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ANTIMICROBIAL EVALUATION OF SOME NEW 3-SUBSTITUTED-4(3H)-QUINAZOLINE

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ABSTRACT

Quinazoline derivatives represent an important class of heterocyclic compounds with diverse pharmacological activities, including antimicrobial, anticancer, anti-inflammatory, and antiviral effects. The present study focuses on the synthesis and antimicrobial evaluation of novel 3-substituted-4(3H)-quinazoline derivatives. The compounds were synthesised via multistep reactions starting from substituted anthranilic acid derivatives, followed by cyclisation and substitution. The synthesised compounds were characterised using spectral techniques such as IR, NMR, and mass spectrometry. The antimicrobial activity of these derivatives was evaluated against selected Gram-positive bacteria (Staphylococcus aureus and Bacillus subtilis), Gram-negative bacteria (Escherichia coli and Pseudomonas aeruginosa), and fungal strains (Candida albicans and Aspergillus niger) using the agar diffusion method. Several derivatives exhibited moderate to significant antimicrobial activity compared to standard drugs. Structure –activity relationship analysis suggested that electron-withdrawing substituents at the 3-position enhance antimicrobial activity. The increasing prevalence of antimicrobial resistance has necessitated the discovery and development of novel therapeutic agents. Quinazoline derivatives have emerged as promising scaffolds in medicinal chemistry due to their diverse biological activities. This research focuses on the synthesis, characterisation, and antimicrobial evaluation of a series of newly developed 3 -substituted-4(3H)-quinazolines. The compounds were assessed against a panel of Gram-positive, Gram-negative bacteria, and fungal strains using standard in vitro methods. The structure-activity relationship (SAR) was explored to identify key functional groups responsible for enhanced

activity. The findings indicate that certain substitutions at the 3-position significantly improve antimicrobial efficacy, providing a foundation for further preclinical investigation. These indicates that 3-substituted-4(3H)-quinazoline derivatives may serve as promising scaffolds for the development of new antimicrobial agents.

KEYWORDS: Quinazoline, antimicrobial activity, synthesis, structure-activity relationship, drug design.

INTRODUCTION

Infectious diseases continue to be one of the major causes of morbidity and mortality worldwide, despite remarkable advances in medical science and drug discovery. These diseases are caused by pathogenic microorganisms such as bacteria, fungi, viruses, and parasites, which invade the host and disrupt normal physiological functions. Among these, bacterial and fungal infections remain a significant public health concern, particularly in developing countries where healthcare resources are limited. The widespre ad occurrence of infectious diseases has led to extensive use of antimicrobial agents over several decades. Antimicrobials have revolutionized medical treatment by reducing infection-related deaths and improving the quality of life. However, the excessive and often irrational use of these agents has resulted in the emergence of antimicrobial resistance (AMR), which poses a serious threat to global health. Antimicrobial resistance reduces the effectiveness of existing drugs, increases treatment costs, prolon gs hospital stays, and leads to higher mortality rates. Consequently, there is an urgent need to discover and develop new antimicrobial agents with novel mechanisms of action to overcome resistant strains.

Antimicrobial resistance has emerged as one of the most critical challenges in modern medicine. Microorganisms develop resistance through various mechanisms such as mutation, enzymatic degradation of drugs, alteration of drug targets, and efflux pumps. The continuous evolution of resistant strains like methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Enterococcus (VRE), and multidrug-resistant Gram-negative bacteria has rendered many conventional antibiotics ineffective. The World Health Organization (WHO) has recognized antimicrobial resistance as a global health emergency. The limited pipeline of new antimicrobial agents further exacerbates the problem, highlighting the necessity for innovative research in antimicrobial drug development. Heterocyclic compounds have gained considerable attention in this regard due to their diverse biological activities and structural versatility.

Heterocyclic compounds constitute a major class of organic compounds that contain at least one heteroatom such as nitrogen, oxygen, or sulfur within a ring system. These compounds play a vital role in medicinal chemistry, as a large proportion of marketed drugs possess heterocyclic moieties. Nitrogen-containing heterocycles are particularly significant due to their ability to interact with biological targets through hydrogen bonding, π–π stacking, and electrostatic interactions. Such interactions enhance binding affinity and specificity, making heterocycles valuable scaffolds in drug design. Among nitrogen-containing heterocycles, quinazoline and quinazolinone derivatives have attracted substantial interest owing to their wide spectrum of pharmacological activities.

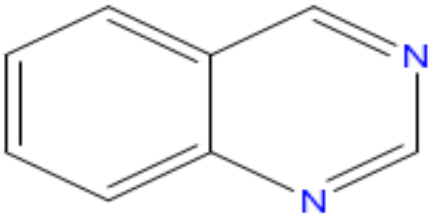


Fig. 1.1 Structure Of Quinazoline

Quinazoline is a bicyclic nitrogen-containing heterocyclic compound consisting of a benzene ring fused with a pyrimidine ring. The presence of two nitrogen atoms in the pyrimidine ring contributes to the unique chemical and biological properties of quinazoline. Quinazoline serves as an important pharmacophore and structural scaffold in medicinal chemistry. The quinazoline nucleus is known for its chemical stability and ease of functionalization at various positions, allowing the synthesis of a wide range of derivatives. Substitutions at different positions of the quinazoline ring significantly influence its biological activity, making it a versatile template for drug development.

Quinazolinones are oxygenated derivatives of quinazoline containing a carbonyl group, which enhances their polarity and biological activity. Among these, 4(3H)-quinazolinone is one of the most extensively studied frameworks due to its pharmacological relevance. The 4(3H)-quinazolinone structure exists predominantly in the keto form and is capable of forming strong hydrogen bonds with biological macromolecules. This structural feature contributes to improved receptor binding and biological efficacy. Quinazolinone derivatives have been reported to exhibit antimicrobial, anticancer, anti-inflammatory, anticonvulsant, and analgesic activities.

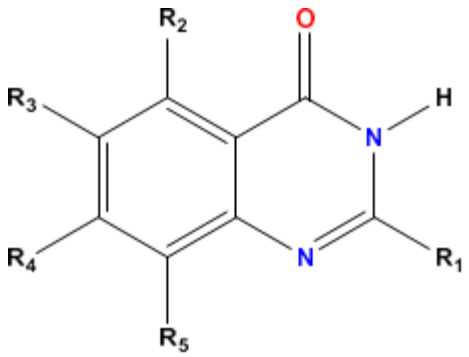


Fig. 1.1 Structure of Quinazoline Showing Substitution.

Table 1.1 Structural Activity Relationship of the Quinazoline.

S. NO.	POSITION	TYPES OF SUBSTITUTION	EFFECT ON ACTIVITY
1.	N-3	Heterocyclic ring	Strongly increases antimicrobial activity
2.	R1	Electron withdrawing group	Improve antibacterial potency
3.	R2/R3	Halogens	Enhances lipophilicity and activity
4.	R4	Nitro group	Improves antifungal activity
5.	R5	Methoxy/alkyl	May improve anti-inflammatory activity
6.	4 – position	Carbonyl group	Essential for receptor binding

Structural modification of the quinazolinone nucleus plays a crucial role in modulating biological activity. Substitution at the 3-position of 4(3H)-quinazolinone has been found to significantly enhance antimicrobial potential. The introduction of various functional groups at this position can alter lipophilicity, electronic distribution, and steric properties of the molecule. These modifications influence the interaction of the compound with microbial enzymes and cellular targets, thereby improving antimicrobial efficacy. Therefore, the design and synthesis of new 3-substituted-4(3H)-quinazoline derivatives represent a promising approach in the search for novel antimicrobial agents.

Numerous studies have demonstrated that quinazoline and quinazolinone derivatives possess significant antimicrobial activity against a wide range of Gram-positive and Gram-negative bacteria, as well as fungal species. The antimicrobial action of these compounds is attributed to their ability to inhibit essential microbial enzymes, disrupt cell wall synthesis, or interfere with nucleic acid synthesis. The structural flexibility of the quinazoline nucleus allows optimization of antimicrobial properties by str ategic substitution. This has encouraged researchers to explore new quinazoline derivatives with improved potency and reduced toxicity.

Despite extensive research on quinazoline derivatives, the continuous emergence of resistant microbial strains necessitates the development of new compounds with enhanced antimicrobial activity. Many reported quinazoline derivatives exhibit moderate activity, indicating the need for further structural optimization. The present study focuses on the synthesis and antimicrobial evaluation of some new 3 - substituted-4(3H)-quinazoline derivatives with the objective of identifying potent antimicrobial candidates. By introducing novel substituents at the 3-position, the study aims to improve biological activity and contribute to the development of new antimicrobial agents.

The rationale behind selecting 3-substituted-4(3H)-quinazoline derivatives lies in their proven pharmacological importance and structural adaptability. The presence of the quinazolinone nucleus provides a strong foundation for antimicrobial activity, while substitution at the 3-position offers opportunities for structural diversification. This study is designed to explore the structure–activity relationship of newly synthesized derivatives and evaluate their antimicrobial potential against selected microbial strains.

MATERIAL AND METHODS –

REAGENT AND SOLVENT

The 2-amino-4-chloro benzoic acid was procured from Sigma Aldrich, Mumbai, India. Triethoxymethane acetate was purchased from CDH, India. Different substituted aniline was purchased from Hi-media, India. The chemicals used for the experimental work were of synthetic grade.

SYNTHESIS

The synthesis comprises the one step process in which, 2-amino-4-chlorobenzoic acid is reacted with the trimethoxy methane and different substituted aniline to synthesize the 3-(4-substituted phenyl) quinazolin-4(3H)-one.

INSTRUMENTS USED

The 1HNMR spectra were obtained at room temperature on a Bruker Avance 400-MHz spectrometer. DMSO-d6 used as solvent. FT-IR spectra were measured at room temperature with a Bruker alpha. Melting points are uncorrected and were determined using a digital melting point apparatus.

SYNTHESIS OF 3-(4-SUBSTITUTED PHENYL)-QUINAZOLIN-4(3H)-ONE

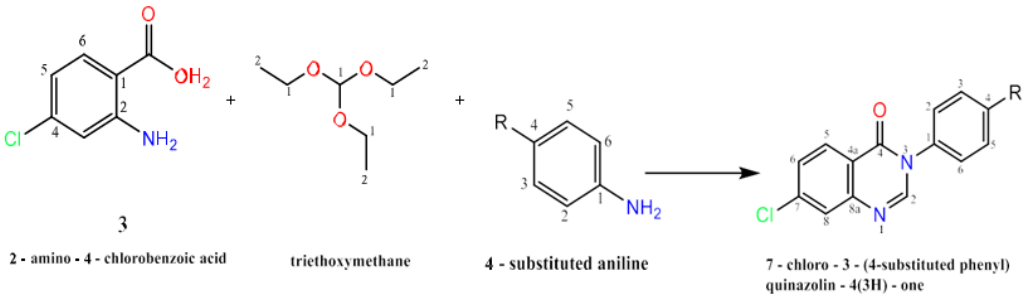


Fig. 2.1 Synthesis of 3-(4-substituted phenyl)-quinazolin-4(3h)-one.

PROCEDURE

Ten compounds, of 3-substituted-4(3H)-quinazolinone derivative have been synthesis by the one pot reaction of 2-amino-4-chlorobenzoic acid (0.01 M) with triethoxy methane (0.03 M) and different substituted aniline (0.01 M) in acidic environment using acetic acid. The reaction mixture was refluxed for 4 hrs. and concentrated under reduced pressure.

The Reaction was monitored by thin layer chromatography by using ethyl acetate: n-hexane (1:1 v/v) as solvent. The absence of the starting material has indication of completion of the reaction. Then the reaction was cooled at room temperature and then added to chilled ice-cold water, the precipitate was obtained immediately. The precipitate was filtered and washed with the ice-cold water several times and dried under vacuum. The compound was then recrystallized with 75% alcohol.

LIST OF THE CHEMICALS AND THEIR QUANTITY USED IN STEP I

Table 2.1 list of Chemicals and their Quantities.

S.NO.	CHEMICAL	MOL. WT. (g/mol)	QUANTITY TAKEN (g)
1.	2-amino-4-chlorobenzoic acid	171.58	1.71
2.	Trimethoxy methane	106.12	1.06
DIFFERENT SUBSTITUTED ANILINE			
1.	4-chloroaniline	127.57	1.27
2.	4-bromoaniline	172.03	1.72
3.	4-nitroaniline	138.13	1.38
4.	4-methylaniline	107.16	1.07
5.	4-ethyl aniline	121.18	1.21
6.	4-butylaniline	149.24	1.49
7.	4-methoxyaniline	123.16	1.23
8.	3,4,5-trimethylaniline	135.21	1.35
9.	3-bromo-4-chloroaniline	206.47	2.06
10.	4-chloro-3-nitroaniline	172.57	1.72

LIST OF FINAL SYNTHESIZED COMPOUNDS

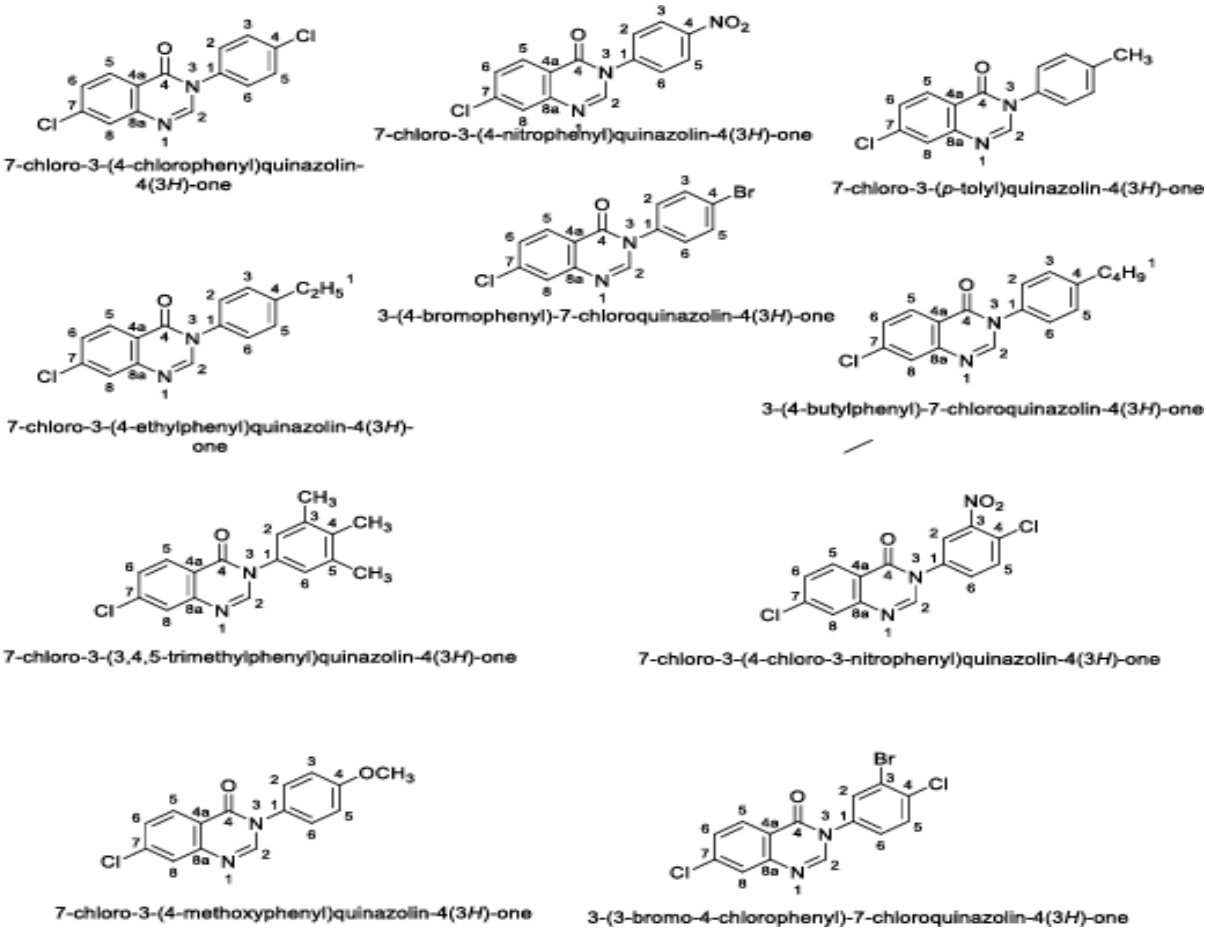


Fig. 2.2 List of Final Synthesized Compounds.

STRUCTURE CHARACTERIZATION

Instrument and equipment

 Melting point: Melting points of the synthesized compounds were determined by open glass capillary method and were uncorrected.

 Solubility: The solubility studies of the synthesized compounds were performed in various solvents at room temperature qualitatively.

 TLC: Thin layer chromatography was performed on precoated silica gel-G glass plates using ethyl acetate: n-hexane (1:1 v/v) as mobile phase to ascertain the purity of the synthesized compounds. UV Chamber was used for detection.

 IR: The infrared spectra of the compounds were recorded on Bruker alpha software.

 1H NMR: 1H NMR spectral analysis of the synthesized compounds was recorded on Bruker Avance III 500 MHz (AV 500) in deuterated DMSO using tetramethylsilane as internal standard.

Physicochemical Characterization –

Physical parameters of the compounds

Table 2.2 physical parameters of the compounds.

Comp.	Mol. Formula	Mol. Wt.	% yield	Melting point (˚C)	R_f value
4A	$C_{14}H_8Cl_2N_2O$	291.13	76	270-272°C	0.65
4B	$C_{14}H_8BrClN_2O$	335.59	56	243-245°C	0.48
4C	$C_{14}H_8ClN_3O_3$	301.69	78	260-262°C	0.58
4D	$C_{15}H_{11}ClN_2O$	270.72	70	176-178°C	0.76
4E	$C_{16}H_{13}ClN_2O$	284.74	68	166-268°C	0.57
4F	$C_{18}H_{17}ClN_2O$	312.80	65	233-235°C	0.80
4G	C15H11ClN2O2	286.72	62	213-215°C	0.62
4H	$C_{17}H_{15}ClN_2O$	298.77	55	255-257°C	0.55
4I	$C_{14}H_7BrCl_2N_2O$	370.03	48	248-250°C	0.56
4J	C14H7Cl2N3O3	336.13	68	250-252°C	0.44

Solubility studies of the synthesized compounds

Table 2.3 solubilities studies.

Compound	Water	Alcohol	Acetone	Glacial Acetic Acid	Benzene	Dimethyl Sulfoxide
4A	-	+++	++	++	-	+++
4B	-	+++	++	++	-	+++
4C	-	+++	++	++	-	+++
4D	-	+++	++	++	-	+++
4E	-	+++	++	++	-	+++
4F	-	+++	++	++	-	+++
4G	-	+++	++	++	-	+++
4H	-	+++	++	++	-	+++
4I	-	+++	++	++	-	+++
4J	-	+++	++	++	-	+++

Insoluble; + = Slightly soluble; ++ = soluble; +++ = Freely soluble The synthesized compounds are

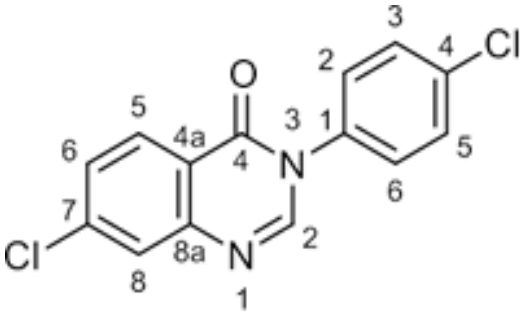
1) Compound 4A: 7-chloro-3-(4-chlorophenyl) quinazolin-4(3H)-one
2) Compound 4B: 3-(4-bromophenyl)-7-chloroquinazolin-4(3H)-one
3) Compound 4C: 7-chloro-3-(4-nitrophenyl) quinazolin-4(3H)-one
4) Compound 4D: 7-chloro-3-(p-tolyl) quinazolin-4(3H)-one
5) Compound 4E: 7-chloro-3-(4-ethylphenyl) quinazolin-4(3H)-one
6) Compound 4F: 3-(4-butylphenyl)-7-chloroquinazolin-4(3H)-one
7) Compound 4G: 7-chloro-3-(4-methoxyphenyl) quinazolin-4(3H)-one
8) Compound 4H: 7-chloro-3-(3,4,5-trimethylphenyl) quinazolin-4(3H)-one
9) Compound 4I: 3-(3-bromo-4-chlorophenyl)-7-chloroquinazolin-4(3H)-one

10) Compound 4J: 7-chloro-3-(4-chloro-3-nitrophenyl) quinazolin-4(3H)-one

SPECTROSCOPIC ANALYSIS OF COMPOUNDS BY IR AND 1HNMR

Compound A –

Structure -



Chemical name:	7-chloro-3-(4-chlorophenyl)quinazolin-4(3H)-one
Chemical Formula:	$C_{14}H_8Cl_2N_2O$
Molecular Weight:	291.13
Log P:	3.88
TLC (R_f value):	0.65

IR data (cm^{-1}): 3438.2 (N-H); 1680.96 (C=O str.); 1410.10 (C=N str.); 1530.91 (C=C str.); 1107.56 (C-N sym. str.); 647.0 (C-Cl).

^{1}HNMR data (ppm): 7.40-7.43 (2H, 3-Substituted phenyl ring); 8.48 (1H, 2nd position of quinazolinone ring); 7.62-7.93 (3H, 5,6,8 position of quinazolinone ring)

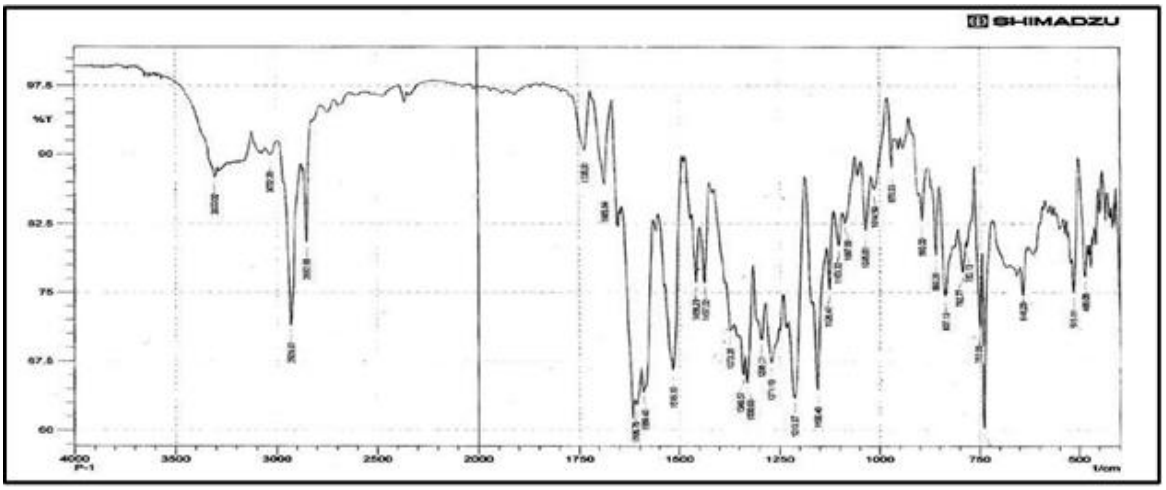
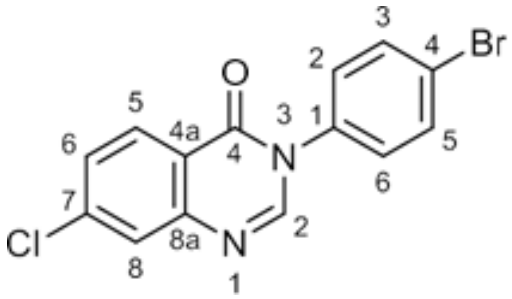


Figure 2.3: IR spectrum of compound 4A.

Compound 4B

Structure



Chemical name: 3-(4-bromophenyl)-7-chloroquinazolin-4(3H)-one

Chemical Formula: $C_{14}H_8BrClN_2O$

Molecular Weight: 335.59

Log P: 4.15

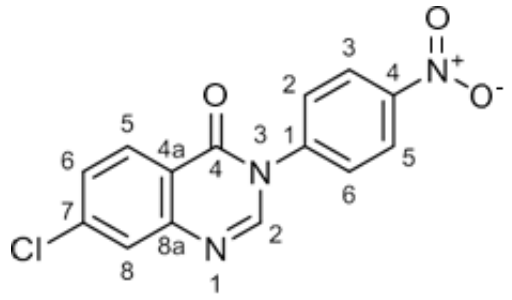
TLC (R_f value): 0.48

IR data (cm^{-1}): 3440.2 (N-H); 1682.96 (C=O str.); 1406.10 (C=N str.); 1524.91 (C=C str.); 1100.56 (C-N sym. str.); 647.0 (C-Cl); 620 (C-Br).

^{1}HNMR data (ppm): 7.60-7.65 (2H, 3-Substituted phenyl ring); 8.48 (1H, 2nd position of quinazolinone ring); 7.62-7.93 (3H, 5,6,8 position of quinazolinone ring)

Compound 4C

Structure



Chemical name: 7-chloro-3-(4-nitrophenyl)quinazolin-4(3H)-one

Chemical Formula: $C_{14}H_8ClN_3O_3$

Molecular Weight: 301.69

Log P: 5.62

TLC (R_f value) 0.58

IR data (cm^{-1}): 3440.2 (N-H); 1682.96 (C=O str.); 1407.10 (C=N str.); 1528.91 (C=C str.); 1102.56 (C-N sym. str.); 1495.51 (N-O asym. str.); 1382.5 (sym. N=O str.); 647.0 (C-Cl).

^{1}HNMR data (ppm): 7.80-8.40 (2H, 3-Substituted phenyl ring); 8.48 (1H, 2nd position of quinazolinone ring); 7.62-7.93 (3H, 5,6,8 position of quinazolinone ring).

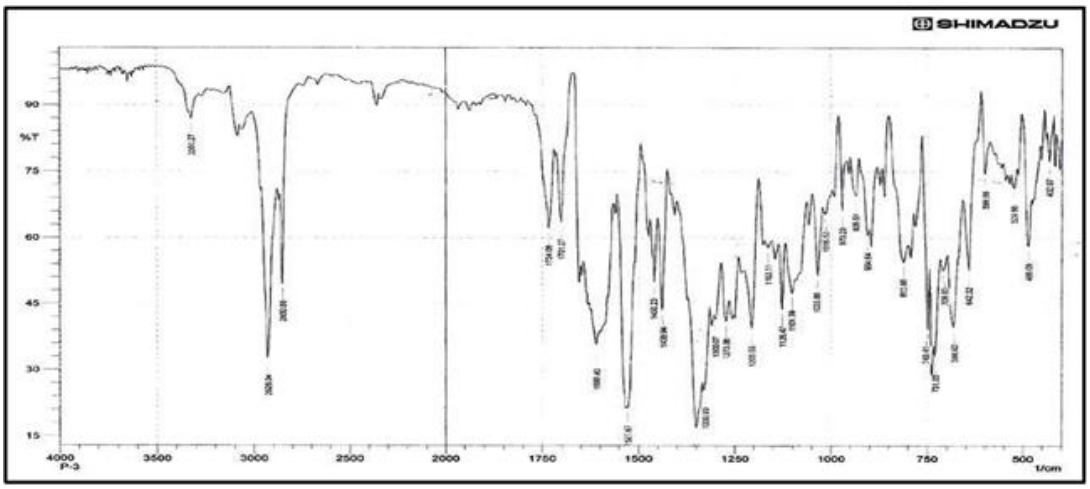
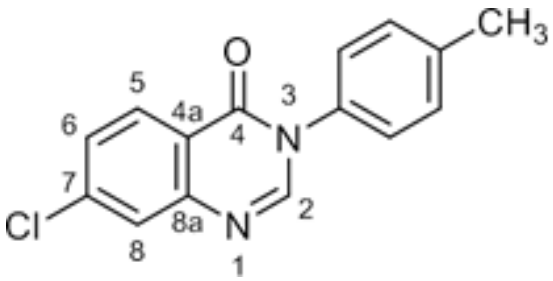


Figure 2.4: IR spectrum of Compound 4C.

Compound 4D -

Structure



Chemical name: 7-chloro-3-(p-tolyl)quinazolin-4(3H)-one

Chemical Formula: $C_{15}H_{11}ClN_2O$

Molecular Weight: 270.72

Log P: 3.81

TLC (R_f value): 0.76

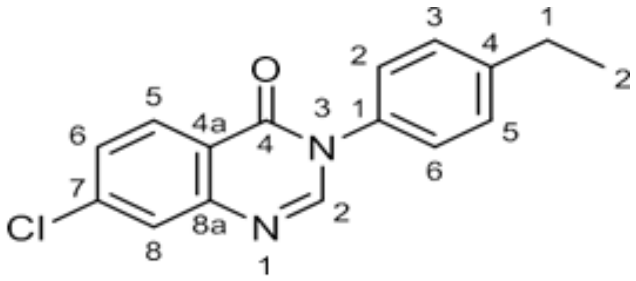
IR data (cm^{-1}): 3436.2 (N-H); 1682.96 (C=O str.); 1412.10 (C=N str.); 1528.91 (C=C str.); 1108.56 (C-N sym. str.); 647.0 (C-Cl)

^{1}HNMR data (ppm): 7.26-7.30 (2H, 3-Substituted phenyl ring); 8.48 (1H, 2nd

position of quinazolinone ring); 7.62-7.93 (3H, 5,6,8 position of quinazolinone ring); 2.38 (O-CH_3)

Compound 4E

Structure



Chemical name:	7-chloro-3-(4-ethylphenyl)quinazolin-4(3H)-one
Chemical Formula:	$C_{16}H_{13}ClN_2O$
Molecular Weight:	284.74
Log P:	4.22
TLC (R_f value):	0.57

IR data (cm^{-1}): 3436.2 (N-H); 1680.52 (C=O str.); 1408.10 (C=N str.); 1532.91 (C=C str.); 1105.56 (C-N sym. str.); 647.0 (C-Cl).

^{1}HNMR data (ppm): 7.31-7.41 (2H, 3-Substituted phenyl ring); 8.48 (1H, 2nd position of quinazolinone ring); 7.62-7.93 (3H, 5,6,8 position of quinazolinone ring); 2.58 (C-CH_2); 1.18 (3H, C-CH_3).

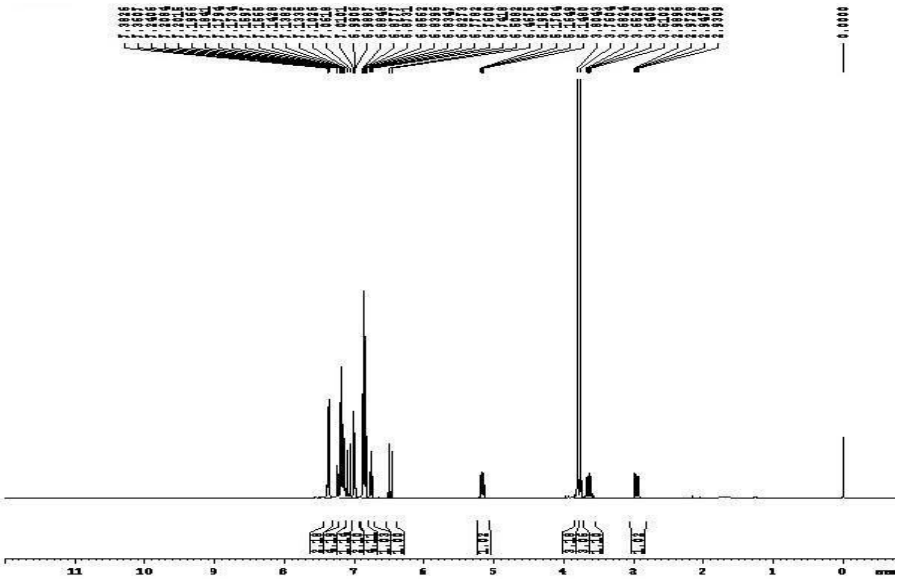
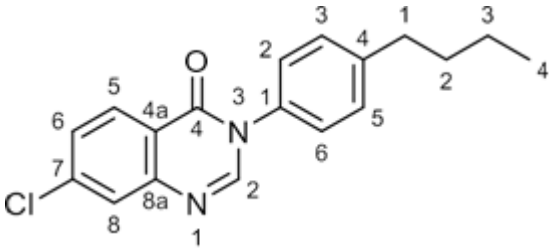


Figure 2.5: ^{1}HNMR spectra of compound 4E.

Compound 4F

Structure:



Chemical name:	3-(4-butylphenyl)-7-chloroquinazolin-4(3H)-one
Chemical Formula:	$C_{18}H_{17}ClN_2O$
Molecular Weight:	312.80
Log P:	5.06
TLC (R_f value)	0.80

IR data (cm^{-1}): 3438.8 (N-H); 1682.56 (C=O str.); 1412.10 (C=N str.); 1528.91 (C=C str.); 1110.56 (C-N sym. str.); 647.0 (C-Cl).

^{1}HNMR data (ppm): 7.40-7.43 (2H, 3-Substituted phenyl ring); 8.48 (1H, 2nd position of quinazolinone ring); 7.62-7.93 (3H, 5,6,8 position of quinazolinone ring); 3.18 (2H, C-CH_2); 2.56 (2H, C-CH_2); 2.08 (2H, C-CH_2); 2.32 (3H, C-CH_3)

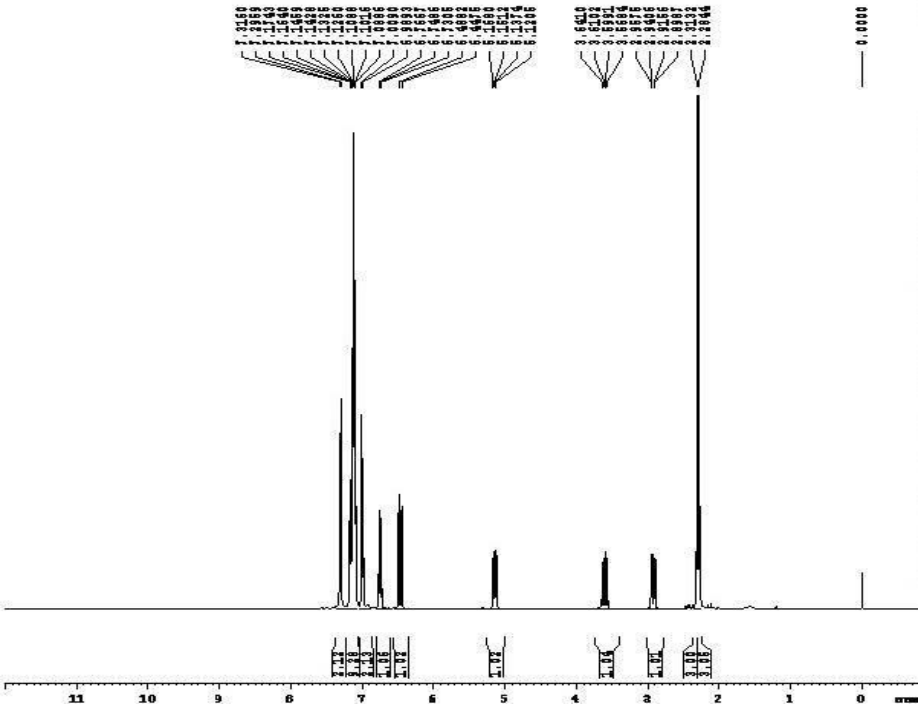
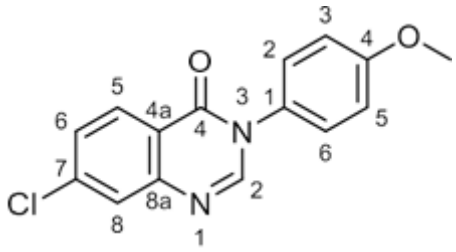


Figure 2.6: ^{1}HNMR spectra of compound 4F.

Compound 4G

Structure



Chemical name: 7-chloro-3-(4-methoxyphenyl)quinazolin-4(3H)-one

Chemical Formula: $C_{15}H_{11}ClN_2O_2$

Molecular Weight: 286.72

Log P: 3.19

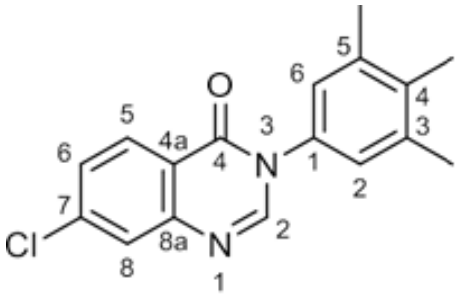
TLC (R_f value) 0.62

IR data (cm^{-1}): 3440.2 (N-H); 1682.20 (C=O str.); 1408.10 (C=N str.); 1528.40 (C=C str.); 1102.32 (C-N sym. str.); 647.0 (C-Cl).

^{1}HNMR data (ppm): 7.02-7.19 (2H, 3-Substituted phenyl ring); 8.48 (1H, 2nd position of quinazolinone ring); 7.62-7.93 (3H, 5,6,8 position of quinazolinone ring); 3.81 (3H, C-O-CH-$_3$).

Compound 4H

Structure



Chemical name: 7-chloro-3-(3,4,5-trimethylphenyl)quinazolin-4(3H)-one

Chemical Formula: $C_{17}H_{15}ClN_2O$

Molecular Weight: 298.77

Log P: 4.78

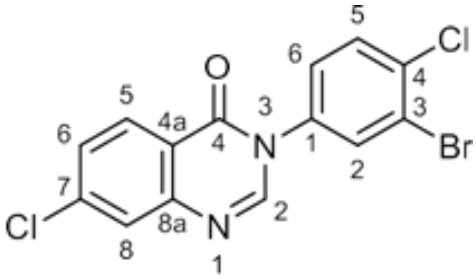
TLC (R_f value) 0.55

IR data (cm^{-1}): 3439.7 (N-H); 1678.96 (C=O str.); 1405.10 (C=N str.); 1528.35 (C=C str.); 1105.26 (C-N sym. str.); 647.0 (C-Cl).

^{1}HNMR data (ppm): 7.57 (1H, 3-Substituted phenyl ring); 8.48 (1H, 2nd position of quinazolinone ring); 7.62-7.93 (3H, 5,6,8 position of quinazolinone ring); 2.18-2.29 (9H, C-CH_3)

Compound 4I

Structure



Chemical name: 3-(3-bromo-4-chlorophenyl)-7-chloroquinazolin-4(3H)-one

Chemical Formula: $C_{14}H_7BrCl_2N_2O$

Molecular Weight: 370.03

Log P: 4.71

TLC (R_f value) 0.56

IR data (cm^{-1}): 3440.2 (N-H); 1679.9 (C=O str.); 1412.20 (C=N str.); 1528.91 (C=C str.); 1107.56 (C-N sym. str.); 647.0 (C-Cl); 620 (C-Br).

^{1}HNMR data (ppm): 7.37-7.63 (3H, 3-Substituted phenyl ring); 8.48 (1H, 2nd position of quinazolinone ring); 7.62-7.93 (3H, 5,6,8 position of quinazolinone ring).

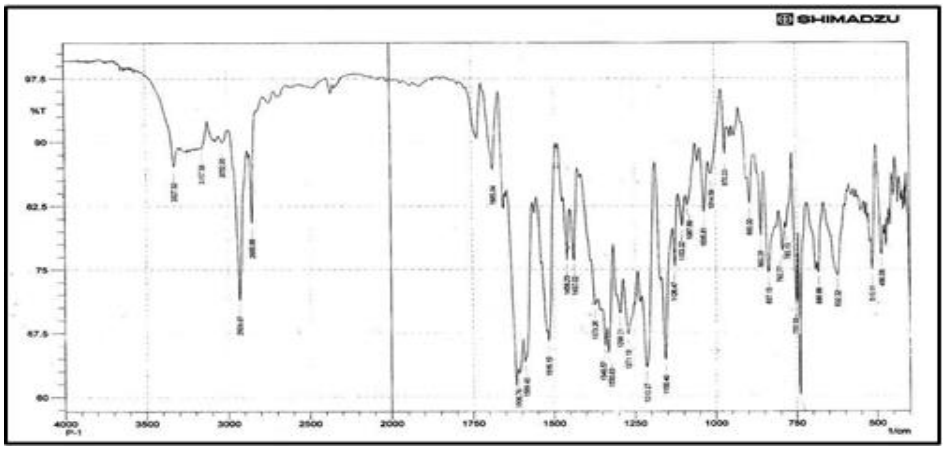
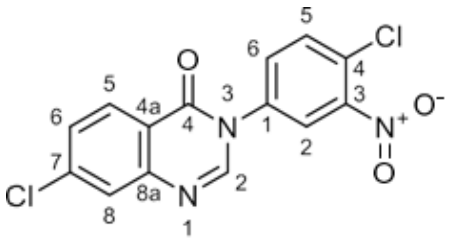


Figure 2.7: IR spectrum of compound 4I

Compound 4J

Structure



Chemical name: 7-chloro-3-(4-chloro-3-nitrophenyl)quinazolin-

4(3H)-one Chemical	Formula:	C14H7Cl2N3O3
Molecular Weight:	336.13	
Log P:	5.88	
TLC (R_f value)	0.44	

IR data (cm^{-1}): 3440.2 (N-H); 1680.96 (C=O str.); 1493.51 (N-O asym. str.); 1382 (sym. N=O str.); 1412.10 (C=N str.); 1528.91 (C=C str.); 1107.56 (C-N sym. str.); C-Cl 647.0 cm-1

^{1}HNMR data (ppm): 7.53-7.71 (2H, Ar. C-H, 1,3,4-oxadiazole); 7.49-7.78 (2H, Ar. C-H,
phenyl ring); 7.68-8.13 (4H, Ar. C-H).

RESULT AND DISCUSSION

Antibacterial activity

Antibacterial activity of the synthesized compounds 3-substitued-4(3H)-quinazolinone (4A-4J) has been carried out for one gram-negative and one gram-positive bacterial strain. In accordance with the data obtained from antibacterial activity, all the synthesized 3-disubstitued-4(3H)-quinazolinone (4A-4J) have showed activity against tested organisms.

The Data of antibacterial activity against the gram-negative bacterial strains (Pseudomonas Aeruginosa) and Gram-positive strain (Staphylococcus Aureus) suggested the order of activity of compounds: 4A > 4C> 4D > 4J> 4I> 4B > 4E > 4H> 4G> 4F. Compounds 4A (18.02±0.24), 4B (12.54±0.28), 4C (17.25±0.24), 4D (15.54±0.20), 4E (11.64±0.26), 4F (8.56±0.29) 4G (9.02±0.24), 4H (9.22±0.25), 4I (13.02±0.26) and 4J (15.25±0.30) has shown zone of inhibition (mm), in comparison to standard drug (Ciprofloxacin, 18.25±0.18; Norfloxacin, 17.64±0.22) has shown good activity against Pseudomonas aeruginosa (gram negative bacteria) at 50µg concentration.

Compounds 4A (21.09±0.27), 4B (14.52±0.28), 4C (20.26±0.30), 4D (13.57±0.25), 4E (11.62±0.31), 4F (11.52±0.27) 4G (11.06±0.26), 4H (11.20±0.25), 4I (15.08±0.24) and 4J (18.22±0.27) has shown zone of inhibition (mm) in comparison to standard drug (Ciprofloxacin, 22.45±0.25; Norfloxacin, 20.65±0.26) has shown good activity against Pseudomonas aeruginosa (gram negative bacteria) at 100µg concentration. The graphical representation of antibacterial activity on gram negative bacterial stain and zone of inhibition was shown.

Antibacterial activity of synthesized 3-substitued-4(3H) quinazolinone derivatives against gram-negative and gram-positive bacteria.

Table 3.1. Zone Inhibition of Compound.

Compound	Zone of inhibition (mm)			
	Pseudomonas Aeruginosa		***Staphylococcus Aureus***	
	50µg	**100µg**	**50µg**	**100µg**
4A	18.02±0.24	21.09±0.27	17.02±0.28	19.02±0.23
4B	12.54±0.27	14.52±0.28	11.54±0.25	13.54±0.25
4C	17.25±0.26	20.26±0.30	16.25±0.24	18.25±0.26
4D	15.54±0.20	13.57±0.25	10.54±0.29	12.54±0.30
4E	11.64±0.26	11.62±0.31	09.64±0.25	11.64±0.27
4F	08.56±0.29	11.52±0.27	07.56±0.32	09.56±0.28
4G	09.02±0.24	11.06±0.26	08.02±0.28	10.02±0.28
4H	09.22±0.25	11.20±0.25	08.22±0.26	10.22±0.29
4I	13.02±0.26	15.08±0.24	12.02±0.25	14.02±0.26
4J	15.25±0.30	18.22±0.27	14.25±0.29	16.25±0.30
Norfloxacin	17.64±0.22	20.65±0.26	18.25±0.16	19.33±0.27
Ciprofloxacin	18.25±0.18	22.45±0.25	18.64±0.25	21.65±0.28

The order of activity of synthesized compound is: 4A > 4C> 4D > 4J> 4I> 4B > 4E > 4H> 4G> 4F. Compounds 4A (17.02±0.28), 4B (11.54±0.25), 4C (16.25±0.24), 4D (10.54±0.29), 4E (9.64±0.25), 4F (7.56±0.32) 4G (8.02±0.28), 4H (8.22±0.26), 4I (12.02±0.25) and 4J (14.25±0.29) has shown zone of inhibition (mm) in comparison to standard drug (Ciprofloxacin, 18.64±0.25; Norfloxacin, 18.25±0.16) has shown good activity against Staphylococcus Aureus (gram positive bacteria) at 50µg concentration.

Compounds 4A (19.02±0.23), 4B (13.54±0.25), 4C (18.25±0.26), 4D (12.54±0.30), 4E (11.64±0.27), 4F (9.56±0.28) 4G (10.02±0.28), 4H (10.22±0.29), 4I (14.02±0.26) and 4J (16.25±0.30) has shown zone of inhibition (mm) in comparison to standard drug (Ciprofloxacin, 21.65±0.26, Norfloxacin, 19.33±0.27) has shown good activity against

Staphylococcus Aureus (gram positive bacteria) at 100µg concentration.

Among all the synthesized 3-substitued-4(3H)-quinazolinone (4A-4J), compounds 4H, 4G and 4F shows mild activity 4B and 4E has showed moderate activity and 4A, 4C, 4D,4J and 4I has shown best activity against all bacterial strains.

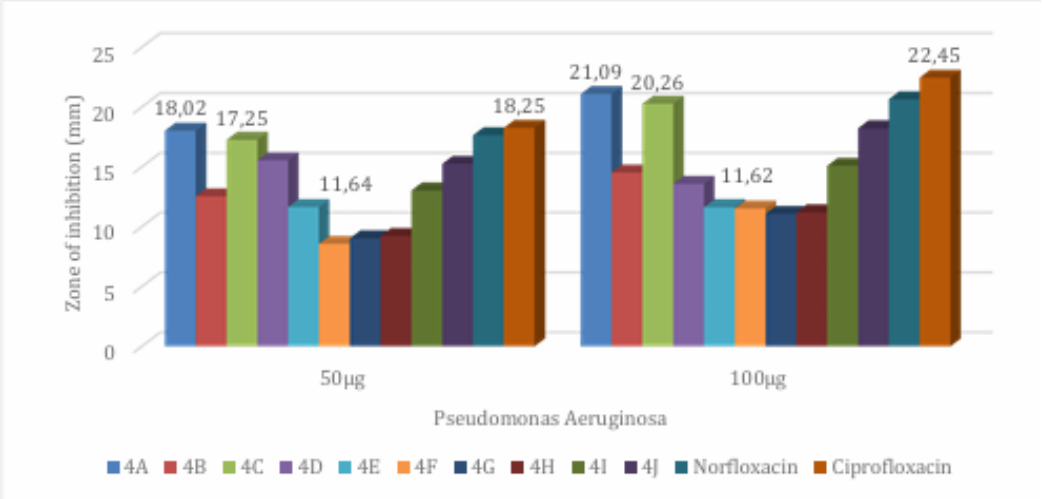


Fig. 3.1 Graph showing Zone of inhibition of the synthesized derivatives against gram-negative bacteria.

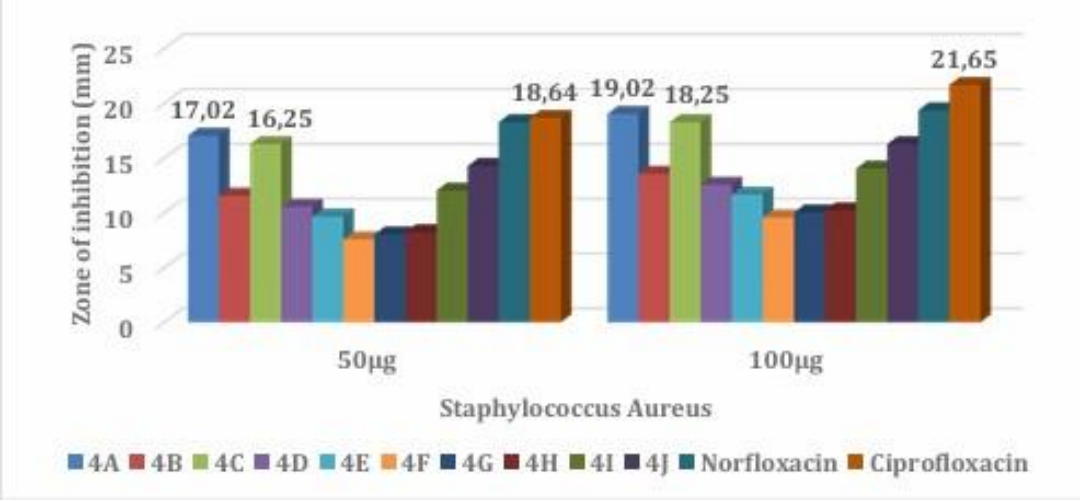


Fig. 3.2 Graph showing Zone of inhibition of the synthesized derivatives against gram-positive bacteria.

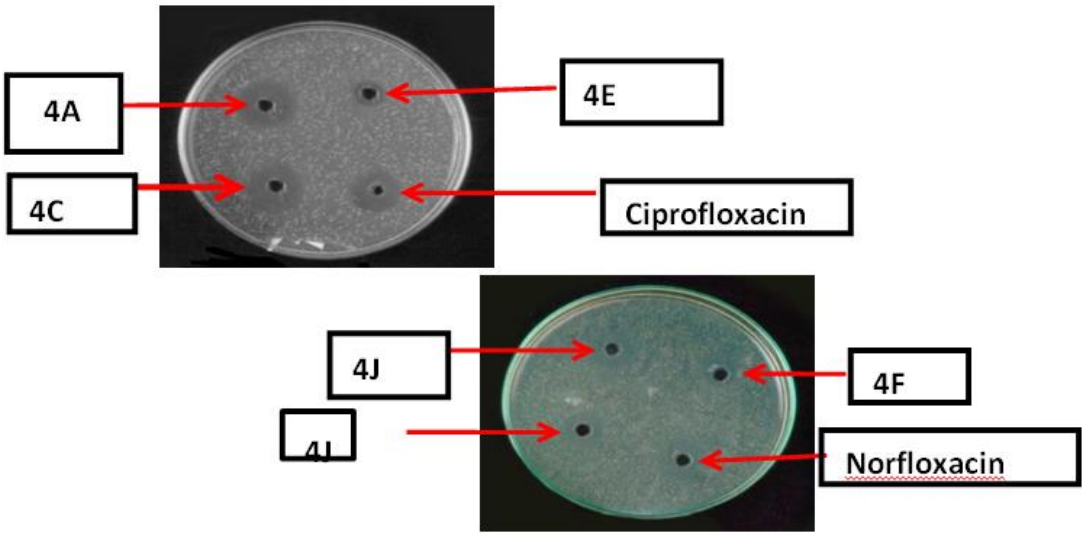


Fig. 3.3 Zone of inhibition of synthesized derivatives against gram-positive bacteria.

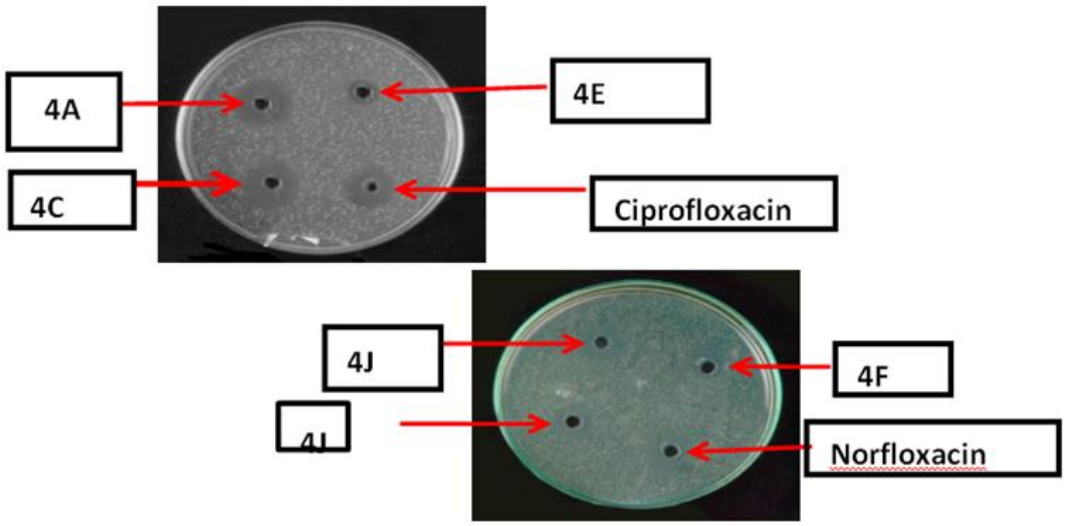


Fig. 3.4 Zone of inhibition of synthesized derivatives against gram-negative bacteria.

Antifungal Activity

In accordance with the data obtained from antifungal activity, all the synthesized 3 substituted 4(3H)-quinazolinone (4A-4J) have showed activity against tested organisms. Antifungal activity of the synthesized compounds has been carried out for two fungal strains i.e. Aspergillus Niger and Fusarium Oxysporum and was shown in Table 5.4.

(A) Activity Against A. Niger

Compounds 4A (18.75±0.15), 4B (14.32±0.24), 4C (16.45±0.30), 4D (14.42±0.29), 4E (13.62±0.27), 4F (12.32±0.36), 4G (10.32±0.16), 4H (11.32±0.20), 4I (15.52±0.36) and 4J (16.82±0.27) has shown zone of inhibition (mm) as compared to standard drug (Fluconazole,

20.23±0.32; Ketoconazole 19.32±0.34) has shown good activity against A. Niger (Fungi strains) at 50µg concentration. Compounds 4A (21.65±0.13), 4B (16.25±0.25), 4C (20.32±0.26), 4D (16.72±0.17), 4E (15.62±0.23), 4F (12.72±0.24), 4G (11.12±0.25), 4H (12.32±0.34), 4I (16.20±0.22) and 4J (19.25±0.24) has shown zone of inhibition (mm) as compared to standard drug (Fluconazole, 25.35±0.24; Ketoconazole 24.28±0.26) has shown good activity against A. Niger (Fungi strains) at 100 µg concentration.

Table 3.2 Antifungal activity of synthesized 3-substitued-4(3H)-quinazolinone derivatives.

COMPOUND	ZONE OF INHIBITION (mm)			
	A. Niger		Fusarium Oxysporum	
CONCENTRATION	50	100	50	100
4A	18.75 ± 0.15	21.65 ± 0.13	18.20 ± 0.15	22.52 ± 0.24
4B	14.32 ± 0.24	16.25 ± 0.25	15.09 ± 0.32	18.47 ± 0.17
4C	16.45 ± 0.30	20.32 ± 0.26	16.54 ± 0.34	20.60 ± 0.36
4D	14.42 ± 0.29	16.72 ± 0.17	15.32 ± 0.26	19.62 ± 0.33
4E	13.62 ± 0.27	15.62 ± 0.23	12.62 ± 0.24	16.42 ± 0.24
4F	12.32 ± 0.36	12.72 ± 0.24	10.23 ± 0.12	13.54 ± 0.13
4G	10.32 ± 0.16	11.12 ± 0.25	9.72 ± 0.39	13.22 ± 0.24
4H	11.32 ± 0.2.	12.32 ± 0.34	10.62 ± 0.26	14.52 ± 0.21
4I	15.52 ± 0.36	16.20 ± 0.22	13.28 ± 0.22	16.44 ± 0.33
4J	16.82 ± 0.27	19.25 ± 0.24	17.2 ± 0.32	21.32 ± 0.36
DMSO (CONTROL)	-	-	-	-
KETOCONAZOLE	19.32 ± 0.34	24.28 ± 0.26	18.25 ± 0.45	23.12 ± 0.36
FLUCONAZOLE	20.23 ± 0.32	25.35 ± 0.24	1932 ± 0.46	24.36 ± 0.25

The order of the activity: 4A> 4J> 4C > 4I > 4D > 4B > 4E > 4F > 4H > 4G.

(B) Activity against Fusarium Oxysporum

Compounds 4A (18.20±0.15), 4B (15.09±0.32), 4C (16.54±0.30), 4D (15.32±0.26), 4E (12.62±0.27), 4F (10.23±0.12), 4G (9.72±0.39), 4H (10.62±0.26), 4I (13.282±0.22) and 4J (17.20±0.32) has shown zone of inhibition (mm) as compared to standard drug (Fluconazole, 19.32±0.46; Ketoconazole 18.25±0.45) has shown good activity against Fusarium Oxysporum (Fungi strains) at 50 µg concentration.

Compounds 4A (22.52±0.24), 4B (18.47±0.17), 4C (20.60±0.36), 4D (19.62±0.33), 4E (16.42±0.24), 4F (13.54±0.13), 4G (13.22±0.24), 4H (14.52±0.21), 4I (16.44±0.33) and 4J (21.32±0.36) has shown zone of inhibition (mm) as compared to standard drug (Fluconazole, 24.36±0.25; Ketoconazole 23.12±0.29) has shown good activity against Fusarium Oxysporum (Fungi strains) at 100 µg concentration.

The Data of antifungal activity against the fungal strains (Aspergillus Niger and Fusarium Oxysporum) suggested the order of activity of compounds: 4A> 4J> 4C > 4I > 4D > 4B > 4E > 4F > 4H > 4G. Among all the synthesized 3-substitued 4(3H)-quinazolinone (4A 4J), compound 4B, 4E & 4F shows mild activity and 4H & 4G has showed moderate activity and 4A, 4J, 4C, 4I & 4D has shown best activity against all fungal strains (Table 5.4). The graphical representation of antifungal activity on fungus strains was shown in Figure 5.7 and zone of inhibition was shown in Figure 5.8 & 5.9.

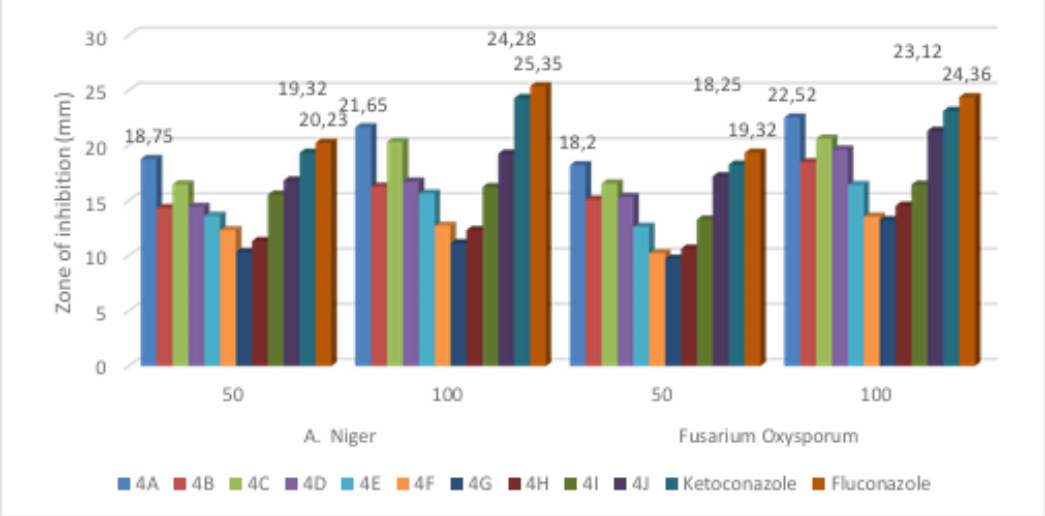


Fig. 3.5 Graph showing Zone of inhibition of the synthesized derivatives against fungi strains.

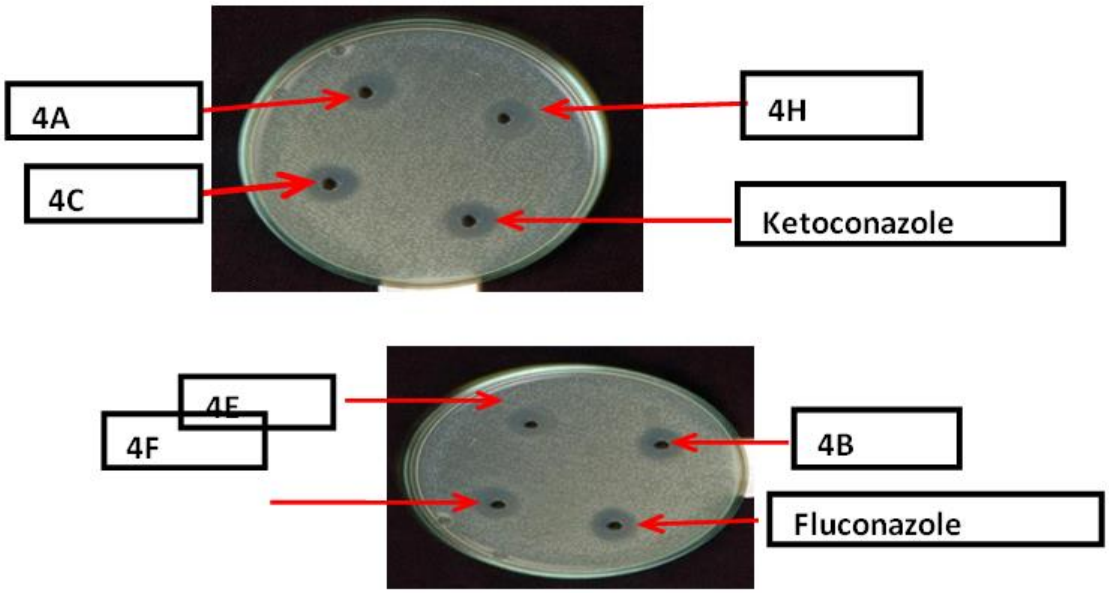


Fig 3.6. Zone of inhibition of synthesized derivatives against *Fusarium Oxysporum.*

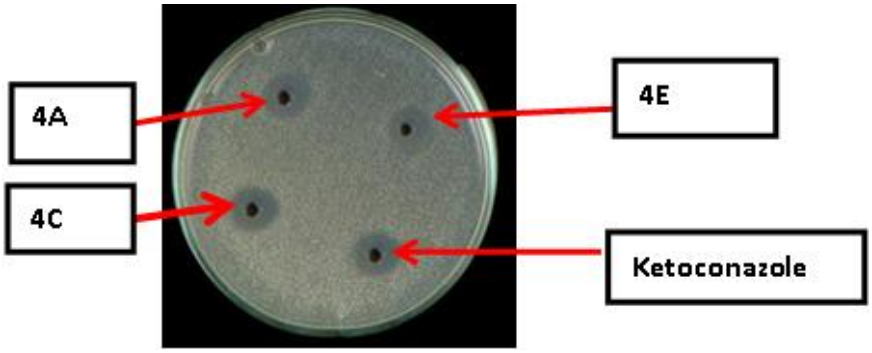


Fig 3.7 Zone of inhibition of synthesized derivatives against *A. Niger.*

The ten new derivatives of 3-substituted 4(3H)-quinazolinone has been prepared and evaluated for their antibacterial activity against one Gram-negative and one gram-positive bacterial strains and two fungal strains are used to carried out antifungal activity using Agar diffusion method. The Ciprofloxacin and Norfloxacin was used as standard for antibacterial activity and Fluconazole and Ketoconazole was used as standard to compare the antifungal potential of the synthesized compounds. The antibacterial and antifungal activity data of 3-substituted-4(3H)-quinazolinone derivatives (4A-4J) indicated that the compounds have significant inhibitory activity on all the bacterial and fungal strains at both 50 µg (0.05 ml) and 100 µg (0.1 ml) dose levels when compared with standard. Among all the compounds tested, compounds 4A, 4C, 4D, 4I and 4J possessed maximum activity in both fungal as well as bacterial strains.

These compounds possessed the halogens on the aromatic ring and thus reveal the positive contribution of electron withdrawing groups to the antimicrobial activity. The antibacterial and antifungal study suggested that the p-chlorophenyl, 3-bromo 4-chloro, 4-chloro-3-nitro and p-nitrophenyl substitution in 3rd position of 4(3H) quinazolinone ring may improve the antibacterial and antifungal activity. Methyl and ethyl group substitution may provide good activity but the at the same time methoxy and trimethyl -group addition diminish the activity of compound.

The new derivatives contain 3-bromo-4-chloro substitution and 4-chloro-3-nitro substitution may provide the better activity in compare to the bromo and ethyl substitution, Additional point is that chloro substitution at 7 positions of 4(3H) quinazolinone may provide the additionally advantages to compounds for better antimicrobial activity. However, further studies on activity and long-term toxicity are to be carried out before any conclusion are drawn, as these categories of drug are known to have potential antimicrobial activity. Testing on different models can further substantiate the antimicrobial activity of the synthesized analogues.

SUMMARY AND CONCLUSION

The practice of medicinal chemistry is devoted to the discovery and development of new agents for treating disease. Quinazolinone, which belongs to the nitrogen-containing heterocyclic compounds, is a constituent for roughly 200 natural alkaloids secluded from a number of families from microorganisms, plants, and animals. By connecting numerous effective groups to the quinazoline moiety, these compounds have been studied due to their biopharmaceutical activities, in particular anticancer, diuretic, anti-inflammatory, anticonvulsant and antihypertensive qualities.

Pharmacologically quinazoline, particularly quinazolin-4-one or quinazolinone are among the most important classes of heterocyclic compounds. The stability of the quinazolinone nucleus has inspired medicinal chemists to introduce many bioactive moieties to this nucleus to synthesize new potential medicinal agents. Substitution at position 3 of quinazolin-4(3H)-ones has been reported to be associated with anti-microbial properties. Introduction of bromine or chlorine atom at positions 7 and 8 can improve their antimicrobial activities. Deoxy vasicinone is an alkaloid with tricyclic 4(3H)-quinazolinone structure and has considerable antimicrobial activity.

Literature survey also revealed that substitution of heterocyclic ring at third position of quinazolin-4(3H)-ones provided potent antimicrobial agent. Based on aforementioned rational and our studies on quinazoline derivatives as attractive candidates for antimicrobial agents, in this thesis, we have designed a number of new quinazoline derivatives containing a 3-phenyl substituent attached with different fragments at 3-position to identify the antimicrobial activities. In an effort to increase the antimicrobial activity of substituted quinazolin-4(3H)-ones, we propose to synthesize some new derivatives of 3-disubstituted 4(3H)-quinazolinone.

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