu) and molecular flexibility (Flex). At this stage of our study, we have also carried out a highly detailed physicochemical characterisation assessment, ranging from the lipophilicity and water solubility properties of the compounds to their pharmacokinetic profiles, drug-likeness criteria and potential toxicity risks.

4. CONCLUSION AND RECOMMENDATIONS

In this study, Schiff base derivatives (**7-11**) containing hydroxyl groups were synthesised and their structural characterisations were carried out. The antioxidant capacities of the compounds were assessed using reduction assays (Fe^{3+} and Cu^{2+}) and free radical scavenging assays (DPPH and ABTS). Compound **7** showed relatively higher activity in the Fe^{3+} reducing power and ABTS radical scavenging assays, which may be attributed to the presence of ortho-hydroxyl and meta-methoxy substituents that can enhance electron-donating ability and radical stabilization. Compound **8** exhibited superior performance in Cu^{2+} reducing power and DPPH radical scavenging assays, which could be associated with the presence of ortho-para dihydroxyl groups facilitating hydrogen atom donation and stabilization of the resulting phenoxyl radicals. Overall, these findings suggest that both the number and positional arrangement of hydroxyl substituents play a crucial role in determining antioxidant activity. These results reveal that the number and position of hydroxyl groups are decisive on antioxidant activity. Antimicrobial test results showed that compound **10** showed higher antibacterial activity against *A. baumannii* strain than GN and CIP due to the presence of ortho-hydroxyl group in its aromatic ring. These findings indicate that the positions of hydroxyl groups play an important role in antibacterial activity. Molecular docking studies revealed that compound **8** had the strongest binding affinities with the enzyme human peroxiredoxin 5 (PDB: 1HD2) and compound **11** with the enzyme bacterial DNA gyrase B (PDB: 4URO). ADME analyses showed that all compounds exhibited drug-like properties and had favourable pharmacokinetic profiles. In conclusion, the data obtained in this study reveal that compounds **7** and **8** are leading candidates for antioxidant and compounds **10** and **11** are leading candidates for antibacterial activity and that the functional groups in their structures have decisive effects on their biological activities.

Research and Publication Ethics Statement

The entire process of the manuscript was carried out in compliance with the research and publication ethics guidelines of the Celal Bayar University Journal of Science.

Author's Contributions

Özlem Gündoğdu Aytaç: Conceptualization, methodology, investigation, software, formal analysis, supervision.

Sertan Aytaç: Conceptualization, methodology, investigation, software, formal analysis.

Kübra Öztürk: Methodology, investigation,, writing, original draft preparation.

Çiğdem Er Çalışkan: Investigation, writing, original draft preparation.

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