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Synthesis, characterization and biological evaluation of quinazoline-4-one derivatives via cyclization of hydrazones

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Abstract

This study investigates the synthesis and biological activity of novel quinazoline-4-one derivatives, synthesized through Schiff base reactions involving hydrazine and various substituted benzaldehydes in ethanol. The synthetic route commenced with the reaction of phthalic anhydride with an amino acid, resulting in the formation of an aromatic amino acid. This intermediate underwent esterification with thionyl chloride and ethanol to yield an aromatic ester. The ester was subsequently converted to an aromatic hydrazide by reaction with 80% aqueous hydrazine in ethanol. The hydrazide was then reacted with different aromatic aldehydes in the presence of a small amount of glacial acetic acid to form the corresponding hydrazone derivatives. In the final step, quinazoline-4-one derivatives were synthesized by reacting the hydrazone with anthranilic acid. The structures of the synthesized compounds were characterized using various spectroscopic techniques, including FT-IR, ^1H -NMR, and ^{13}C -NMR. The biological activities of these novel derivatives were evaluated, offering insights into their potential applications in medicinal chemistry.

Keywords: Quinazoline-4-one, hydrazone, phthalic anhydride, biological activities

Introduction

Heterocyclic compounds differ significantly from homocyclic compounds due to their incorporation of various elemental constituents alongside carbon in cyclic structures. While homocyclic rings consist of a single element, heterocycles feature carbon atoms along with other components such as oxygen, nitrogen, and sulfur ^[1, 2]. Hydrazones represent a category of azomethines characterized by a $-\text{C}=\text{N}-\text{NH}_2$ bond ^[3]. Within hydrazones, the azomethine moiety has garnered significant attention due to the dual electrophilic and nucleophilic properties of carbon, juxtaposed with both nitrogen atoms possessing nucleophilic attributes. A typical formula of hydrazone class of organic compounds is $\text{R}_1\text{R}_2\text{C}=\text{NNH}_2$ Where R_1 and R_2 similar or different aryl, alkyl groups as show in Figure 1.

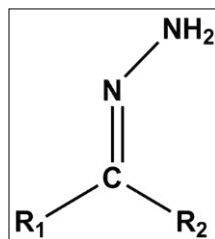


Fig 1: Structural formula of hydrazone

The term hydrazone was coined by Fischer in 1888 ^[4]. Due to the simplicity of these venerable ligation reactions, hydrazones has also had a pervasive influence on numerous other research fields ever since. The total of hydrazone derivatives displays keto-enol

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tautomerism facilitated by intermolecular proton transference, where the configuration of cis-trans depends on various factors including the azomethine linkage, solvent conditions, pH level, and concentration. These derivatives are acknowledged as entities capable of functioning as both proton donors and acceptors, exhibiting both intermolecular and intramolecular interactions through hydrogen bonding. The distinct characteristics observed in hydrazone derivatives highlight their significant importance in the field of organic compounds [5]. Quinazoline comprises a fused benzene ring and a pyrimidine ring (Figure 2), with a chemical formula of $C_8H_6N_2$. This compound, formerly identified as benzo-1,3-diazine, is a fused bicyclic compound. The initial synthesis of quinazoline took place in 1903 by Gabriel, following its first isolation from the Chinese plant aseru. The first documented instance of a compound containing the quinazoline nucleus was reported by Peter Gries in 1869.

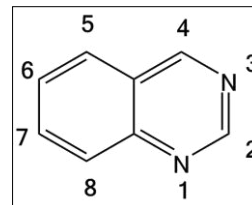


Fig 2: Structural formula of quinazoline

The structure of quinazoline molecules is determined by the positioning of the oxygen and hydrogen atoms bonded to the nitrogen atom. A widely acknowledged system of numbering is used to classify quinazolines and quinazolinones into specific categories: 4(3H)-quinazolinone (3H-1,3-quinazolin-4-one), 2(1H)-quinazolinone (1H-1,3-quinazolin-2-one), and 2,4(1H,3H)-quinazolinone (1H,3H-1,3-quinazolin-2,4-dione), as shown in Figure 3.

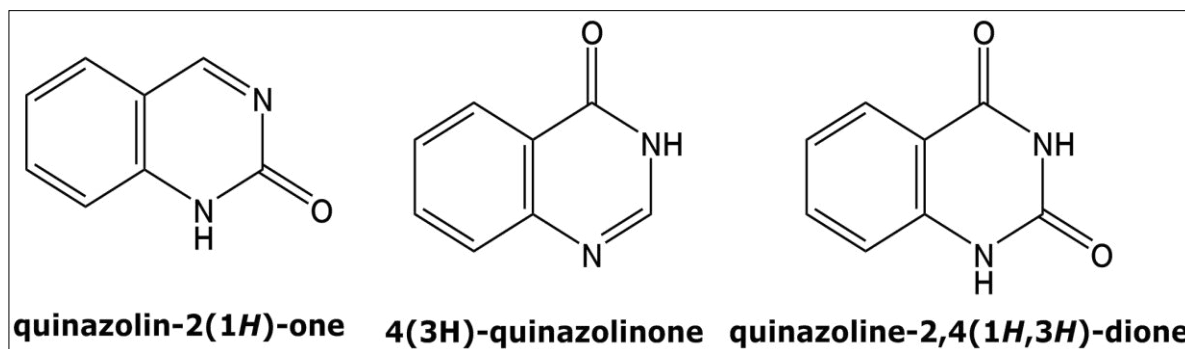


Fig 3: Structural types of quinazolinone

However, among the various quinazolinone structures proposed in Fig. 3, the 4(3H)-quinazolinones stand out as the most commonly found. They exist either as intermediates or as natural products in numerous suggested biosynthetic pathways [6]. This prevalence can be attributed in part to their structural origin from the anthranilates, such as anthranilic acid, various esters, isatoic anhydride, anthranilamide, and anthranilonitrile [7, 8].

Literature reviews indicate that the synthesis of quinazolinones can be accomplished using anthranilic acid [9-12], 2-aminobenzamide [13], and 2-aminobenzonitrile, along with their derivatives [6]. Natural products based on quinazolinones that require more structurally complex precursors have been synthesized indirectly through methods such as thioamide formation, oxidation of dehydro-quinazolinone, and aza-Wittig condensation [14, 15]. Quinazolin-4(3H)-one derivatives are heterocyclic compounds featuring multiple nitrogen atoms and are recognized as promising biologically active substances [16]. The biological properties of 4(3H)-quinazolinones vary depending on the nature of the substituents within the ring system, with reported activities including antifungal, antibacterial, antitubercular, antiviral, anticancer, and anticonvulsant effects [17, 24].

Materials and Methods

Materials

All reagents used in this study (Benzaldehyde, 4-Chlorobenzaldehyde, 4-nitrobenzaldehyde, 4-Bromobenzaldehyde, 4-methoxybenzaldehyde, 2-amino benzoic acid, 1, 4-dioxane, methanol, and acetone) were

sourced from Aldrich, Fluka, and BDH they used without further purification.

Instrumentation

The instrumentations used in this study were Fourier Transform Infrared (FT-IR) Shimadzu FTIR-8400 spectrometer, and NMR analysis was conducted on a Bruker spectroscopic ultra-shield magnets 400 MHz. Melting points of the compounds were recorded on electrothermal melting point apparatus

Procedure

Synthesis of aromatic amino acid (N-phthaloyl amino acid) (1a): Combine 15 g of phthalic anhydride with 7.5 g of amino acid in 75 mL of acetic acid. Heat the mixture gradually over a period of 4 hours. After the heating process is complete, cool the mixture, which will result in the precipitation of N-phthaloyl amino acid.

Synthesis of ester (2a)

Dissolve 10 g of aromatic amine in 100 mL of absolute ethanol. Next, in an ice bath, add 0.1 mol of thionyl chloride ($SOCl_2$) to the solution. Maintain the reaction for 30 minutes while keeping the mixture chilled.

Synthesis of hydrazide (3a)

Combine 0.01 mol of carboxylic acid esters with 3.5 mL of an 80% aqueous solution of hydrazine. Then, add 50 mL of absolute ethanol to the mixture and reflux the solution for 4 hours. After refluxing, allow the mixture to cool, then perform filtration and wash the resulting precipitate with

cold distilled water. Finally, measure the melting point of the obtained product.

General synthesis method hydrazone analogues 4(a-e)

All novel hydrazone analogues 4(a-e) were obtained from the reaction of 1,5- hydrazide (3a) and aldehydes according to the general synthesis method for hydrazone analogues. Dissolve 0.01 mol of the prepared hydrazide in 100 mL of

absolute ethanol. Next, add 0.05 mol of the suitable aldehydes and a small amount of glacial acetic acid. Allow the resulting mixture to react for 6 hours, then cool to room temperature. After filtration, the solvent evaporated, and the resulting residues 4(a-e) were recrystallised using absolute ethanol. Table 1 shows the physical properties of synthesized hydrazones 4(a-d).

Table 1: The physical properties of synthesized hydrazone derivatives 4(a-e).

Compound	X	Molecular formula	Melting point (°C)	Color	Yield %
4a	H	C ₁₇ H ₁₃ O ₃ N ₃	251-253	Yellow	69
4b	4-Br	C ₁₇ H ₁₂ O ₃ N ₃ Br	222-224	Red	73
4c	4-Cl	C ₁₇ H ₁₂ O ₃ N ₃ Cl	229-231	Light yellow	72
4d	4-NO ₂	C ₁₇ H ₁₂ O ₃ N ₄	234-236	brown	70
4e	4-OCH ₃	C ₁₈ H ₁₅ O ₄ N ₃	200-202	Yellow	65

General synthesis quinazoline-4-one derivatives 5(a-e)

All novel quinazoline-4-one derivatives were synthesized from the reaction of 2-amino benzoic acid (Anthranilic acid) and hydrazones, following the standard procedure for quinazoline -4- one synthesis. In a heat-resistant glass flask, 0.01 mol of hydrazones was mixed with 0.01 mol (1.37 g) of

2-amino benzoic acid. The mixture was heated on a hotplate for 10-15 min to initiate fusion. After cooling to room temperature, the resulting residue was collected and recrystallized from a mixture of 1,4-dioxane and ethanol. Table 2 shows the physical properties of synthesized quinazoline-4-one derivatives 5(a-e).

Table 2: The physical properties of synthesized quinazoline -4- one derivatives 5(a-e)

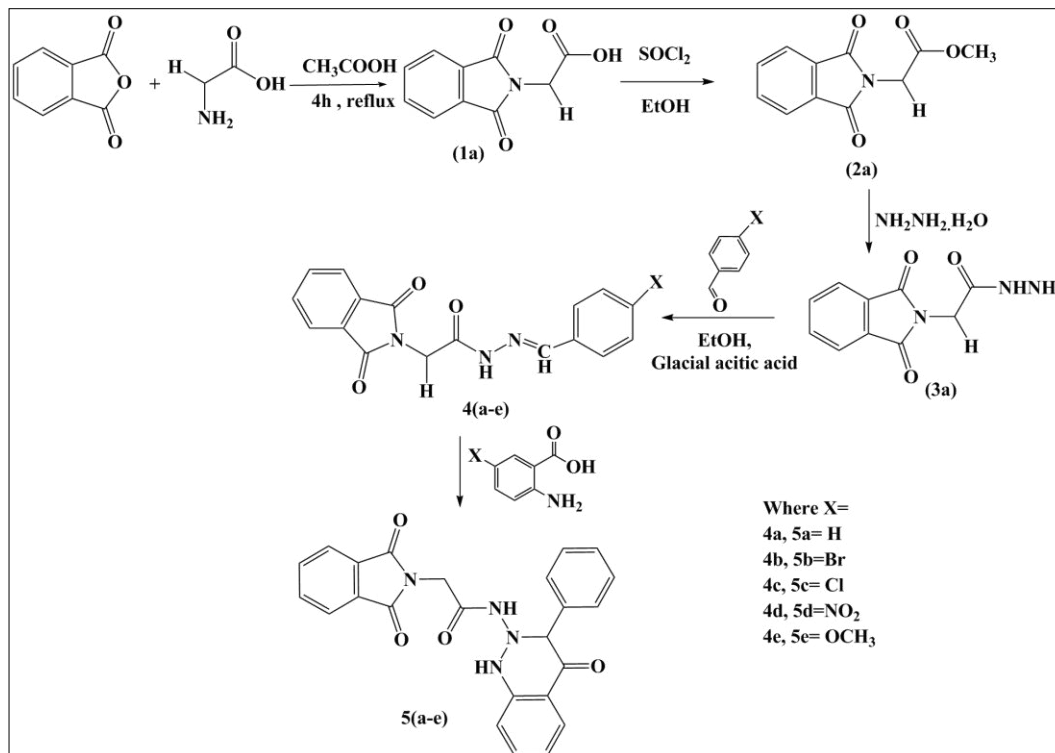
Compound	X	Molecular formula	Melting point (°C)	Color	Yield %
5a	H	C ₂₄ H ₁₇ O ₄ N ₃	240-241	White	70
5b	4-Br	C ₂₄ H ₁₆ O ₄ N ₃ Br	230-232	Yellow	69
5c	4-Cl	C ₂₄ H ₁₆ O ₄ N ₃ Cl	240-241	Reddish brown	68
5d	4-NO ₂	C ₂₄ H ₁₆ O ₆ N ₄	172-174	Brown	65
5e	4-OCH ₃	C ₂₅ H ₁₉ O ₅ N ₃	208-210	Yellow	62

Biological activity study

The biological activity of the synthesized quinazoline-4-one derivatives was assessed against two pathogenic bacterial strains: *Staphylococcus aureus* and *Escherichia coli*. The study involved determining the Minimum Inhibitory Concentration (MIC) of the compounds 5(a-e). Solutions of the compounds were prepared at concentrations of 25, 50, and 75 mg/mL using dimethyl sulfoxide (DMSO) as a solvent. The results were assessed after 24 hours, evaluating the sensitivity of the bacterial strains to the derivatives based on the diameter of the inhibition zones formed around the wells in the agar plates. A larger inhibition zone diameter indicated higher biological activity of the compounds. The inhibition zones of the synthesized compounds were compared to those of standard antibiotics for reference.

Results and Discussion

The synthesis of novel compounds commenced with the preparation of an aromatic amino acid through the reaction of phthalic anhydride with the corresponding amino acid. This was followed by the formation of an aromatic ester via the reaction of the aromatic amino acid with ethanol in the presence of thionyl chloride. Subsequently, the aromatic hydrazide was synthesized from the ester using 80% aqueous hydrazine in an ethanol medium. The hydrazide was then reacted with a variety of aromatic aldehydes, with the addition of a small quantity of glacial acetic acid, to yield hydrazone derivatives. Finally, quinazoline-4-one derivatives were successfully synthesized through the reaction of the hydrazones with anthranilic acid. This sequence of reactions not only illustrates the efficacy of the synthetic approach but also sets the stage for discussing the resulting compounds and their potential applications. All synthesized thioanthraquinone analogues are presented in Scheme 1.



Scheme 1: Synthesis pathway for hydrazone 4(a-e) and quinazoline-4-one 5(a-e) derivatives.

Characterization of hydrazone derivatives 4(a-e)

The analysis demonstrated distinct physical characteristics in the synthesized compounds compared to the starting materials, as revealed by infrared spectroscopy. The spectra indicated various functional group vibrations, including

those related to carbonyl amide, C=N stretching, and aromatic C=C vibrations. Additional peaks were observed for N-H and C-H stretching, as detailed in Table 3 and illustrated in Figure 4 and 5.

Table 3: The physical properties of synthesized quinazoline -4- one derivatives 5(a-e)

Com. No.	FT-IR, (KBr), cm ⁻¹ Fixed bands in structure							Altered structural bands
	$\nu_{\text{N-H}}$	$\nu(\text{=CH})$ arom.	$\nu(\text{C-H})$ aliph	$\nu\text{C=O}$	$\nu\text{C=N}$	$\nu\text{C=CAr}$	$\nu\text{C-N}$	
4a	3348	3082	2949	1746	1605	1561	1211	
4b	3220	3045	2978	1665	1610	1580	1248	ν (C-Br), 625
4c	3224	3086	2988	1667	1597	1558	1258	ν (C-Cl), 820
4d	3341	3079	2888	1677	1595	1537	1279	ν (NO ₂) 1350
4e	3286	3093	2963	1740	1610	1495	1218	

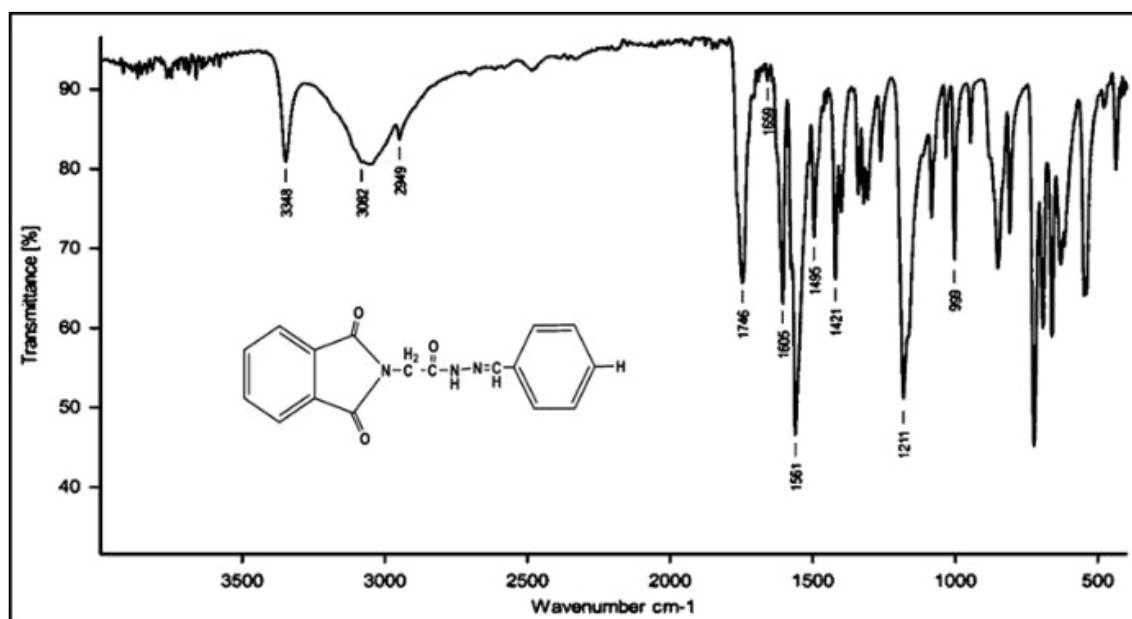


Fig 4: The FT-IR spectrum of compound 4a

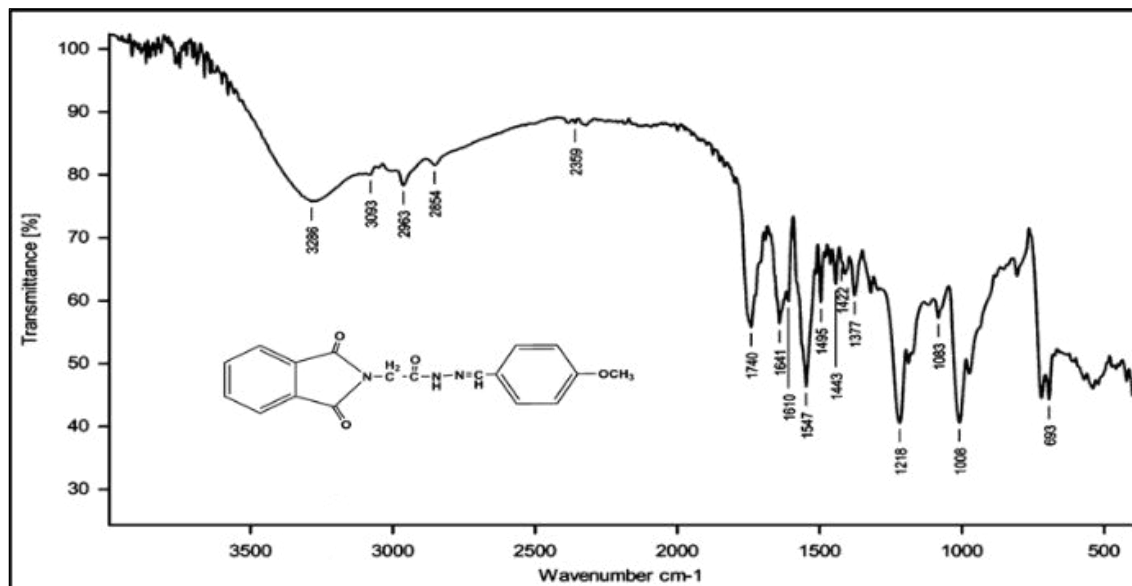


Fig 5: The FT-IR spectrum of compound 4e

The ^1H -NMR spectrum of compounds was obtained using dimethyl sulfoxide as the solvent with deuterium lock. The ^1H -NMR spectral data of Hydrazone are shown in Table 4.

Table 4: The ^1H -NMR data of compounds 4(a-e)

Compound	Structures	^1H NMR Spectral data (δ ppm)
4a		3.421 (s, 2H, CH_2) 5.720 (s, 1H, $\text{CH}=\text{N}$) 7.872-8.172 (m, 9H, CH_{arom}) 11.55 (s, 1H, N-H)
4b		3.210 (s, 2H, CH_2) 5.20 (s, 1H, CH) 7.94 -8.290 (m, 8H, CH_{arom}) 10.89(s, 1H, N-H)
4c		2.910 (s, 2H, CH_2) 6.09 (s, 1H, CH) 7.11-8.09 (m, 8H, CH_{arom}) 10.65 (s, 1H, N-H)
4d		3.080 (s, 2H, CH_2) 5.19 (s, 1H, CH) 7.81-8.29 (m, 8H, CH_{arom}) 11.65(s, 1H, N-H)
4e		3.410 (s, 2H CH_2 ,) 3.831 (s, 3H, CH_3) 4.800 (s, 1H, $\text{CH}=\text{N}$) 7.048-8.643 (m, 8H, CH_{arom}) 12.051 (s, 1H, N-H)

The ^{13}C -NMR spectrum of compounds was obtained using DMSO with deuterium lock. The ^1H -NMR spectral data of Hydrazone are shown in Table 5.

Table 5: ^{13}C -NMR data of compounds 4(a-e)

Compound	^{13}C -NMR Spectral data (δ ppm)
4a	165.10, 178.55, (124.29, 125.59, 127.61, 128.62, 129.36, 131.81 and 133.04 C_{arom}), 69.29, 53.49.
4b	168.12, 182.33, (127.53, 128.55, 128.84, 129.12, 129.82, 132.01 and 133.17 C_{arom}), 71.15, 55.33.
4c	169.43, 180.21, (126.35, 126.49, 127.24, 128.21, 128.28, 131.11 and 132.57 C_{arom}), 70.55, 52.11.
4d	(173.03, 184.23, (125.25, 125.59, 127.33, 127.66, 129.21, 133.16 and 133.67 C_{arom}), 74.52, 57.16, 29.88.
4e	(180.180.16, 161.10, (121.70, 123.71, 125.65, 126.12, 127.52, and 129.16 C_{arom}) 76.54, 55.85, 26.05.

Characterization of quinazoline-4-one derivatives 5(a-e)

The analysis demonstrated distinct physical characteristics in the synthesized compounds compared to the starting materials, as revealed by infrared spectroscopy. The spectra indicated various functional group vibrations, including

those related to carbonyl amide, C–N stretching, and aromatic C=C vibrations. Additional peaks were observed for N–H and C–H stretching, as detailed in Table 6 and illustrated in Figure 6 and 7.

Table 6: The physical properties of synthesized quinazoline -4- one derivatives 5(a-e)

Com. No.	FT-IR, (KBr), cm^{-1}						Altered structural bands
	$\nu\text{N-H}$	$\nu(\text{=CH})$ Ar	$\nu(\text{C-H})$ Aliph	$\nu\text{C=O}$	$\nu\text{C=CAr}$	$\nu\text{C-N}$	
5a	3384	3054	2903	1666	1563	1247	
5b	3351	3094	2911	1653	1603	1228	$\nu(\text{C-Br})$, 673
5c	3331	3002	2908	1653	1599	1291	$\nu(\text{C-Cl})$, 837
5d	3223	3012	2914	1649	1597	1182	$\nu(\text{NO}_2)$ 1366, 1566
5e	3173	3017	2897	1660	1563	1224	$\nu(\text{C-O})$, 1494

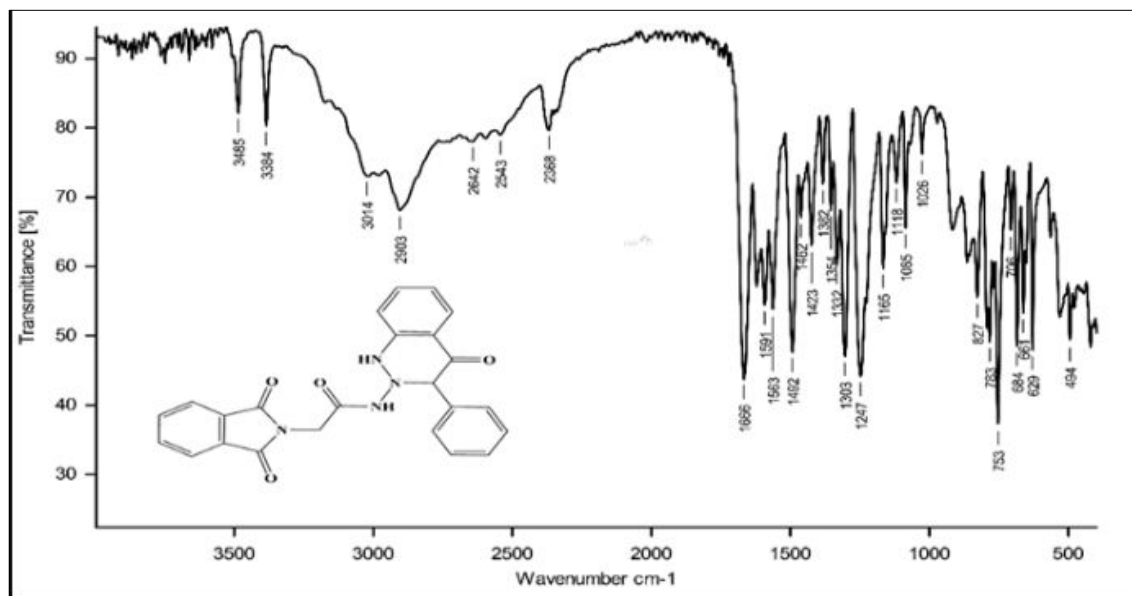


Fig 6: The FT-IR spectrum of compound 5a.

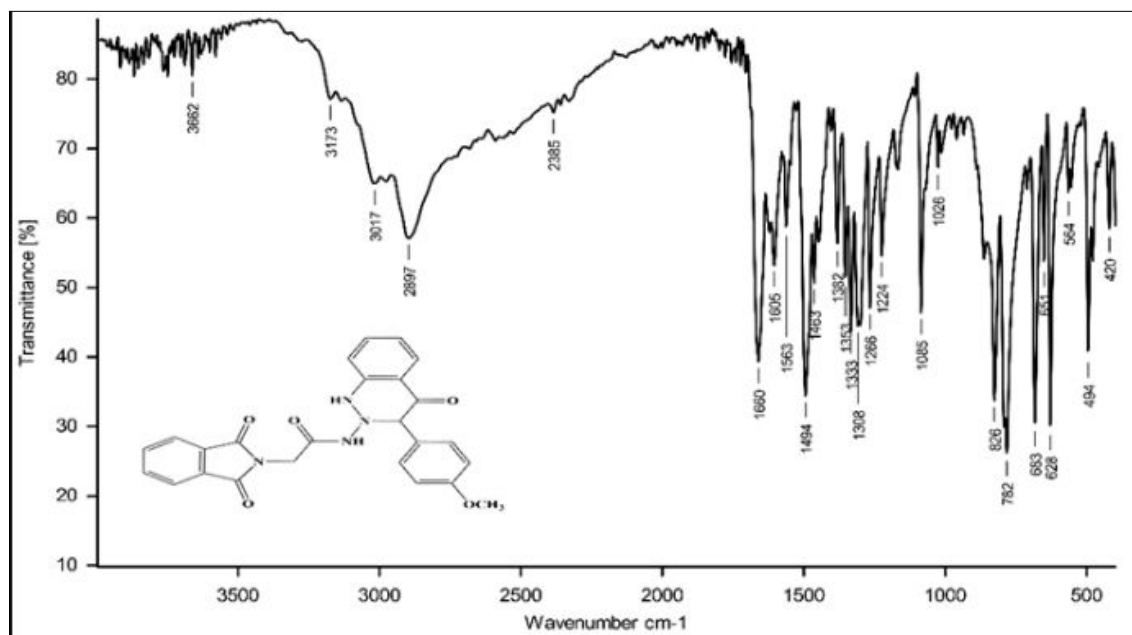
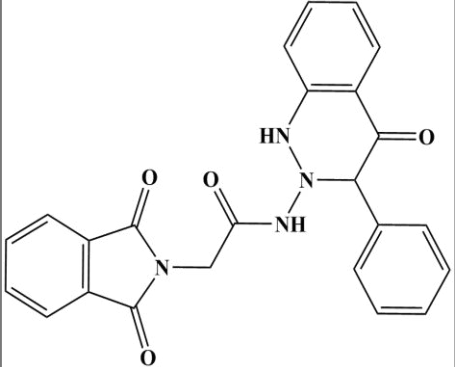
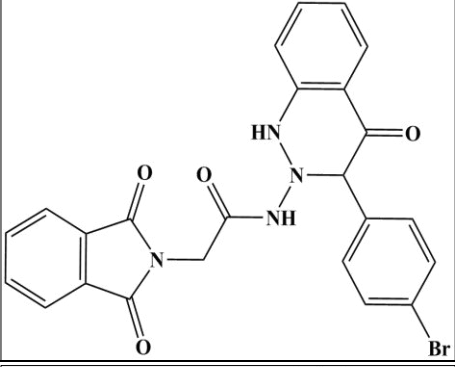
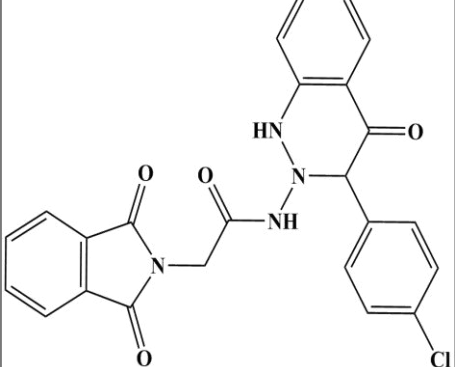
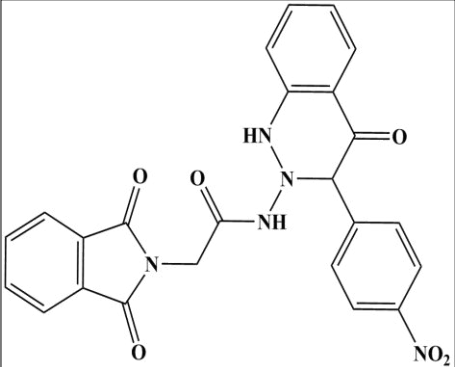
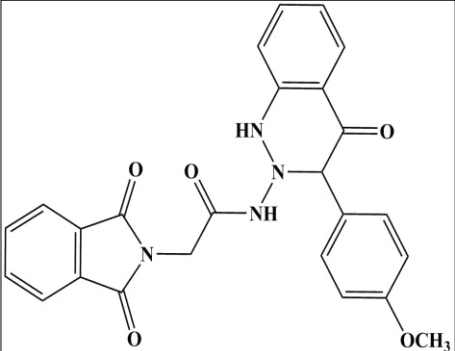


Fig 7: The FT-IR spectrum of compound 5e

The $^1\text{H-NMR}$ spectral data of Quinazoline -4- one derivatives are shown in Table 7.

Table 7: ¹H NMR data of compounds 5(a-e)

Compound	Structures	¹ H NMR Spectral data (δ ppm)
5a		3.410 (s, 2H, CH ₂) 5.720 (s, 1H, CH=N) 7.546 -7.882 (m, 14H, CH _{arom}) 8.088 (s, 1H, H-N-CO) 9.496 (s, 1H, H-N-C=CH)
5b		3.023 (s, 2H, CH ₂) 5.982 (s, 1H, CH=N) 7.987 -8.231 (m, 13H, CH _{arom}) 7.788 (s, 1H, H-N-CO) 9.4353 (s, 1H, H-N-C=CH)
5c		3.018 (s, 2H, CH ₂) 5.921 (s, 1H, CH=N) 7.622 -7.932 (m, 13H, CH _{arom}) 8.101 (s, 1H, H-N-CO) 10.05 (s, 1H, H-N-C=CH)
5d		3.010 (s, 2H, CH ₂) 6.211 (s, 1H, CH=N) 7.925-8.432 (m, 13H, CH _{arom}) 8.870 (s, 1H, H-N-CO) 10.486 (s, 1H, H-N-C=CH)
5e		3.416 (s, 2H, CH ₂) 4.396 (s, 3H) 5.606 (s, 1H, CH=N) 7.212 -7.884 (m, 14H, CH _{arom}) 8.081 (s, 1H, H-N-CO) 10.064 (s, 1H, H-N-C=CH)

The ^{13}C -NMR spectrum of compounds was obtained using dimethyl sulfoxide as the solvent with

deuterium lock. The ^1H -NMR spectral data of Quinazoline-4-one derivatives are shown in Table 8.

Table 8: ^{13}C -NMR data of compounds 5(a-e).

Compound	^{13}C -NMR Spectral data (δ ppm)
5a	161.10, 170.06, 184.20, (119.01, 122.40, 125.60, 127.61, 129.55, 130.49, 131.62, 133.06 and 134.20 C_{arom}), 68.02, 31.28.
5b	162.08, 171.33, 183.43, (122.11, 126.10, 127.51, 128.05, 132.66, 134.12, 135.02 and 135.70 C_{arom}), 73.27, 56.77.
5c	162.59, 170.43, 178.81, (123.16, 125.14, 126.31, 127.25, 133.56, 133.82, 136.05 and 135.66 C_{arom}), 71.75, 57.37.
5d	159.07, 169.13, 179.21, (124.12, 125.24, 126.01, 127.35, 131.16, 132.42, 135.24 and 136.11 C_{arom}), 73.23, 56.07.
5e	(155.08, 161.10, 170.06, (125.60, 127.61, 129.55, 130.49, 131.62, 133.06, and 134.20 C_{arom}), 70.02, 59.42, 29.88.

Assessment of the biological activity of the synthesized quinazoline-4-one derivatives 5(a-e)

The synthesized quinazoline-4-one derivatives demonstrated significant inhibitory efficacy against *Staphylococcus aureus* and notable inhibitory activity against *Escherichia*

coli. As presented in Table 9 and Figure 8, the relationship between concentration and inhibition was dose-dependent, with higher inhibition percentages observed at a concentration of 75 mg/mL.

Table 9: Biological activity of the synthesized quinazoline-4-one derivatives 5(a-e).

Comp. No.	<i>Escherichia coli</i>			<i>Staphylococcus aureus</i>		
Conc. mg/ml	25	50	75	25	50	75
4c	0	2	5	1	3	5
4d	0	0	1	1	1	2
5b	0	1	2	0	0	1
5c	0	1	1	0	2	2
5d	0	0	0	1	1	2
Amoxicillin	2	4	5	2	5	7
Ampicillin	2	3	5	2	4	6
Ciprofloxacin	1	2	5	2	3	5
Blank disk	0	0	0	0	0	0

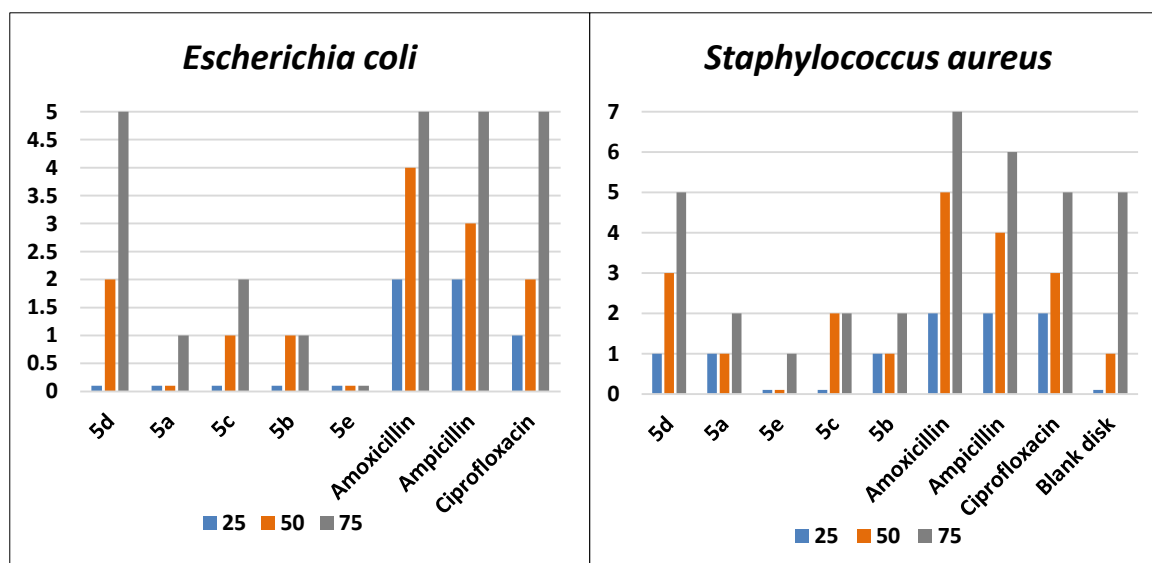


Fig 8: Inhibitory activity values of the synthesized quinazoline-4-one derivatives 5(a-e) against *E. coli* and *S. Aureus*

Conclusion

The target compounds, which include hydrazone derivatives, Quinazoline-4-one derivatives, and Schiff bases, were successfully synthesized using phthalic anhydride as the starting material. The chemical structures of these compounds were elucidated and confirmed through Fourier-Transform Infrared (FT-IR), proton (^1H), carbon (^{13}C) Nuclear Magnetic Resonance (NMR) spectroscopy. Preliminary bioactivity assessments indicated that several of the synthesized compounds (As detailed in Table 9) exhibit significant biological activity. This suggests potential applications for these novel derivatives in pharmaceutical and therapeutic contexts, warranting further investigation into their efficacy and mechanisms of action.

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