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Original Article

Design, Synthesis, Characterization of New Isatin Derivatives with Sulfonamide Moiety as Potential Antibacterial Agents

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Abstract

Background: *Klebsiella pneumoniae* is a clinically significant, multidrug-resistant (MDR) pathogen in humans and a major cause of hospital-acquired infections, leading to increased morbidity and mortality due to limited treatment options. According to the World Health Organization (WHO), antimicrobial resistance is responsible for approximately 1.27 million deaths globally each year. molecular operating environment (MOE) software was used for molecular docking studies to identify the most promising compounds prior to synthesis. New isatin derivatives were synthesized through the reaction of (Z)-ethyl 4-(5-fluoro-2-oxoindolin-3-ylideneamino) benzoate (A1) and (Z)-ethyl 4-(5-methyl-2-oxoindolin-3-ylideneamino) benzoate (A2) with sulfadiazine. The synthesized derivatives were characterized using FT-IR and ^{1}H-NMR spectroscopy. The antibacterial activity of the compounds was evaluated in vitro by measuring the inhibition zones and comparing them with those produced by the standard antibiotic amikacin. **Aim:** This study aimed to design, synthesize, characterize, and evaluate the antibacterial potential of new isatin derivatives containing a sulfonamide moiety, using molecular docking and in vitro assays against *K. pneumoniae*. **Methodology:**Molecular docking was performed using MOE 2015. 10 software programs against the target protein (PDB: 8QK2, chain A). Two Schiff base intermediates (A1–A2) were synthesized from substituted isatin and ethyl-4-aminobenzoate, followed by reaction with sulfadiazine to produce final derivatives (B1–B2). Structural characterization was performed using FT-IR, ^{1}H-NMR, melting point determination, and TLC. Antibacterial activity was assessed using the agar well diffusion method. **Results:** Docking analysis showed that derivative B2 had the highest docking score (-8.395), while B1 scored (-7.954), with interactions involving Phe141, Trp46, Arg80, and Asn79. FT-IR and ^{1}H-NMR analyses confirmed the successful synthesis of the derivative. Biological evaluation demonstrated that B2 exhibited stronger antibacterial activity than B1, particularly at the higher concentration (0.06), producing inhibition zones up to 35 mm. These findings indicate that B2 is the most promising derivative against *k. pneumoniae*. **Conclusion:**The integration of sulfonamide moieties with isatin-based structures significantly enhanced antibacterial activity. Molecular docking results indicated B2 exhibited the strongest binding affinity compared to B1, while biological assays confirmed B2 as the most promising antibacterial activity against *K. Pneumoniae*. These findings support the potential of isatin–sulfonamide hybrids as effective scaffolds for future antimicrobial drug development.

Keywords:*Antimicrobial activity; Isatin; hybrid compounds; K. pneumoniae; Schiff bases*.

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Introduction

The investigation of medicinally privileged heterocyclic scaffolds represents an important subject in the field of drug discovery. The isatin (1H-indole-2,3-dione, Figure 1) moiety is prevalent in nature (Nagham *et al*., 2020), and its derivatives exhibit a range of pharmacological properties, including anticancer, antitubercular, anti-HIV, antimalarial, and antibacterial activities (Guo, 2018). Isatin is a derivative of indole that contains two cyclic carbonyl groups, one with five members and the other with six, with carbonyl groups at the second and third positions and nitrogen at the first position. It is considered a suitable moiety for chemical ring conversion reactions (Nain, 2023).

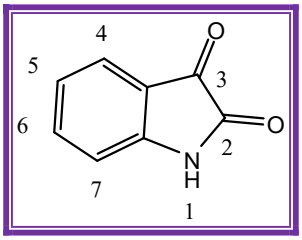


Figure 1: *Structure of Isatin*

In addition, the emergence of antibiotic-resistant bacterial strains has become a worldwide health concern. Multidrug-resistant (MDR) microorganisms are increasingly associated with severe illnesses that have restricted treatment alternatives, presenting a significant challenge to global public health systems (Ahmed *et al*., 2024). According to the World Health Organization (WHO), antimicrobial resistance is responsible for approximately 1.27 million deaths globally each year(Murray et al., 2022). *Klebsiella pneumoniae* is a serious multidrug-resistant bacterium, especially in healthcare settings. It is a Gram-negative bacterium that causes many hospital-acquired diseases, such as pneumonia, sepsis, and urinary tract infections (Zhu *et al*., 2021). Its ability to develop resistance, particularly to β-lactams and carbapenems, placed it on the WHO list of critical infectious agents requiring urgent development of new treatment options (Bassetti *et al*., 2018).

Isatin has been identified as a crucial element in numerous studies concerning the development of antibacterial agents. Various chemical modifications, such as Schiff base formation, N-alkylation/acylation, and metal complexation, have allowed researchers to synthesize diverse chemical entities, many of which exhibited promising antibacterial activity (Tehrani *et al*., 2016). Schiff bases are well-known ligands derived from aromatic aldehydes and alkyl diamines, categorized by the number of donor atoms they possess, including uni-, di-, tri-, and tetradentate ligands (Hernández-Molina and Mederos, 2003). Schiff bases are essential intermediates in the synthesis of diverse molecules with commercial and medicinal applications, enabled by processes such as ring closure, cycloaddition, and substitution reactions. Moreover, they demonstrate a wide range of biological activities, including anti-inflammatory, allergen-inhibitory, and antioxidant properties (Thakor *et al*., 2024). Schiff bases are frequently used as intermediates in the synthesis of therapeutic compounds because they provide a flexible framework for introducing specific functionalities and improving the pharmacokinetic properties of drugs (Tsacheva *et al*., 2023). These characteristics contribute significantly to the development of new antibacterial agents, particularly against resistant strains such as *K. pneumoniae*.

Materials and Methods

The molecular operating environment program was used in an in silico study to show the precise binding of the synthesized derivatives with target receptors. The melting points were measured uncorrected using an electrothermal 9200 instrument. The 1020 GS-silica gel 60 type was employed to follow the reaction progression. A Fourier transform infrared (FT-IR) spectrophotometer (8400s, Shimadzu, KBr) was utilized to identify the synthesized derivatives, Pharmacy Faculty, Kufa University. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were acquired using a 300 MHz Bruker spectrometer at Tehran University, Iran.

Molecular Docking part

Molecular docking studies were performed using the Molecular Operating Environment 2015.10 software to investigate the binding affinity of the synthesized compounds (B1 and B2) against the target protein (PDB: 8qk2/chain A). The crystal structure of the protein was retrieved and prepared by removing water molecules, adding hydrogen atoms, and correcting ionization states to ensure proper protonation. The ligands (B1 and B2) were built and energy-minimized within MOE to obtain stable 3D conformations prior to docking. The active site was identified based on the co-crystallized binding pocket, involving key amino acids, including Phe141, Trp46, Arg80, and Asn79. Docking simulations were carried out using the default MOE placement method followed by energy minimization refinement. The binding affinity of the ligand-protein complexes was evaluated using the S-score function, and conformational stability was assessed based on RMSD values.

Chemical part

1.General procedure for the synthesis of schiff bases derivatives A (1-2)(Altalhi, 2023)

The synthesis of Schiff base derivatives A (1-2) is shown in scheme 1. By dissolving the reactants in absolute ethanol with four to five drops of glacial acetic acid, the condensation reaction between the same molar ratio of 5-fluoro isatin, 5-methyl isatin (0.006 mol, 1 g), and ethyl-4-amino benzoate (0.006 mol, 1 g) was mixed. After raising the reaction temperature to 65–70°C, it was refluxed for 48 hours while being stirred. The reaction steps (hexane: ethyl acetate, 3:2 v/v) were followed using TLC analysis. The resulting Schiff base was finely recrystallized from ethanol after being filtered and repeatedly washed in distilled water and cold water.

Table 1. Physical properties of schiff bases derivatives (A 1-2)

Symbol	Chemical formula	Color	Yield %	M.Wt	M.P	R_f
A1	$C_{17}H_{13}FN_2O_3$	Yellow	85	312.30	170 – 172 °C	0.65
A2	$C_{18}H_{16}N_2O_3$	Red	88	308.33	95 - 97°C	0.7

Compound A1 (C17H13FN2O3), The FT-IR (cm^{-1}) showed some clear peaks of absorption bands, 1691cm^{-1} stretching bands of (C=N) Schiff base, 3221cm^{-1} stretching bands of (NH) group of amide, 2935 cm^{-1} stretching bands of (C-H) aromatic ring, 1602 cm^{-1} stretching bands of (C=O) amide, 1512 cm^{-1} stretching bands of (C=C) aromatic ring, the absorption band at 1176 and 1107 cm^{-1} was due to stretching bands of the ester (C-O).

Compound A2 ($C_{18}H_{16}N_2O_3$), The FT-IR (cm^{-1}) showed some clear peaks of absorption bands, 1668 cm^{-1} stretching bands of (C=N) Schiff base, 3221cm^{-1} stretching bands of (NH) group of amide, 2929 cm^{-1} stretching bands of (C-H) aromatic ring, 1621 cm^{-1} stretching bands of (C=O) amide, 1512 cm^{-1} stretching bands of (C=C) aromatic ring, the absorption band at 1153 and 1097 cm^{-1} was due to stretching bands of the ester (C-O) (AntoArockia *et al* 2013)

2.General procedure for the Synthesis of isatin derivatives B (1-2) (Alibeg and Mohammed 2024, Patil *et al*. 2023)

The produced ligands in the first stage were mixed in equal moles (0.002 mol, 0.5 g) of Schiff base derivatives with sulfadiazine (0.002 mol, 0.4 g) in 20 ml of N, N-dimethyl formamide as a solvent. Refluxing the reaction mixture for 12 hrs. The reaction's termination was confirmed by thin layer chromatography (TLC) using a 3:2 v/v hexane to ethyl acetate ratio. Crushed ice was added after the fluid had been reduced by half. After a day, the raw material was removed by filtering, washed with cold water, and then recrystallized from hot ethanol.

Table 2. Physical properties of isatin derivatives (B 1-2)

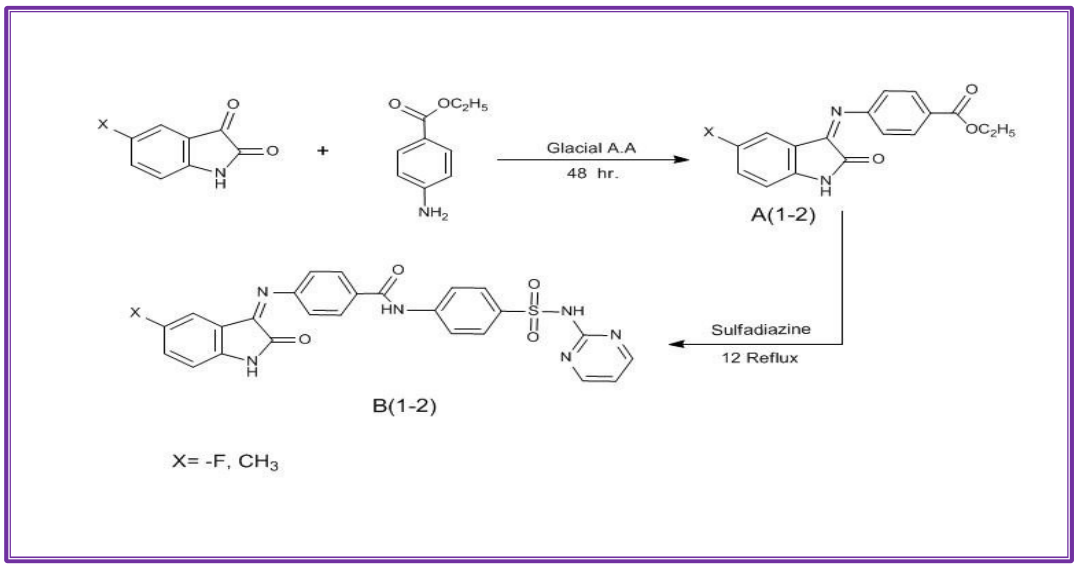
Symbol	Chemical formula	Color	Yield %	M.Wt	M.P	R_f
B1	$C_{25}H_{17}FN_6O_4S$	Brown	83	516.50	148 – 150 °C	0.55
B2	$C_{26}H_{20}N_6O_4S$	Yellow	95	512.54	103 – 105 °C	0.65

Compound B1 ($C_{25}H_{17}FN_6O_4S$), The FT-IR (cm^{-1}) showed some clear peaks of absorption bands, 1618 cm^{-1} stretching bands of newly (C=O) amide group, 1699 cm^{-1} stretching bands of (HC=N) pyrimidine group of amide, 2954 cm^{-1} stretching bands of (C-H) aromatic ring, 1523 cm^{-1} stretching bands of (C=C) aromatic ring, the absorption band at 1278 and 1190 cm^{-1} was due to two stretching bands of the (SO_2) group.

1H-NMR (300 MHz, DMSO-d6) δ of compound B1: δ 8.47 (s, 1H, NH-C=O amide), 10.58 (s, 1H, NH-C=O isatin), 7.97 (s, 1H, NH-SO_2), 7.01-7.93 (m, aromatic ring-H).

Compound B2 ($C_{26}H_{20}N_6O_4S$), The FT-IR (cm^{-1}) showed some clear peaks of absorption bands, 1620 cm^{-1} stretching bands of newly (C=O) amide group, 1662 cm^{-1} stretching bands of (HC=N) pyrimidine group of amide, 2981 cm^{-1} stretching bands of (C-H) aromatic ring, 1523 cm^{-1} stretching bands of (C=C) aromatic ring, the absorption band at 1278 and 1172 cm^{-1} was due to two stretching bands of the (SO_2) group.

1H-NMR (300 MHz, DMSO-d6) of compound B2: δ8.47 (s, 1H, NH-C=O amide), 10.37 (s, 1H, NH-C=O isatin), 7.97 (s, 1H, NH-SO2), 2.22 (s, 3H, -CH_3), 7.00-7.94 (m, aromatic Ring-H). The synthetic pathway is illustrated in (scheme 1).



Scheme 1: Synthesis of intermediate and final compounds

Antibacterial activity part

The antibacterial activity of the synthesized compound was evaluated using the agar well diffusion method as described by Fahad *et al*. (2019) with slight modifications. The compounds B1 and B2 were dissolved in dimethyl-sulfoxide (DMSO) to prepare final concentrations of 0.05 mg/mL and 0.06 mg/mL, respectively. Clinical isolates *k.pneumoniae* obtained from different clinical samples were suspended in sterile normal saline and adjusted to 0.5 MacFarland standard (≈1.5 × 10^8 CFU/mL). The solution with bacterial strain was inoculated onto Muller-Hinton agar (Hi-Media) plates under aseptic conditions. Well of 8 mm diameter were then prepared in the agar and filled 75 µL of each compound solution. Amikacin was used as a positive control. Finally, the plates were incubated at 37 for 24 hours. After incubation, antibacterial activity was determined by measuring the diameter of inhibition zones in millimeters and comparing them with the standard antibiotic.

Results

Docking part:

The software program Molecular Operating Environment (MOE), specifically version 2015.10, was used to carry out molecular docking. The compound's activity is assessed using the S. score and the RMSD. The S. score shows the binding affinity between the ligand molecule and the target protein,

with a lower score suggesting a greater contact with the receptor. The RMSD (root mean square deviation) shows the average distance between the ligand atoms and the tested active site. According to table 3, the synthesized derivative B2 had the highest docking score (-8.395) in a protein sequence (PDB code: 8qk2/chain A) when compared to the other derivative B1 (-7.954) and figures (2), (3), and (4).

Table 3. S score and RMSD with Binding site of amino acids in 8qk2/chain A

Symbol	R- group	S. score ΔG (Kcal/mol)	RMSD	Binding site Number	Amino acids
B1	F	-7.954	1.111	4	Phe 141, Trp 46, Arg 80, Asn79
B2	CH_3	-8.395	1.783	4	Phe 141, Trp 46, Arg 80, Asn79
Standard Ligand	-	-8.236	1.632	4	Phe 141, Trp 46, Arg 80, Asn79

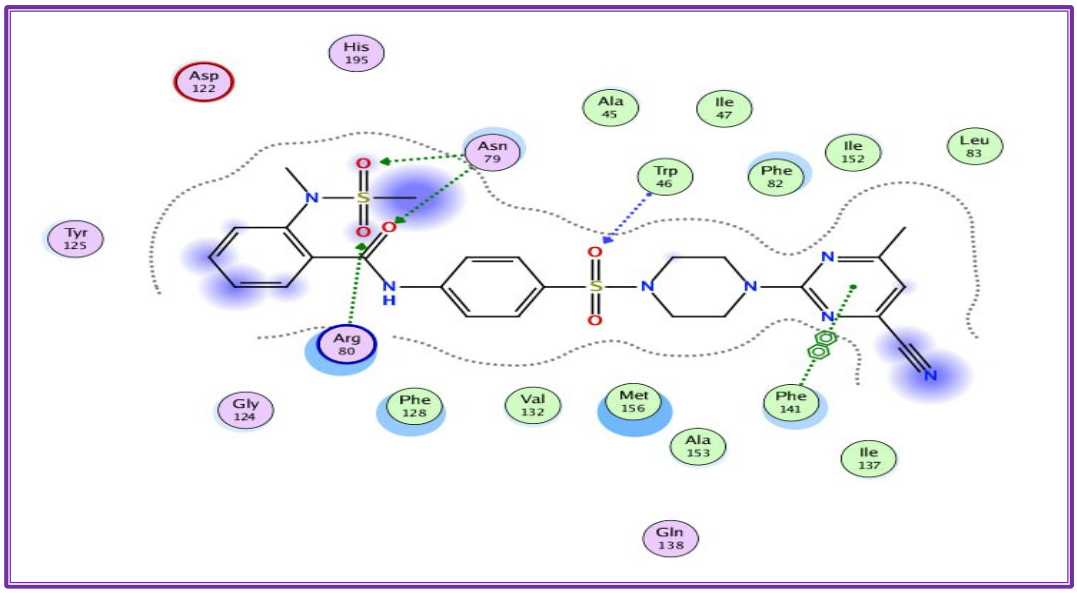


Figure 2: Describes the Two-Dimensional Image of standard ligand Binding with 8qk2/chain A

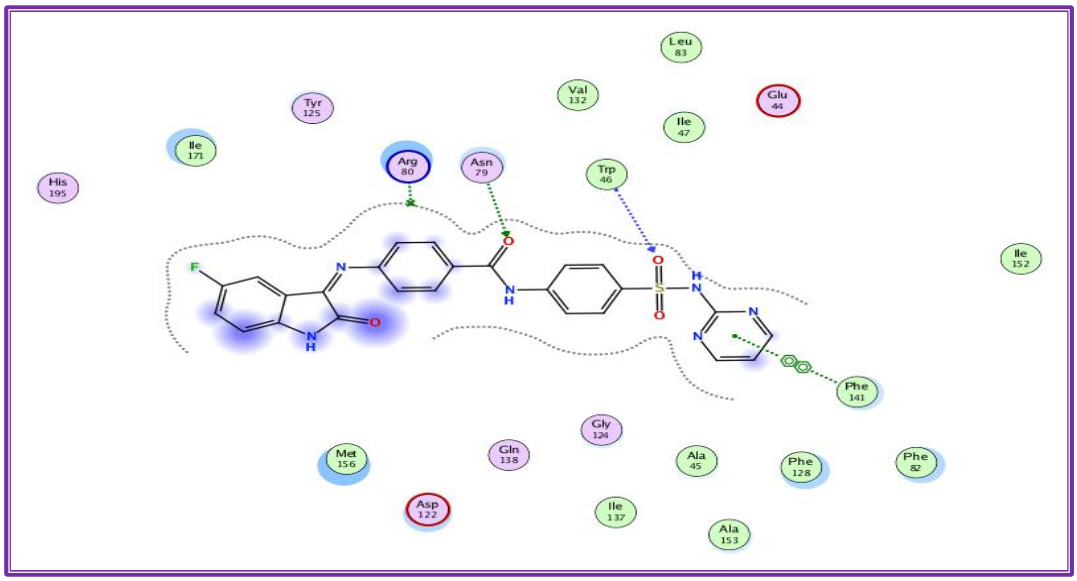


Figure 3: Describes the Two-Dimensional Image of Compound B1 Binding with 8qk2/chain A

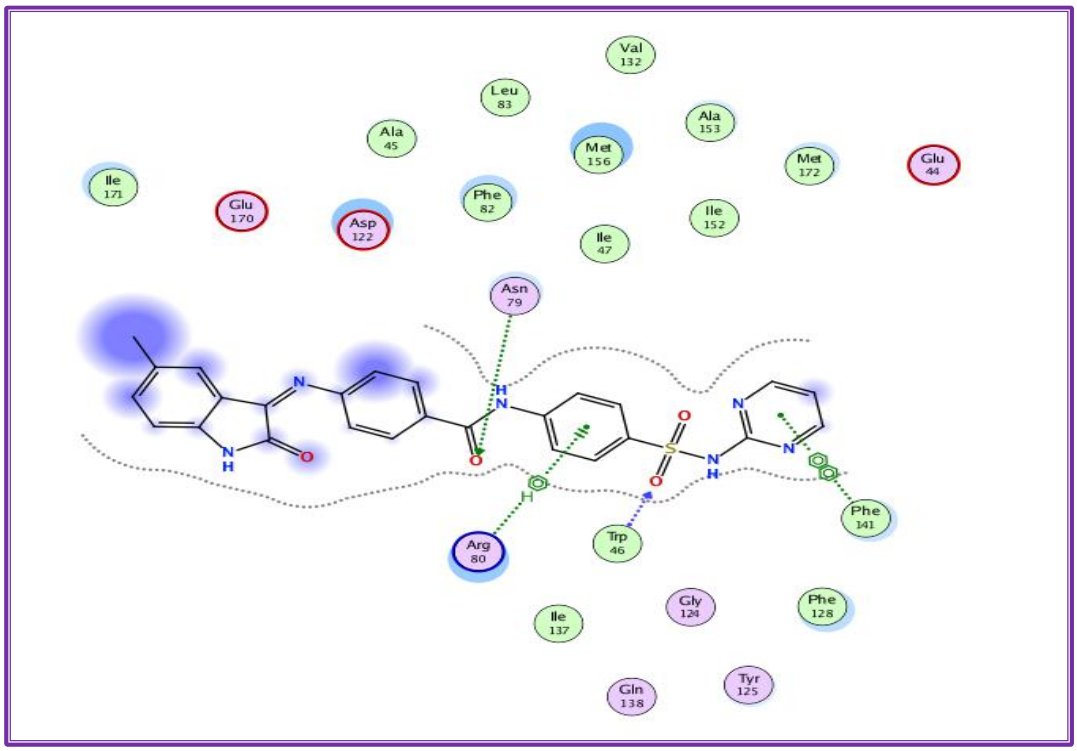


Figure 4: Describes the Two-Dimensional Image of Compound B2 Binding with 8qk2/chain A

Organic Identification

FT-IR spectroscopy confirmed the formation of the synthesized compounds. Characteristic absorption bands corresponding to the imine (C=N) group were observed at 1691 cm^{-1} and 1668 cm^{-1}, indicating successful formation of Schiff base derivatives. In the second step, the formation of the final isatin–sulfadiazine derivatives B1 and B2 was confirmed by the appearance of new amide (C=O) bands at 1618 cm^{-1} and 1620 cm^{-1}, respectively. The disappearance of the primary amine (NH_2) peak further supported the successful completion of the reaction.

^{1}H-NMR spectra also confirmed the structures of the synthesized compounds. Common signals included δ 8.47 ppm (s, 1H, NH–C=O amide), δ 10.58 ppm (s, 1H, NH–C=O isatin), δ 7.97 ppm (s, 1H, NH–SO_2), and δ 7.01–7.93 ppm (m, aromatic protons). For compound B2, an additional signal was observed at δ 2.22 ppm (s, 3H, CH_3), confirming the presence of a methyl substituent (Fahad et al., 2019).

Biological Part

The distribution of clinical samples collected for the evaluation of isatin derivatives is shown in Figure 5. Following isolation and screening, the antibacterial activity of the synthesized isatin derivatives was evaluated by measuring inhibition zone diameters, which are presented in the form of a bar chart (Figure 6). The comparison of inhibition zones for istitin derivatives showed variations depending on the derivative type and concentration. The first derivative at 0.05 concentration exhibited a median inhibition zone around 10 mm, with a wide range extending up to approximately 25 mm. Similarly, the first derivative at 0.06 concentration had a slightly higher median and a comparable distribution. In contrast, the second derivative at 0.05 concentration demonstrated a notably larger median inhibition zone, exceeding 15 mm, with values reaching up to 25 mm. The second derivative at 0.06 concentration also showed a broader range and higher maximum inhibition (around 35 mm), suggesting greater antibacterial activity compared to the first derivative. Overall, the second derivative, especially at 0.06 concentration, appeared to be the most effective among the tested conditions.

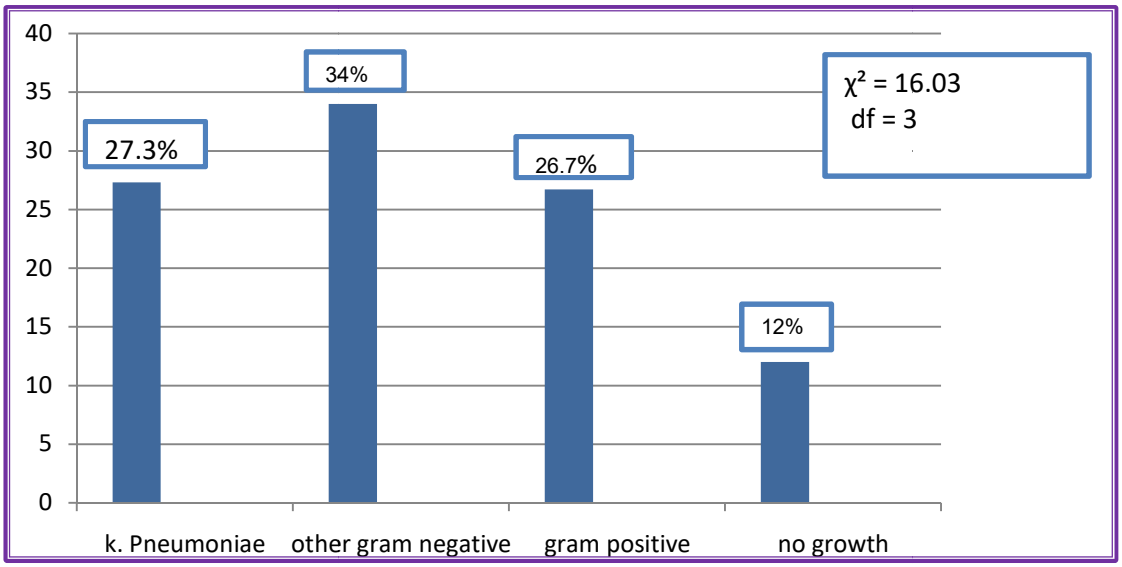


Figure 5: The Distribution of Bacterial Isolates Among Clinical Samples

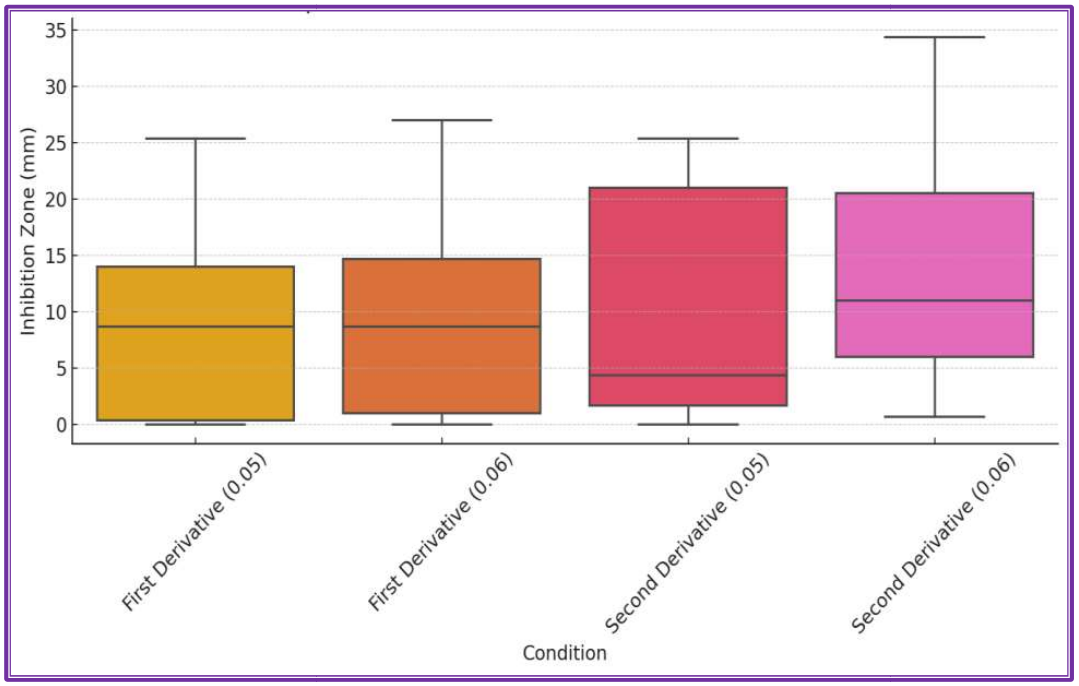


Figure 6: Inhibition Zone Comparison Between First and Second Istitin Derivatives at Two Concentrations.

The interaction plot illustrates the effects of compound type and concentration on the mean inhibition zone. For the first derivative, the mean inhibition zone remained relatively stable, showing only a slight increase from approximately 9.8 mm at 0.05 concentration to about 10.2 mm at 0.06 concentration. In contrast, the second derivative exhibited a marked increase in mean inhibition zone, rising from around 9.3 mm at 0.05 concentration to approximately 13.5 mm at 0.06 concentration. These findings suggest that the second derivative's antibacterial activity is more concentration-dependent compared to the first derivative, Figure (6).

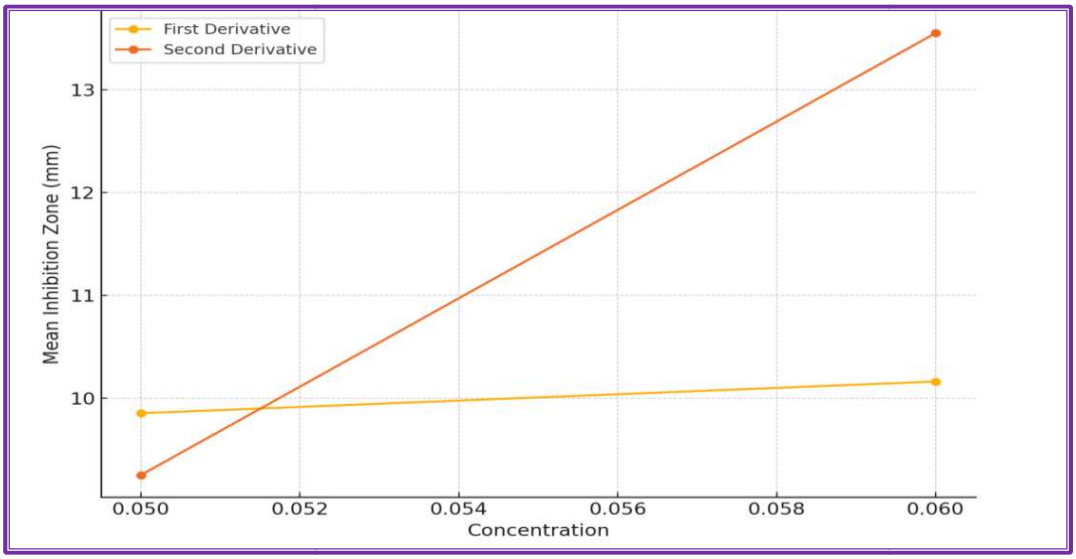


Figure 6: Effect of Compound Type and Concentration on Mean Inhibition Zone: An Interaction Plot

Discussion

The molecular docking results showed a clear difference in the binding strength of the prepared compounds to the target protein. Compound B2 recorded the highest binding event value compared to B1 and the standard ligand, indicating that it possesses more stable binding ability within the protein's active site. The remarkable superiority of compound B2 may be attributed to the presence of a methyl group. This alkyl group enhances hydrophobic interactions within the protein's active pocket, thus increasing binding stability (Altamimi *et al*., 2023).The results also showed that all compounds bound to the same active amino acids (Phe141, Asn79, Trp46, and Arg80) within binding site 4, indicating that these amino acids constitute an important part of the catalytic or binding site of the target protein. The results of this study are consistent with several recent studies indicating that isatin derivatives possess a high affinity for binding to bacterial proteins and that increased hydrophobic interactions contribute to improving the docking score and increasing the stability of the protein-ligand complex (Yamini *et al*., 2023; Radwan *et al*., 2023). The results (FT-IR and ^{1}H-NMR) indicate the successful preparation of the target compounds and confirmation of their formation as required (Raksha *et al*., 2024). The appearance of the (C=N) amide bond and the disappearance of the (C=O) group in the second step confirm successful conjugation with sulfadiazine and the formation of the final isatin derivatives (Mukhlif and Al-Mudhafar, 2023). The results (^{1}H-NMR) also support the proposed structure through the appearance of the characteristic signals of the amide groups and the isatin group, in addition to the methyl group specific to the B2 compound (Hawas *et al*., 2023). These results generally confirm the validity of the chemical structures of the prepared compound. The biological results indicate that the prepared compounds exhibited activity against *Klebsiella pneumoniae*(Hassan *et al*., 2022), suggesting biological activity linked to their ability to bind to the active site of the target protein. The difference in activity between the two compounds can be explained by their structural nature, specifically the presence of an alkyl or halogen group, which may affect cell permeability and the extent of their effect on the biological target. Furthermore, the consistency of the molecular docking results with the biological results supports the reliability of this study. These results are consistent with previous studies that reported isatin derivatives possess antibacterial activity based on structural modifications and hydrophobic interactions (Zhang *et al*., 2023).

Limitations

One of the main limitations of this research is the small sample size and the limited availability of samples from various clinical infections, which limits the representation of the genetic diversity of

bacteria. Furthermore, the evaluation of isatin compounds was carried out in vitro, and no animal experiments were conducted to confirm their effectiveness.

Future Scope

Future studies should recommend taking more clinical samples and using other genetic profiling techniques such as whole genome sequencing, which may contribute to a better understanding of the epidemiological relationship between bacterial isolates and their resistance.

Conclusion

In conclusion, *Klebsiella pneumoniae* clinical isolates exhibited considerable resistance to several commonly used antibiotics. indicating the need for the development of alternative antimicrobial agents. In response to this challenge, new isatin-sulfadiazine derivatives were successfully synthesized and evaluated for their antibacterial activity. Among the tested compounds, B2 showed the highest inhibited activity against *K. pneumoniae* isolates, which was consistent with molecular docking results against the protein (PDB ID: 8QK2). These findings suggest that B2 is a promising antibacterial agent, although further in vivo studies are required to confirm its efficacy and safety.

Conflict of Interest

The authors declare that they have no competing interests.

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