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Evaluation of Anti-Bacterial Activity of Novel Quinazoline Derivatives

Vikas P. Patil, Swapnil P. Chaudhari, Amarjit P. Rajput, Dheeraj T. Baviskar.

1.KVP's Sanstha's Institute of Pharmaceutical Education, Boradi 425 428, Tal-Shirpur,MS India

ABSTRACT

In the present study, a series of novel quinazoline derivatives were synthesized by condensation with different aromatic amines via cyclized intermediate 2-phenyl-1, 3-benzoxazin-4-one.The chemical structures were confirmed by means of IR, H^1 NMR. These compounds were screened for anti-bacterial (Staphylococcus aureus ATCC-9144, Escherichia coli ATCC-25922, activities by paper disc diffusion technique. The potency of antibiotic content in samples can be determined by chemical, physical or biological means. An assay was performed to determine the ability of an antibiotic to kill or inhibit the growth of living microorganism. The inhibition of microbial growth under standardized conditions may be utilized for demonstrating the therapeutic efficacy of drugs. Microorganisms employed in biological assay were of various types of bacteria for amino acid & antibiotics, fungi for vitamins & trace elements. The synthesized compounds were evaluated for anti-bacterial activity. Some of these synthesized compounds show significant anti-bacterial activity.

Keywords: Quinazoline derivatives, Aromatic amines, Paper Disc Diffusion Technique, Anti-bacterial activity.

*Corresponding Author Email: vp_57@rediffmail.com

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INTRODUCTION

The objective of my study was to synthesize and characterize some novel quinazoline derivatives and its in–vitro pharmacological activity evaluation. In this study I have use anthranillic acid and benzoyl chloride as a starting material for the synthesis of substituted quinazoline derivatives. The anthranillic acid and benzoyl chloride forms aromatic cyclic product known as benzoxizone which in the later step reacts with primary aromatic amines to give substituted quinazoline derivatives. Thus the derivatives obtained were check for various parameters. Therefore, the project was planned by keeping into the focus on the following aspects,

A) Characterization of Compound:-

1. Melting point
2. Solubility
3. Chromatographic profile by using TLC

B) Instrumental Analysis:-

1. IR spectroscopy
2. H^1 NMR spectroscopy

C) Pharmacological activity study: -

1. Antibacterial Method

-Cup plate Method

The search of new anti-microbial agents with reduced toxicity and lower side effects is continuous process. One of the most frequently encountered heterocyclic compound in medicinal chemistry is quinazoline-4(3H)-one and its derivatives were reported to possess diverse biological applications including anti-bacterial, anti-microbial [1-5], analgesic and anti-inflammatory [6,7],anti-convulsant[8], anti-cancer [9], anti-tubercular [10], anti-malarial [11], anti-viral[12] and anti-helmintic[13] activities. The literature survey revealed that the presence of substituted aromatic ring at position 3 as well as substituent like methyl and phenyl groups at position 2 is necessary requirement for its medicinal properties. The process involved in the identification of new compounds for the treatment of human disease is prolonged, expensive and unpredictable endeavor.[2] A promising new approach to drug discovery concerns with synthesis and screening of combinatorial libraries in order to identify new compounds that express high affinity and specificity for a pharmacologically relevant, biomolecular target. Advances in molecular biology, automated chemical synthesis and robotics have facilitated the formulation of vast libraries of structurally related molecules. An essential aspect of screening large combinatorial libraries is the ability to identify the active components in these complex mixtures, which is

usually based on the strength of binding to a selected target macromolecule.[3] Quinazoline-4-one nucleus comprises of benzene ring fused with pyrimidine ring and ketone group at fourth position. Based on the above reports, we have synthesized various quinazoline derivatives and evaluated them for anti-bacterial activity.

MATERIALS AND METHODS

Chemicals:

Benzoxazine, Glacial acetic acid, Aniline, Phenyl hydrazine, P-methoxy aniline, Ethanol, Methanol, Benzene, Petroleum ether, Chloroform, Hexane, Acetone, Ethyl acetate, Carbon tetrachloride, Toluene, Activated charcoal, Water

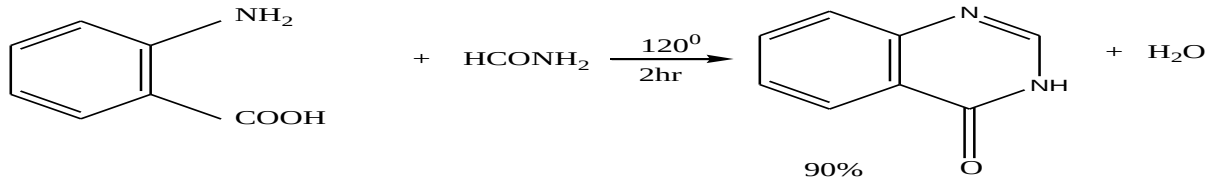
Synthetic methodology:

Synthesis of quinazolones:

Quinazolones are easily prepared by a variety of methods and can be converted to any of the common derivatives of quinazoline viz, (dihydroquinazoline, and tetrahydroquinazoline).

Synthesis of 4-quinazolones:

The most common synthesis of 4-quinazolones is a reaction which was first described by V. Niementowski in 1895 where in anthranilic acid is heated in an open container with excess formamide at 120^0c, water is expelled and a nearly quantitative conversion to 4-quinazolone is achieved.



It has been carried out with a variety of substituted anthranilic acids to give the corresponding Bz-substituted 4-quinazolones.

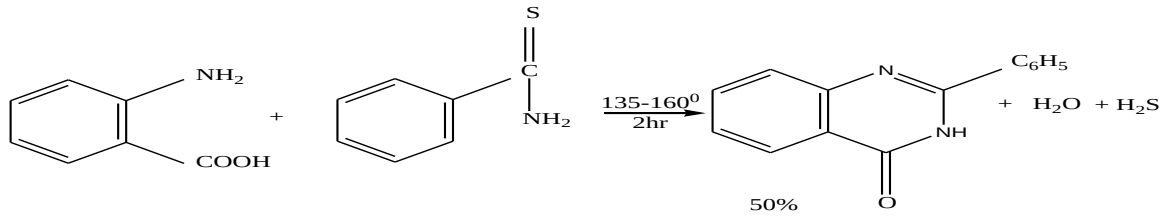
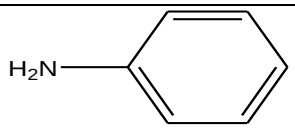


Table.1: Shows the compounds and their aromatic substitution:

Sr. No	Compound Code	Ar
1.	QP 1.	 Aniline

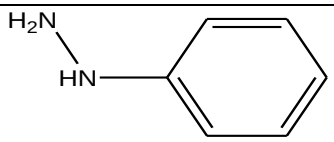
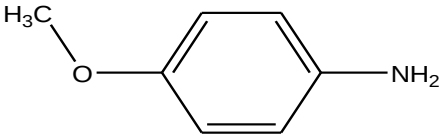
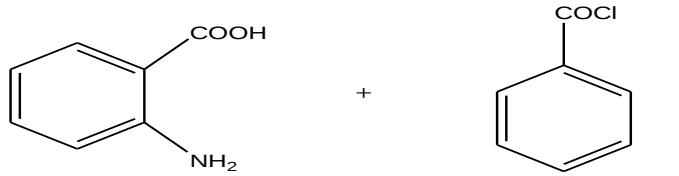
2.	**QP 2.**	 phenyl hydrazine
3.	**QP 3.**	 p-methoxy aniline

Table 2: Shows the Compounds and their Chemical Names

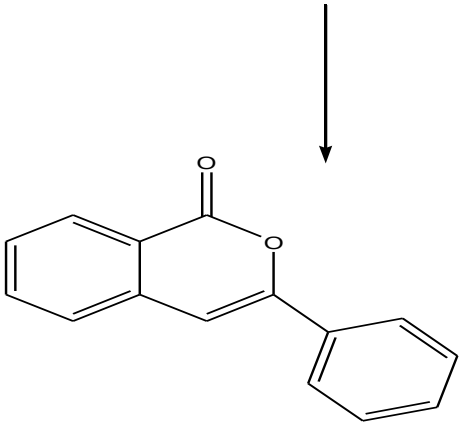
Sr. No.	Compounds	Chemical name
1.	**QP 1.**	3-(cyclohexa-2,4-dienyl)-2-phenylquinazolin-4(3H)-one.
2.	**QP 2.**	3-(cyclohexa-2,4-dienylamino)-2-phenylquinazolin-4(3H)-one.
3.	**QP 3.**	3-(4-methoxycyclohexa-2,4-dienyl)-2-phenylquinazolin-4(3H)-one.

Synthesis of 2-phenyl-1, 3-benzoxazin-4-one[20]:

Anthranilic acid (0.1mol) was dissolved in 50 ml of pyridine. To this benzoyl chloride (0.2 mol) was added dropwise with constant stirring at low temperature. When the addition of benzoyl chloride was completed, mixture was treated with 10% sodium-bi-carbonate solution (15 ml). After the effervescence ceased, mixture was filtered and washed repeatedly with water to remove inorganic materials. The crude drug thus obtained was recrystallised from ethanol. The yield and melting point were predicted in Table 4 and 5.



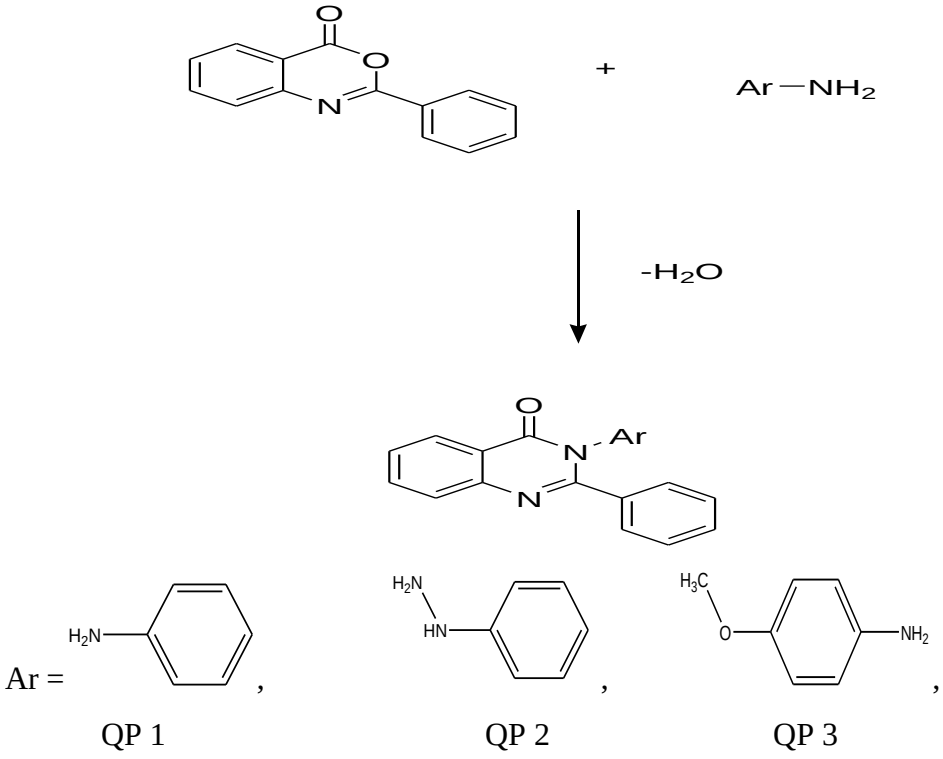
Anthranilic Acid Benzoyl Chloride



Benzoxazine - 4- One

Synthesis-of 2, 3-diphenyl quinazoline-4(3h)-one[20]:

An equimolar (0.01) mixture of Benzoxazine and aromatic amines was refluxed for 4hrs with 10ml of glacial acetic acid. The mixture was cooled to room temperature and poured into crushed ice, filter and then washed with water. The solid thus obtained was recrystallised from ethanol. The yield and melting point were predicted in Table-4 and 5.



Scheme 1:- synthesis of novel quinazoline derivatives.

Reagents: (i) Benzoyl chloride, (ii) Acetic acid, refluxed for 4hrs.

A) Characterization of Compound:-

1. Melting point: -

   Melting points of compounds were determined by open capillary method.

2. Chromatographic profile:-

TLC: -

Purity of compounds was checked on silica gel TLC plates (0.25 mm thickness) coated over glass plate as stationary phase and the spot was visually detected by Iodine vapor.

B) Instrumental Analysis:-

1. IR spectroscopy: IR spectra were recorded on Shimadzu 8400 FTIR spectrophotometer using KBr disc method.
2. H^1 NMR spectroscopy: H^1 NMR spectra were recorded on FTIR H^1 NMR Spectrophotometer. Varian mercury YH-300 using $CDCL_3$–d_6 as an internal standard.

RESULTS AND DISCUSSION

The quinazoline derivatives were synthesized using different materials. The melting points were determined by open end capillary tube and the purity of the compounds were checked by TLC using silica gel G as stationary phase and visually detected by iodine vapor and spectral data were analyzed by H^1 NMR and FT-IR spectroscopy.

Table 3: Data of Synthesized Compounds

Compound	Mol formula	Mol wt.	M.P. (^oC)	%Yield	R_f values
QP1	$C_{20}H_{13}N_3O_2$	327	155 -157 ^oC	80.12%	0.6
QP2	$C_{23}H_{16}N_2O$	336	130-132 ^oC	72.34%	0.4
QP3	$C_{20}H_{14}N_2O_2$	314	145-147 ^oC	83.79%	0.8

Table 4:- FTIR Spectral Data Interpretation

Peak(cm^{-1})	Functional Group
QP1	
3040	C-H (Stretching Ar-Ring)
1686	C=O (Stretching)
1627	C=N (Stretching)-
1230	C=C (Ring Stretching)
653, 705	C=C-H
QP2	
3054	C-H (Stretching Ar-Ring)-
1679	C=O (Stretching)-
1605	C=N (Stretching)
1229	C-N (Stretching)
1505,1393,1314	C=C (Ring Stretching)
698,771	C=C-H (Bending)
QP3	
3458	O-H (Stretching)
3060	C-H (Stretching Ar-Ring)
1652	C=O (Stretching)
1608, 1320	C-N (Stretching)-
1506	C=C (Ring Stretching)
697, 752	C=C-H (Bending)

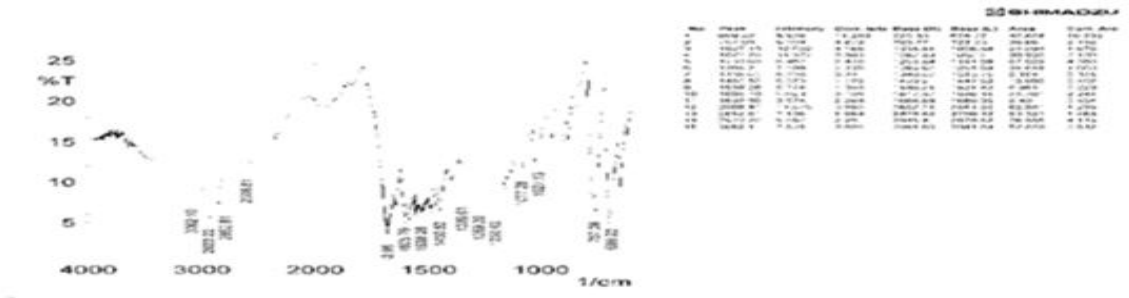


Figure 1:-FTIR Spectra of QP 1.

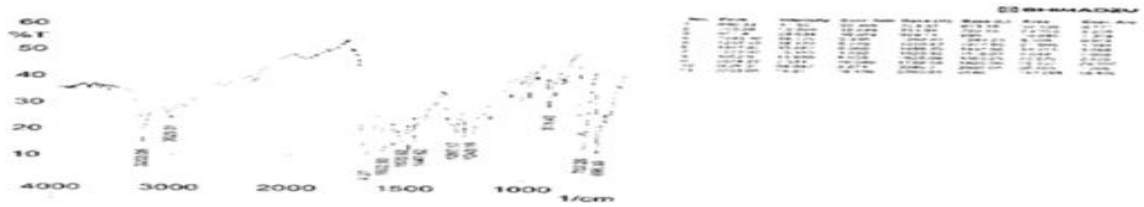


Figure 2: FTIR spectra of QP 2.

Figure 3: FTIR Spectra of QP 3.

Table 5:- NMR Spectral Data Interpretation

Peak (ppm)	Functional Group
QP1	
7.49 – 8.00	Ar-H (Fused with Pyridine 4- One)
7.26 – 7.64	Ar-H (Attached at 2nd Position)
6.67 – 8.97	Ar-H (Attached at 3rd Position)
QP2	
7.41 – 7.91	Ar-H (Fused with Pyridine 4- One)
7.29 – 7.63	Ar-H (Attached at 2nd Position)
6.77 – 7.65	Ar-H (Attached at 3rd Position)
QP3	
7.47 – 7.87	Ar-H (Fused with Pyridine 4- One)
7.26 – 7.62	Ar-H (Attached at 2nd Position)
6.54 – 7.22	Ar-H (Attached at 3rd Position)

Figure 4: Zone of inhibition for synthesize compounds QP 1, QP 2, & QP 3 against *staphylococcus aureus* organism

Figure 5: zone of inhibition for synthesize compounds QP 1, QP 2, & QP 3 against *e coli* organism

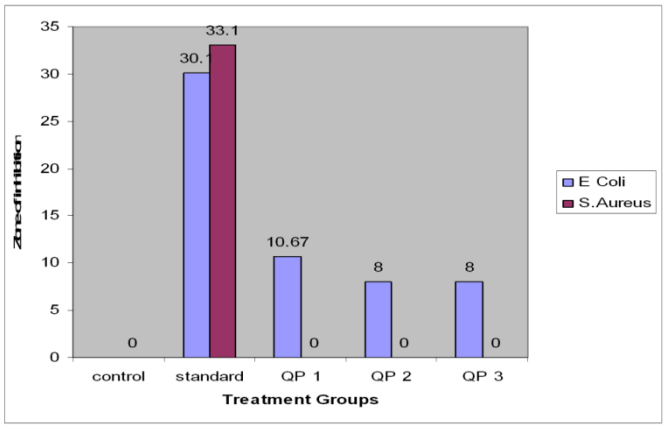


Figure 6: zone of inhibition with different treatment groups

The title compounds synthesized were evaluated for anti-bacterial activity by using diffusion assay or cup plate method. Among these synthesized compounds QP1, QP2, QP3, showed significant anti-bacterial activity against *Escherichia coli* and compounds QP1, QP2, QP3, showed no anti-bacterial activity against *Staphylococcus aureus* at 10µg/ml. Chloramphenicol was used as a standard drug.

Table 6: Anti-Bacterial activity data of Synthesized Compounds

Sr.No.	Compound Code	Name of Micro-organism	Zone of Inhibition (dm in mm)10µg/ml
1.	Control	*E. Coli* NCIM 2109	No Zone
		Staphylococcus Aureus NCIM 2079	No Zone
2.	QP1 (Aniline)	*E. Coli* NCIM 2109	10.67
		Staphylococcus Aureus NCIM 2079	No Zone
3.	QP2 (Phenyl hydrazine)	*E. Coli* NCIM 2109	8
		Staphylococcus Aureus NCIM 2079	No Zone
4.	QP3(p-methoxy aniline)	*E. Coli* NCIM 2109	8
		Staphylococcus Aureus NCIM 2079	No Zone
5.	Standard Chloramphenicol	*E. Coli* NCIM 2109	30.1
		Staphylococcus Aureus NCIM 2079	33.1

CONCLUSION

In the present investigation of newly synthesize quinazoline derivatives were characterized by determining melting point, solubility and chromatographic profile such as TLC. Another significant work as been reported in the present investigation is instrumental analysis such as FTIR, H^1 NMR of the new derivatives which has not been studied and reported earlier. Among the synthesized compounds QP1, QP2 and QP3, the QP1 is highly active against Gram –ve micro-organism i.e. E-coli having zone of inhibition 10.67 mm and the compound QP2 and QP3 are moderately active against Gram –ve micro-organism, i.e. E-coli having zone of inhibition 8 mm and 8 mm when compared with that of standard drug Chloramphenicol having zone of inhibition 30.1 mm against E-coli micro-organism. Among the synthesized compounds QP1, QP2 and QP3 all three compounds has no antibacterial activity against Gram positive organism i.e. Staphylococcus aureus when compared with that of standard drug, chloramphenicol having zone of inhibition 33.1 mm against *Staphylococcus aureus* micro-organism. Thus it can be concluded that the new quinazoline derivative possess good antibacterial activity.

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