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ORIGINAL RESEARCH ARTICLE

Synthesis of new derivatives metochloro bromide drugs from 3-carboxy indole and evaluation of some their biological activities

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ABSTRACT

The discovery of new 2-Carboxy indole-based molecules with strong antibacterial properties remains a major emphasis in medicinal chemistry. In this study, a number of hybrid compounds (B1-B8) were created by functionalizing 2- Carboxy indole derivatives with a variety of heterocyclic frameworks such as benzothiazole and substituted aromatic groups. The synthesis process included several steps, including the manufacture of indole-3-carbonyl chloride, and condensation with potassium salts to produce gibberellin derivatives. The synthesized compounds were structurally confirmed using M.P (TLC), FT-IR, and NMR (^{1}H and ^{13}C) spectroscopy. This study synthesized and characterized new indole-based derivatives using FT-IR and NMR methods. Several compounds demonstrated strong antibacterial and antifungal action, with compound B3 being the most effective. The structure-activity connection research found that electron-withdrawing groups increased activity, while bulky or electron-donating groups decreased it.

Keywords: metochloro bromide; biological activity; 3-carboxy indole

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1. Introduction

2- Carboxy indole is a heterocyclic organic molecule with a fused benzene and pyrrole ring structure that occurs naturally[1,2]. It is a critical precursor for a variety of alkaloids[3], medicines[4], and natural bioactive chemicals[5]. 2- Carboxy indole derivatives have critical roles in biological processes such as cell signaling, plant growth regulation, and microbial metabolism[6]. 2- Carboxy indole is intensively explored in drug development due to its wide range of applications, including cancer therapy and antibacterial agents[7,8]. 2-Carboxyindole is an organic compound belonging to the indole family, characterized by the presence of a carboxyl group (-COOH) attached to the second position of the indole ring. This compound serves as a key intermediate in the synthesis of various bioactive compounds with antibacterial, anticancer, and antiviral activities due to its versatile structure[9]. The Mannich reaction produces β-amino carbonyl compounds by combining an amine, formaldehyde, and an enolizable molecule, this reaction is very important in medicinal chemistry because it allows for the synthesis of bioactive compounds such as alkaloids and pharmaceuticals[10]. 2- Carboxy indole, with its nucleophilic nitrogen, easily undergoes the Mannich reaction, yielding functionalized derivatives with improved biological characteristics. Many indole-Mannich adducts have promising anticancer, antibacterial, and neuroactive properties, making this reaction a valuable tool for developing new medicinal molecules[11]. One such 2- Carboxy indole

indole-related system is 2-amino benzothiazole, a fused heterocyclic molecule with powerful antibacterial, anticancer, and anti-inflammatory effects. It is structurally comparable to indole in terms of electrical conjugation and biological importance[12]. Both frameworks are commonly utilized as favored structures in drug design, where they undergo functionalization reactions such as the Mannich reaction to yield novel bioactive molecules[13,14].

2. Materials and methods

Sigma and Fluka chemicals were used without any further purification. Melting points were determined using a Cole-Parmer Stuart melting point device. The infrared spectra were collected using a Shimadzu FT-IR-8400.0 Charles/ FT-IR spectrophotometer and KBr pellets. The 1H-NMR spectra of the synthesized compounds were obtained using a Bruker 400.0 MHz nuclear magnetic resonance instrument.

2.1. Synthesis Indole-3-carbonyl chloride (SOCl2) [A]

A mixture of (1.04g) of 2-Carboxy indole and (0.77g) $SoCl_2$ mixed to synthesize Indole-3-carbonyl chloride and was prepared by utilizing (25) ml of chloroform, several small amounts of. Subsequently, the mixture was refluxed for 15 hours while maintaining constant stirring. The outcome was refined using recrystallization from chloroform[15].

2.2. Synthesis of N-[2-(2-chlorobenzoyl)-amino acetyl]-indole-3-carbonyl chloride

N-[2-(2-chlorobenzoyl)-amino acetyl]-indole-3-carbonyl chloride was produced by refluxing a mixture of metochloro Bromide (0.599 g) with (0.355 g) from Indole-3-carbonyl chloride by the presence of 1 ml formaldehyde and 10 ml DMF, the mixture put in water bath for (5) hours with stirring. The mixture contained. The resulted compound weight was 0.76 gm precipitate[16].

2.3. Synthesis of 2-amino benzothiazole derivatives

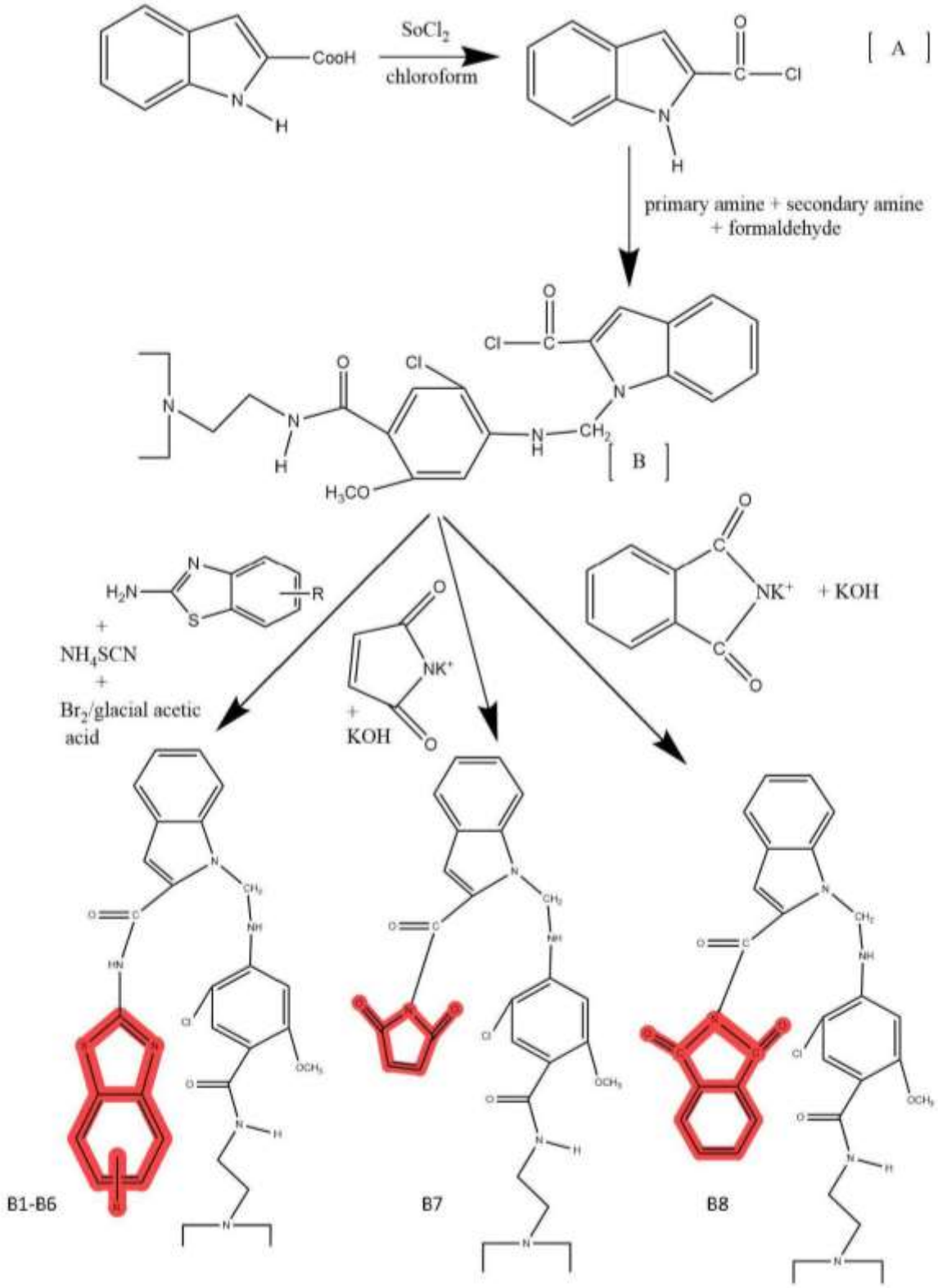
A combination of compound (0.008 mol) in (20 ml) 100% ethanol and (0.008 mol) potassium carbonate anhydrous was refluxed and applied dropwise to a solution of (0.008 mol) substituted-2-aminobenzothiazole derivatives (1,3 benzothiazole, 5-Bromo-1,3-benzothiazole, 5-chloro-1,3-benzothiazole, 5-nitro-1,3-benzothiazole, and 5-methoxy-1,3-benzothiazole) from [B1 to B6] in 30 ml of 100% ethanol. The reaction mixture was refluxed for 10 hours. After cooling, the precipitate was separated, filtered, and recrystallized using ethanol as the solvent[17].

2.4. Synthesis of Gibberellin Salts

The synthesis of (B7) and (B8) compound has been dissolved in (25ml) of absolute ethanol then (0.01mol) of prepared potassium, phthalimide or potassium succinimide has been added gradually to compound (B) with stirring. The resulted mixture was refluxed for six hours with continuous stirring then has been cooled to room temperature. The formed precipitate was filtered, washed with $NaHCO_3$ solution then with water, and finally purified by recrystallization from acetone[18].

2.5. Biological activity study

The approach was utilized to examine the antibacterial activities of the synthesized compounds towards microbes such as E. coli, staph, and Pseudomonas aeruginosa. The cup plate. Trimethoprim was used as the slenderized antibiotic. Furthermore, the media used is nutritional agar and DMSO combined. The sample volume and solution for all evaluated compounds are 0.15 ml. They are extracting samples from cups containing agar material on a Petri plate. Previously, the microorganisms were incubated. The examination is carried out in cups, each holding 0.15 mL of chemical solution. The Petri plates were then incubated at 37°C for 48 hours. The inhibition zones for each medication were determined in millimeters[19].

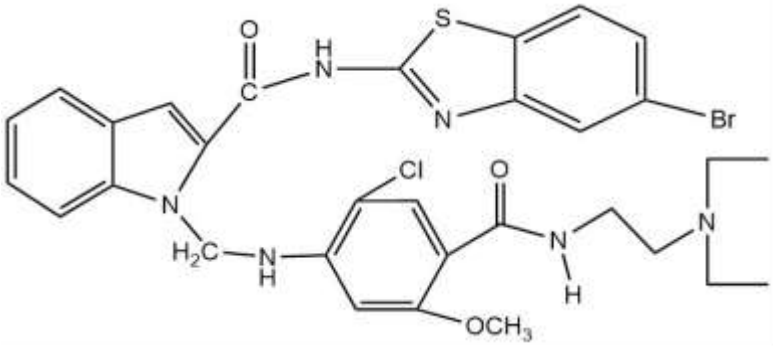
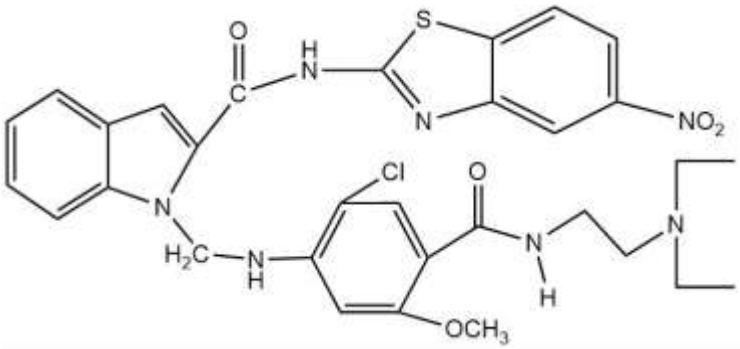
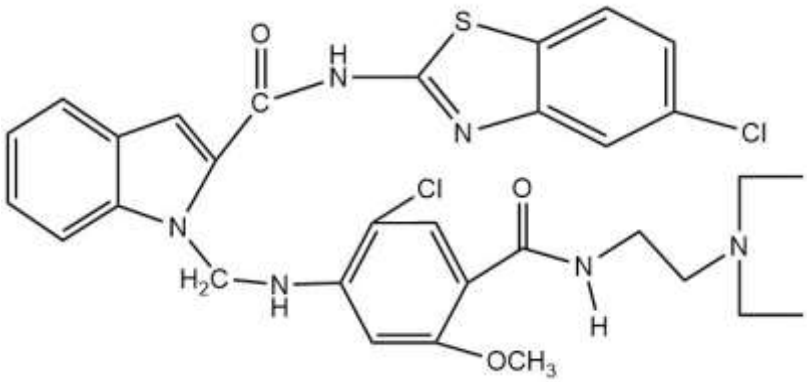


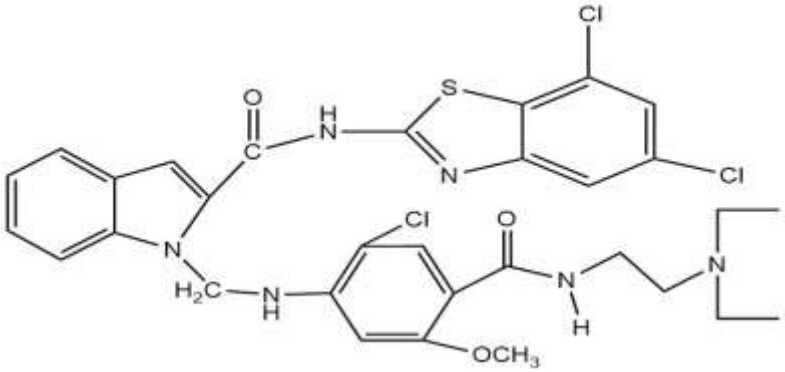
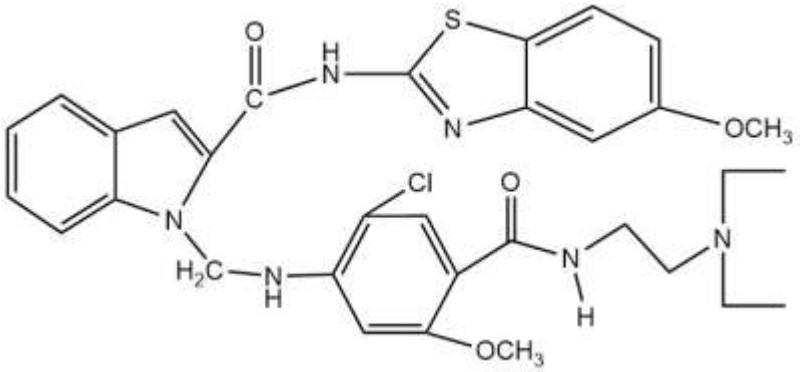
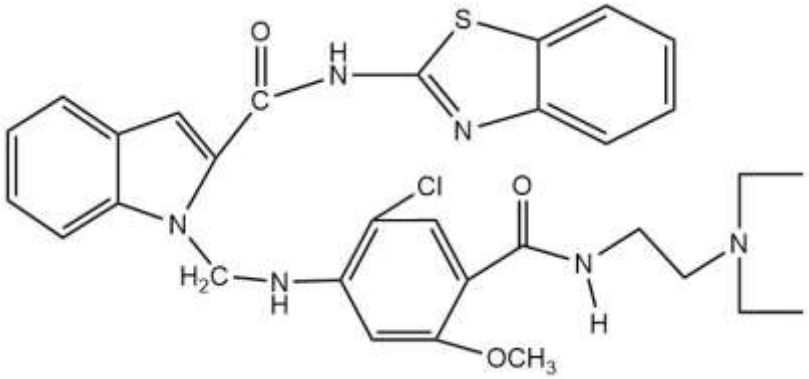
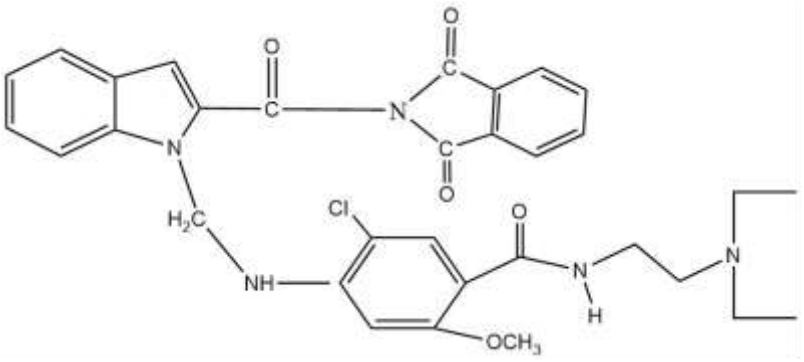
3. Results and discussion

Scheme (1) depicted synthetic shiff base derivatives. All derivatives were characterized using melting point, TLC, FT-IR, and H1-NMR.

The compounds synthesized by this work were identified and characterized by different techniques and the result were recorded in the coming tables and figures. **Table 1** shows the physical characteristics of produced compounds.

Table 1. Physical properties for the synthesized compounds.

Comp No.	Structure	Color	Melting point
B1	 N-[(1H-indol-3-yl)methyl]-2-[(2-chloro-4-methoxyphenyl)amino]-N'-[5-bromo-1,3-thiazol-2-yl] -N-(2-aminoethyl)acetamide	Pale brown	149-151
B2	 N-[(1H-indol-3-yl)methyl]-N'-[4-nitrophenyl]-1,3-thiazol-2-yl] with 2-[(2-chloro-4-formylphenyl)amino]-N-(2-aminoethyl)acetamide	Brown	136-138
B3	 N-[(1H-indol-3-yl)methyl]-N'-[5-chlorothiazol-2-yl] derivative bearing a 2-[(2-chloro-4-methoxybenzoyl)amino]-N-(2-aminoethyl) acetamide	Dark brown	340- 342

Comp No.	Structure	Color	Melting point
B4	 N-[(1H-indol-3-yl)methyl]-N'-[4,5-dichlorothiazol-2-yl] linked to 2-[(2-chloro-4-formylphenyl)amino]-N-(2-aminoethyl)acetamide	Brown	149-151
B5	 N-[(1H-indol-3-yl)methyl]-N'-[5-(4-methoxyphenyl)-1,3-thiazol-2-yl] 2-[(2-chloro-4-formylphenyl)amino]-N-(2-aminoethyl)acetamide substituent	Dark rid	>250
B6	 N-[(1H-indol-3-yl)methyl]-N'-[benzothiazol-2-yl] with 2-[(2-chloro-4-formylphenyl)amino]-N-(2-aminoethyl)acetamide	Pale brown	146-148
B7	 N-[(1H-indol-3-yl)methyl]-N'-[1,3-dioxoisoindolin-2-yl] linked to 2-[(2-chloro-4-formylphenyl)amino]-N-(2-aminoethyl)acetamide	White	207-209

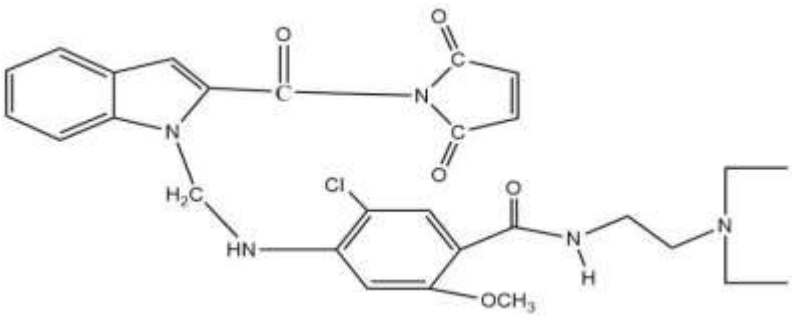
Comp No.	Structure	Color	Melting point
B8	 N-[(1H-indol-3-yl)methyl]-N'-[1,2,4-oxadiazol-3-yl] attached to a 2-[(2-chloro-4-formylphenyl)amino]-N-(2-aminoethyl)acetamide	Pale brown	221-223

Table 1. (*Continued*)

TLC is employed to characterize these derivatives first, **Table 2** and **Figures 1 to 8** show The FT-IR spectra of the synthesized compounds B1–B8 revealed characteristic absorption bands consistent with their proposed chemical structures. Broad bands in the 3346–3448 cm^{-1} region are attributed to the stretching vibrations of O–H and N–H groups, confirming the presence of hydroxyl and amide functionalities. The aromatic and aliphatic C–H stretching appeared in the expected range of 2772–2956 cm^{-1} across all compounds. Strong bands between 1647–1772 cm^{-1} were assigned to the carbonyl (C=O) groups, where shifts in the stretching frequency correlate with electronic effects of the substituents on the aryl or heteroaryl moieties [20]. For instance, B2 and B8 exhibited absorption near 1762 cm^{-1}, reflecting the presence of electron-withdrawing NO_2 or imide groups, respectively, which enhance C=O polarization. B3 and B4 displayed dual halogen substituents (Cl or Cl_2), which slightly shifted the C=O frequency, possibly due to inductive effects [21]. The C–N stretching vibrations were observed in the range of 1024–1327 cm^{-1}, confirming the formation of the amide and thiazole/thiazolidinone linkages. Additionally, characteristic out-of-plane C–H bending vibrations appeared around 744–761 cm^{-1}, affirming the aromatic nature of the scaffold. The presence of strong peaks at ~1188 cm^{-1} and 1238 cm^{-1} in most compounds further supports the existence of aryl ether (OCH_3) or thiazole rings[22]. Notably, B7 and B8, bearing phthalimide and succinimide moieties, showed relatively different patterns in carbonyl regions due to imide dual carbonyl character. Overall, the FT-IR results confirm the successful synthesis of the target hybrid molecules incorporating indole, amide, and heteroaromatic pharmacophores, and spectral variations align well with the nature and position of the functional groups present in each compound[23].

Table 2. provides detailed FT-IR spectral information on compounds (B1-B8).

No of Compound	υ (C–H) aromatic	υ (C–H) aliphatic	υ (O–H)	υ (N–H)	υ (C=O)	υ (C–H) bending	υ (C–N)
B1	2775	2949.16	3448.72, 3356.14	3109.25	1697.36, 1647.21	744.52	1236.37, 1188.15,
B2	2783	2951.09	3409.94, 3201.83	3109.25	1701.22, 1658.85	744.52	1238.30, 1188.15,
B3	2783	2947.23	3423.65, 3292.49	3116.97	1772.58, 1649.14	744.52, 761.88	1233.30, 1026.13
B4	2772	2947.23	3444.87, 3346.50	3196.05, 3116.97	1699.29,	744.52	1058.92, 1024.20
B5	2788	2951.09	3354.21	—	1699.29, 1651.07	744.52	1290.38, 1238.30,
B6	2792	2945.30	3360.64, 3292.49	3107.32	1697.36,	742.59	1238.30, 1188.15,
B7	2772	2956.87	3352.28, 3182.55	3043.67	1701.22,	744.52, 717.52	1286.52, 1327.03
B8	2784	2945.30	3367.71, 3292.49	3113.11	1762.94, 1656.85	744.52, 723.31	1286.52, 1325.10,

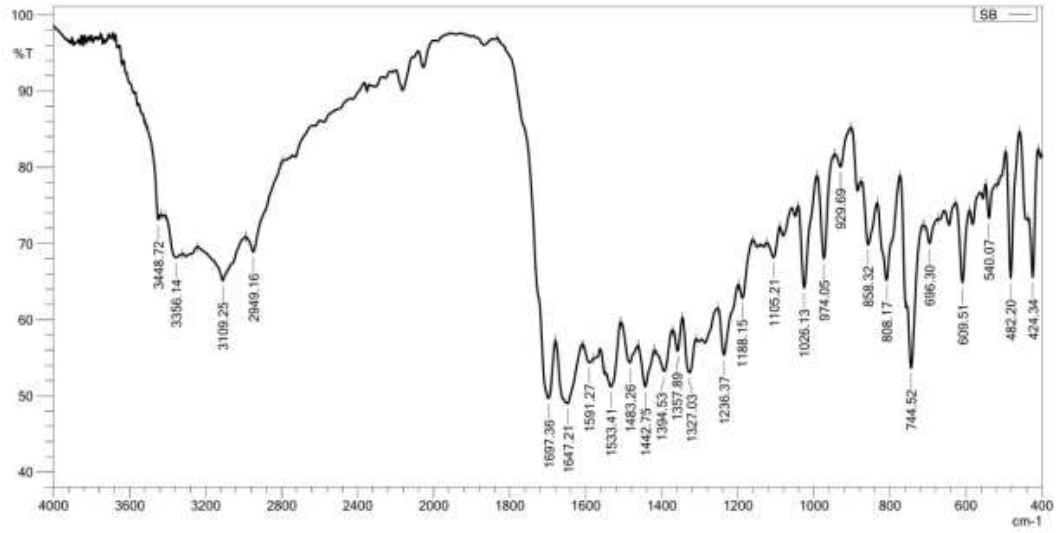


Figure 1. FT-IR for B1.

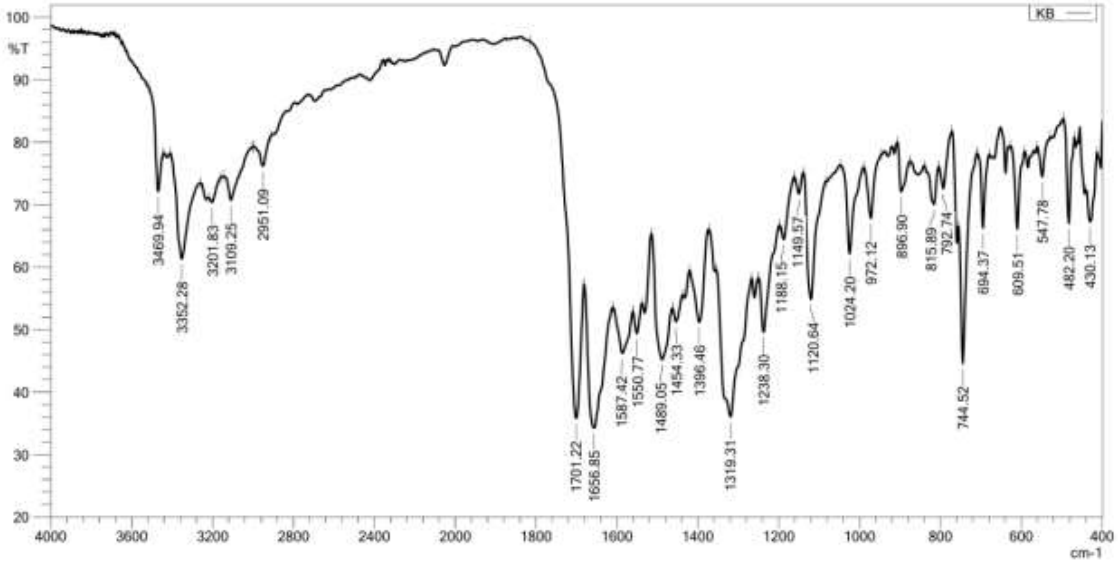


Figure 2. FT-IR for B2.

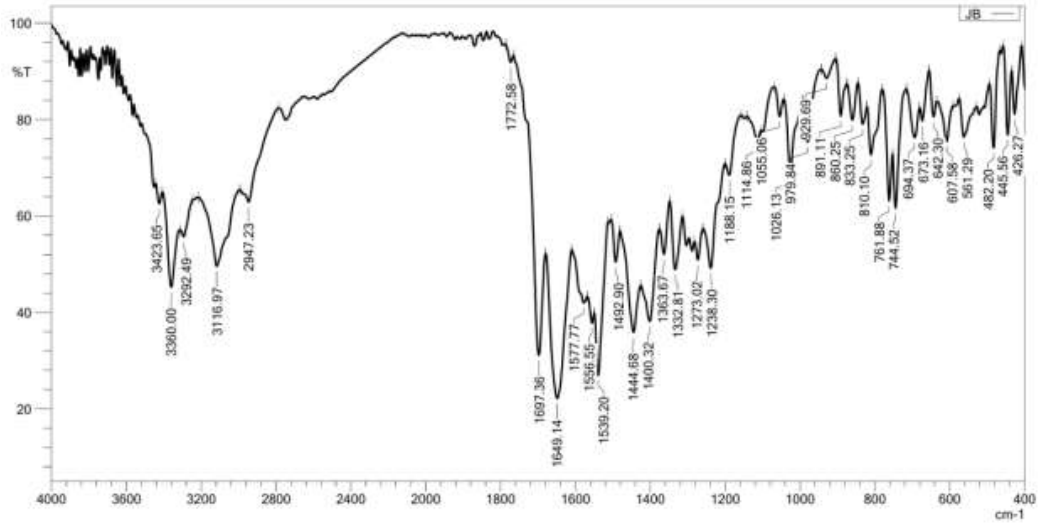


Figure 3. FT-IR for B3.

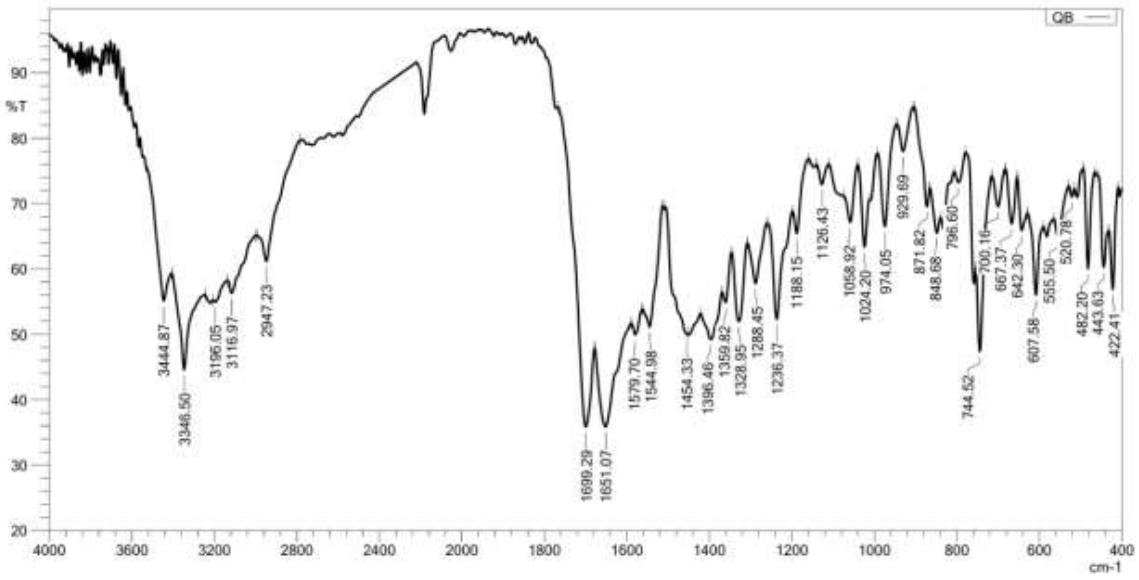


Figure 4. FT-IR for B4.

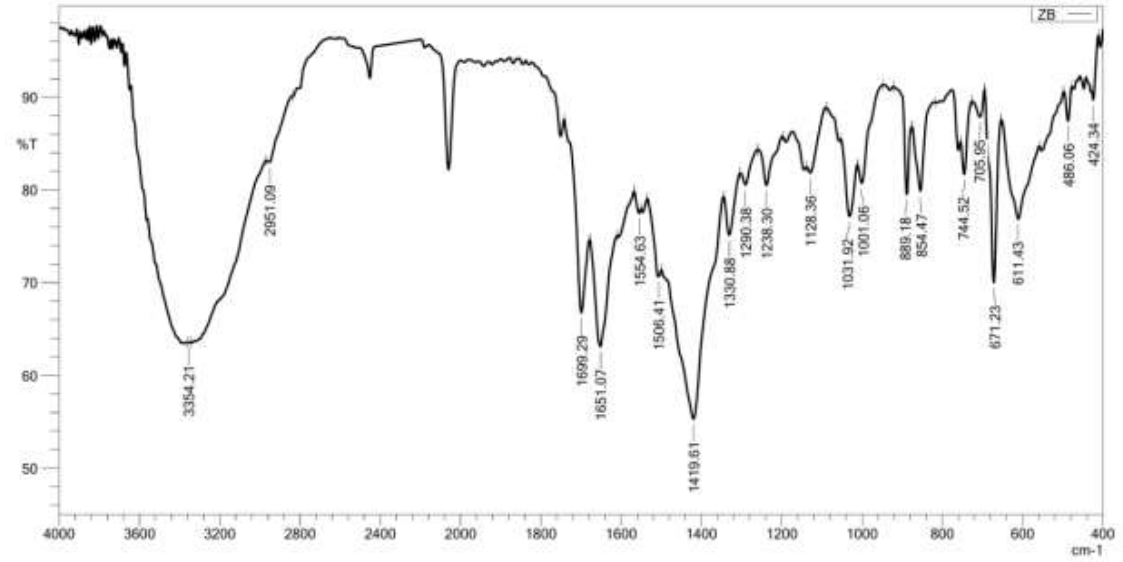


Figure 5. FT-IR for B5.

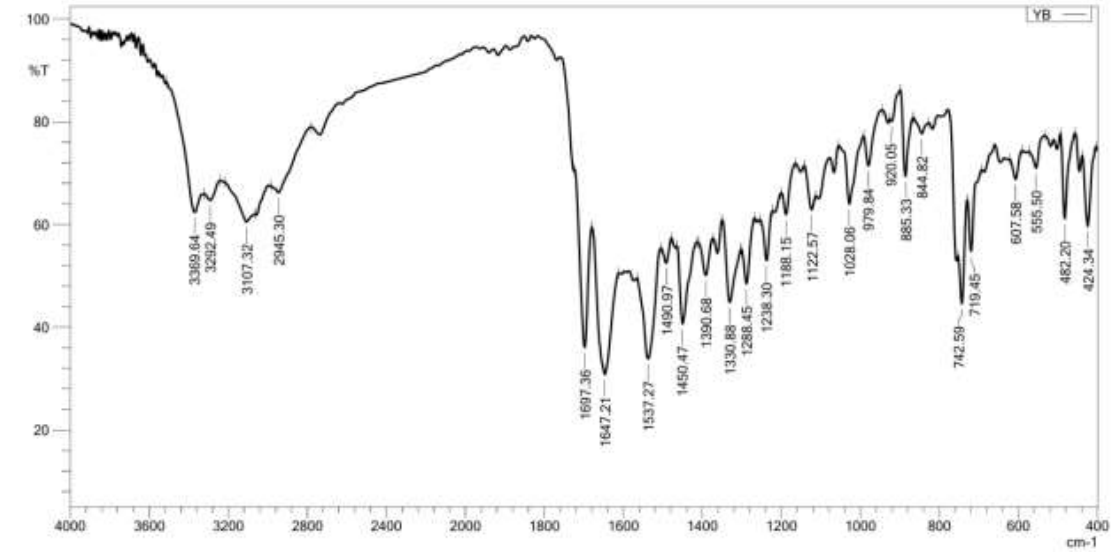


Figure 6. FT-IR for B6.

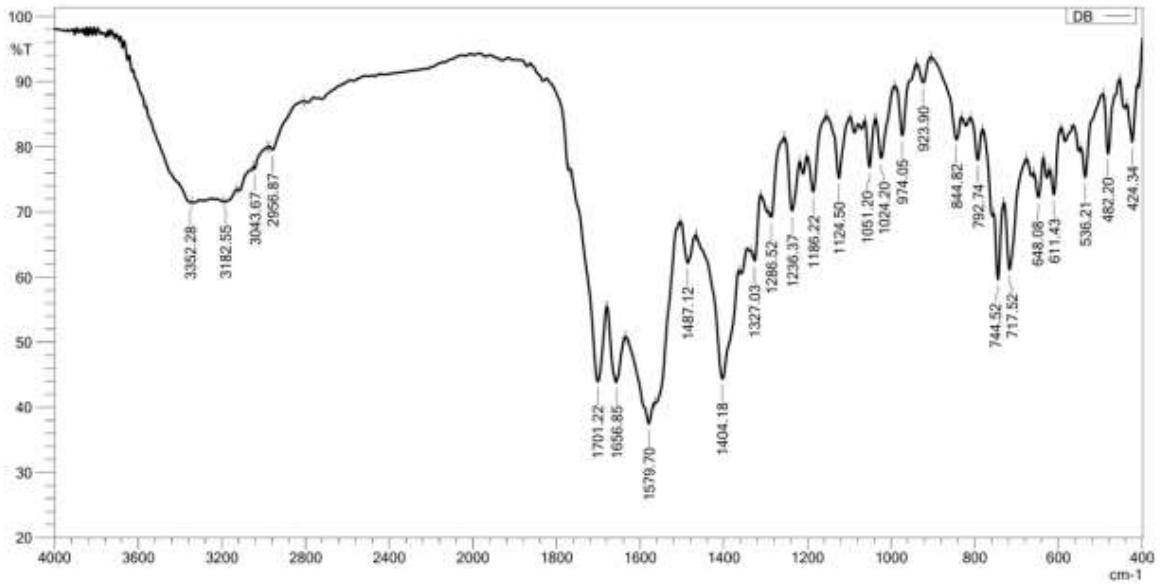


Figure 7. FT-IR for B7.

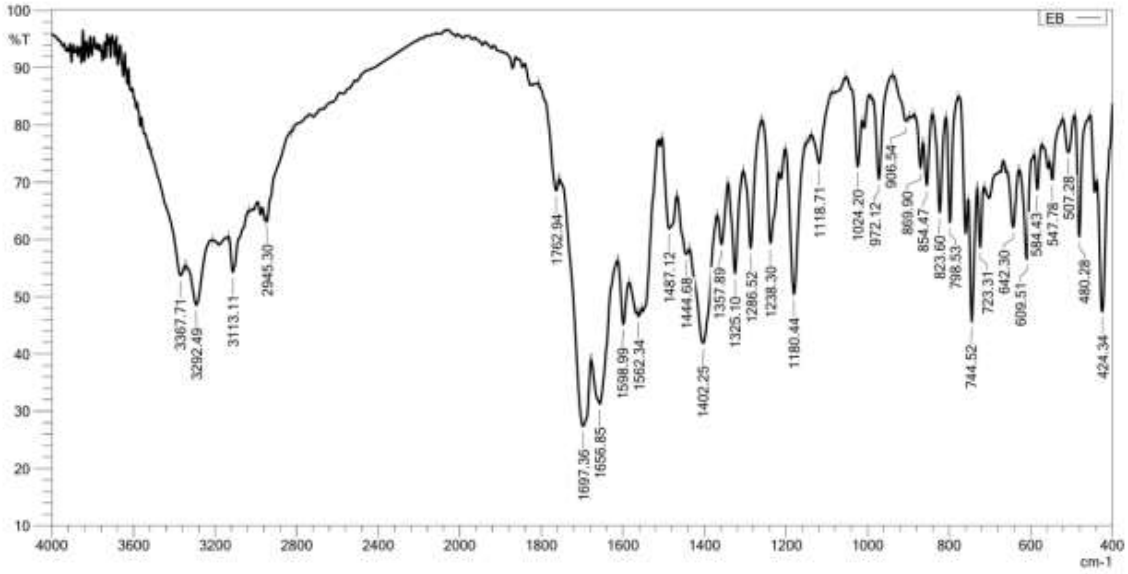


Figure 8. FT-IR for B8.

The synthesized molecule's structure was validated using ^{13}C-NMR and ^{1}H-NMR spectroscopy. For B1 compound, the ^{1}H-NMR spectrum (400 MHz, DMSO-d_6) shows consistent indications with the hypothesized structure. A singlet at (δ 9.04) ppm indicates the indole N-H proton, which normally resonates downfield owing to hydrogen bonding and aromatic deshielding. Multiple signals between (δ 7.00-7.91) ppm correspond to aromatic protons of both indole and substituted phenyl rings, which include the 2-chloro and 4-formyl substituents[24]. A distinct doublet around (δ 8.31) ppm likely indicates the proton next to the electron-drawing chlorine atom. The moiety's secondary amine N-H produces a wide signal at (δ 6.68) ppm. The aliphatic region has various peaks between (δ 2.0-4.5) ppm, including a multiple at δ 4.53 ppm and a singlet at (δ 3.09) ppm. These correspond to the CH_2 linker between indole and nitrogen and the CH_2 nearer the terminal ethylene diamine, respectively[25]. The ethylene diamine tail's methylene protons exhibit a triplet-like pattern at (δ 2.31) and (δ 2.05) ppm. The singlet at (δ 3.38) ppm corresponds to the methoxy (-OCH_3) group. The ^{13}C-NMR spectrum reveals carbonyl signals at (δ ~160-170) ppm, aromatic carbons between (δ 110-150) ppm, a methoxy carbon at (δ 55) ppm, and aliphatic CH_2 carbons between (δ 35-45) ppm. These spectrum properties confirm the effective synthesis of the intended indole-thiazole derivative and fit well with previously reported values in the literature.

For B2, The ^{1}H-NMR and ^{13}C-NMR spectra indicate a successful synthesis for the nitrophenyl-thiazole derivative. In the ^{1}H-NMR spectrum (DMSO-d_6, 300 MHz), the indole N-H proton shows as a singlet near (δ 9.0) ppm. Aromatic protons of the indole, nitrophenyl, as well as chlorobenzene rings appear between (δ 7.0-8.3) ppm, indicating the expected splitting pattern[26]. A wide signal at (δ ~6.6) ppm indicates the N-H proton. A signal near (δ 3.3) ppm attributed to the methylene group next to the nitrogen of the ethylene diamine chain. Additional aliphatic CH_2 groups show between (δ 2.0-4.5) ppm. The ^{13}C-NMR spectra (125 MHz) shows strong carbonyl signals at (δ 165-170) ppm for amide and groups, and nitro-substituted aromatic carbons at (δ 125-145) ppm. CH_2 groups are confirmed with signals at (δ 35-45) ppm. The aromatic protons and carbons migrate downfield, indicating that the NO_2 and Cl electron-withdrawing groups increase deshielding, as reported in literature for comparable nitroarylse[23]. These results corroborate the structure and purity of the synthesized chemical.

For B4, ^{1}H-NMR and ^{13}C-NMR data confirm the effective synthesis of the dichlorophenyl-thiazole derivative. In the ^{1}H-NMR spectrum, the indole N-H proton shows downfield near (δ 10.46-11.80) ppm, which is typical for indole systems due to hydrogen bonding and aromatic deshielding. Aromatic protons from indole, thiazole, and dichlorophenyl rings resonate in the anticipated range of (δ 6.9-7.9) ppm. The N-H and amide protons show large signals at (δ 6.6-6.9) ppm. Aliphatic methylene groups, including the CH_2 bridge between the indole and nitrogen and the ethylene diamine chain, emerge in the area of (δ 2.0-4.5) ppm, while additional signals at (δ 3.13-3.80) ppm correspond to CH_2-N protons (27). The ^{13}C-NMR spectrum clearly shows carbonyl signals (C=O) from both the and amide moieties in the (δ 160-170) ppm range. Aromatic and hetero aromatic carbons are found at (δ 110-150) ppm, corresponding to substituted indole, thiazole, and dichlorophenyl units. The aliphatic methylene carbons resonate at (δ 35-50) ppm[17].

For B7, 2-Carboxy indole N-H proton shows downfield at (δ 10.99-11.31) ppm, whereas several aromatic proton signals are detected between (δ 6.59-8.61) ppm, accounting for the indole, phthalimide, and dichlorobenzene ring systems. Aliphatic CH_2 groups are detected at (δ 2.14-4.91) ppm, including signals from the methylene bridge between 2-Carboxy indole and nitrogen, the ethylene diamine chain, and the linker to the phthalimide ring. The occurrence of wide singlets in the (δ 6.85-6.99) ppm range supports the NH environment[27]. The ^13C-NMR spectrum (125 MHz) exhibits predicted signals in the (δ 160-170) ppm region, corresponding to the carbonyl carbons of the amide, phthalimide, and functions. Aromatic and hetero aromatic carbons emerge at (δ 110-150) ppm, corresponding to substituted indole, phthalimide, and dichlorophenyl rings. Aliphatic CH_2 carbons are detected between (δ 35-50) ppm, indicating the presence of ethylene and methylene linkers[23].

Last compound B8, the 2-Carboxy indole N-H proton is observed downfield at (δ 11.14-11.21) ppm. This is consistent with published observations for N-H of unsubstituted indole rings, which frequently appear about 11 ppm due to hydrogen bonding and deshielding effects. Aromatic protons from the indole, substituted phenyl ring, and oxadiazole system show in the range (δ 6.66-8.61) ppm, with well-resolved multiples between (δ 6.90-7.94) ppm, confirming the presence of multiple aromatic environments. Signals at (δ 9.08) ppm are presumably from amide or N-H protons. A singlet at (δ 3.38) ppm indicates a methylene group next to nitrogen (CH_2-N), whereas multiples at (δ 2.98-4.50) ppm establish the existence of the ethylene diamine linker. Additional resonances at (δ 5.31) ppm and (δ 5.94) ppm are attributed to exchangeable NH_2 protons either aldehyde hydrogen (CHO) within the formyl-substituted aromatic ring[25].

The carbonyl carbons of amide, and aldehyde functionalities occur in the (δ 160-170) ppm, as expected. Aromatic and heterocyclic carbons resonate at (δ 110-150) ppm, indicating the presence of indole and substituted phenyl rings. The methylene and ethylene carbons exhibit peaks in the (δ 35-50) ppm range. The deshielded carbon signals point to the existence of electron-drawing groups like the chloro substituent and oxadiazole heterocycle, which are known to move neighboring carbon resonances downfield. The observed chemical shifts and splitting patterns are completely consistent with the suggested structure. The presence of

essential NH, CH_2, and aldehyde signals, as well as clear signal separation in both aromatic and aliphatic regions, confirms the compound's identity and purity[27].

4. Antibacterial activity

The antibacterial activity of the synthesized compounds (B1-B8) was tested against gram-positive, gram-negative bacteria, and fungi (*C. albicans*), and compared with ampicillin for bacteria and fluconazole for candida with the results reported as an inhibitory zone for all compounds. The results are reported in **Table 3**.

Table 3. antibacterial activity for the synthesized compounds.

N.A	*S.aureus ATCC: 25923*	*E.faecalis MTCC: 35550*	*E.coli MTCC: 443*	*A.baumanii MTCC: 1425*	*C.albicans MTCC: 2091*
B1	25	20	17	28	30
B2	23	30	12	17	30
B3	26	18	16	25	40
B4	27	15	15	15	30
B5	15	N.A	N.A	N.A	10
B6	20	15	15	15	30
B7	20	N.A	N.A	N.A	35
B8	N.A	N.A	N.A	N.A	20
ampicillin	28	26	20	28	-
fluconazole	-	-	-	-	44

The antibacterial activity of compounds B1-B8 varied significantly, demonstrating the impact of structural characteristics on biological performance. Among all tested compounds, compound B3 showed the highest overall antibacterial and antifungal activity, particularly against *Candida albicans* (40 mm inhibition zone) and *S. aureus* (26 mm), most likely due to its incorporation of a chloro-substituted thiazole ring and methoxy benzoyl moiety, that enhance lipophilicity and facilitate easier absorption into microbial cell membranes[28]. Compound B1, which contained a bromo-substituted thiazole, also demonstrated strong broad-spectrum activity, particularly against A. baumannii (28 mm) and C. albicans (30 mm), implying that halogenation at the thiazole ring provides positively to antimicrobial effects, potentially through increased hydrophobicity and electronic contact with bacterial enzymes[29]. B2, containing a nitro phenyl substitution, demonstrated significant antifungal activity (30 mm) and strong inhibition of *E. faecalis* (30 mm). This may be attributed to the electron-withdrawing nature of the NO_2 group, enhancing the reactivity and promoting interaction with microbial targets[30]. In contrast, B5, with a 4-methoxyphenyl substituent and without halogen atoms, displayed extremely weak or no activity against bacterial strains. This suggests that electron-donating groups like $-OCH_3$ may diminish antimicrobial efficacy when not accompanied by other activating groups. Compound B4, with a 4,5-dichlorothiazole system, displayed moderate activity, which could be related to steric hindrance produced by di-substitution, impacting target binding or diffusion[31].

Compounds B6, B7, and B8, which contain complex heterocyclic systems including benzothiazole, phthalimide, and oxadiazole, demonstrated selective or diminished antibacterial activity. This could be due to the FT-IR larger molecular size or poorer solubility, which limits the FT-IR bioavailability and ability to reach microbial targets. Notably, B7 retained high antifungal activity (35 mm), indicating that the phthalimide core may have selective interaction with fungal cells, as reported in prior research. The results clearly reveal that the inclusion of halogen substituents, such as chlorine (Cl) and bromine (Br), as well as electron-withdrawing groups like the nitro group (NO_2), on aromatic or heterocyclic frameworks greatly boosts antibacterial efficacy. This improvement is most likely due to enhanced lipophilicity, improved membrane permeability, and stronger

electronic interactions with bacterial enzymes and cellular targets, which all contribute to higher bioavailability and more efficient microbial suppression[32]. Bulky or electronically neutral groups, like methoxy (-OCH_3) or unsubstituted rings, FT-IR antibacterial activity. These substituents may produce steric hindrance, restrict molecule diffusion across bacterial membranes, or fail to fully activate the pharmacophore for significant biological interaction. Collectively, these findings are consistent with widely accepted structure-activity relationship (SAR) principles in medicinal chemistry, particularly for indole-based antibacterial agents, where the balance of electronic effects and molecular size is critical for achieving maximum antimicrobial activity[7].

5. Conclusion

Finally, this study successfully demonstrated the synthesis and characterization of a unique series of indole-based derivatives with various heterocyclic and aromatic moieties. The synthesized compounds' structural integrity was confirmed by comprehensive spectroscopic approaches, including FT-IR, ^1H-NMR, and ^13C-NMR, which supported the production of important functional groups such as imide, and substituted aromatic rings. The FT-IR spectrum data, in particular, confirmed the conversion of acyl chloride precursors to the required and imide structures. Biological assessment found that several of the synthesized compounds had significant antibacterial activity, with compound B3 being the most powerful, particularly against *Candida albicans* and *Staphylococcus aureus*. The study's structure-activity relationship analysis revealed that electron-withdrawing groups (e.g., Cl, Br, and NO_2) improved antibacterial efficacy, while electron-donating groups (e.g., -OCH_3) or bulky moieties decreased activity. These findings indicate that fine-tuning the electrical and steric characteristics of indole-based hybrids is critical for improving biological efficacy. Overall, this study sheds light on the design of indole-centered molecular scaffolds and promotes the FT-IR continuing development as prospective antibacterial agents.

Conflict of interest

The authors declare no conflict of interest.

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