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Research Article

Synthesis, Characterization And Antimicrobial Evaluation Of Novel Quinazolines

Pallavi Kamble¹, Dnyaneshwar Patil^{*1}, Vijay Navghare², Rajkumar Moon³

¹Department of Pharmaceutical Chemistry, Indira College of Pharmacy, Nanded.

²Department of Pharmacology, Indira College of Pharmacy, Nanded.

³Department of Pharmaceutics, School of Pharmacy, S.R.T.M. University, Nanded

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ABSTRACT

The increasing prevalence of antimicrobial resistance has created an urgent need for the development of novel therapeutic agents with enhanced efficacy and improved safety profiles. Quinazoline derivatives represent an important class of nitrogen-containing heterocyclic compounds that exhibit diverse pharmacological activities, including potent antimicrobial properties. The present study focuses on the synthesis, characterization, and antimicrobial evaluation of a series of novel quinazoline derivatives. The target compounds were synthesized through appropriate synthetic routes and purified using standard laboratory techniques. Structural characterization was performed using physicochemical and spectroscopic methods such as melting point determination, Fourier-transform infrared (FT-IR) spectroscopy, proton nuclear magnetic resonance (¹H NMR) and mass spectrometry to confirm their chemical structures. The synthesized compounds were evaluated for their antimicrobial activity against selected Gram-positive and Gram-negative bacterial strains, as well as fungal pathogens, using standard microbiological methods. Several derivatives demonstrated promising antimicrobial activity, with some exhibiting comparable or superior potency to the reference antimicrobial agents. Structure–activity relationship analysis indicated that the nature and position of substituents on the quinazoline nucleus significantly influenced biological activity. These findings suggest that the newly synthesized quinazoline derivatives may serve as promising lead molecules for the development of novel antimicrobial agents and warrant further pharmacological and mechanistic investigations.

***Corresponding Author:** Dnyaneshwar Patil

Address: Department of Pharmaceutical Chemistry, Indira College of Pharmacy, Nanded.

Email ✉: patildnyaneshwar670@gmail.com

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INTRODUCTION

Quinazoline is a bicyclic heterocyclic compound consisting of a benzene ring fused with a

pyrimidine ring. The molecular formula of quinazoline is $C_8H_6N_2$.¹

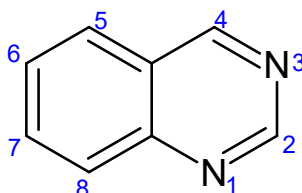


Fig. 1. Structure of Quinazoline

The basic structure of quinazoline can be modified by introducing different substituents at various positions, including C-2, C-4, C-6 and C-7.² Such modifications significantly influence pharmacological properties of the molecule. Quinazoline is a light yellow crystalline solid and is also known as 1,3-diazanaphthalene, which comprises one benzene and one pyrimidine ring.³ Synthesis of quinazoline was first reported through decarboxylation of 2-carboxy derivative by August Bischler and Lang in 1895.^{4,5} Anthranilic acid on treatment with amide resulted in 4-oxo-3,4-dihydroquinazolines by Niementowski synthesis.⁶ Other isomers of quinazoline are quinoxaline, cinnoline and phthalazine.⁷ Quinazolines are also the building blocks of more than 200 natural alkaloids isolated from plants, microorganisms and animals.^{8,9} Vasicine ($\pm$) (peganine) was the first known quinazoline alkaloid which was isolated from *Adhatoda vasica* in 1888. It is highly effective against bronchodilator activity.¹⁰

The pharmacological properties of quinazolines include acaricide, anticancer, antimicrobial, antifungal, antiviral, anti-inflammatory, diuretic, muscle relaxant, antitubercular, CNS depressive, anti-convulsant, and weedicide, to name just a few. Quinolines are also noteworthy in pharmaceutical chemistry.¹¹ The only three licenced drugs with a quinazoline composition on the market are

prazosin hydrochloride, doxazosine mesylate, and terazosine hydrochloride.¹²

Materials

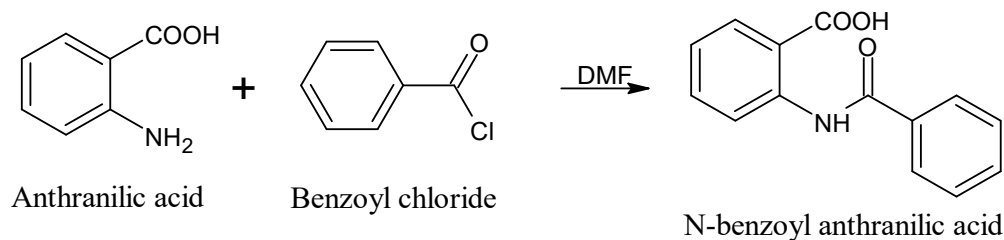
Anilines, anthranilic acid and benzoyl chloride were procured from Sigma-Aldrich and SD fine chemicals. All other chemicals are of AR grade. Melting points were determined in open capillaries on a Metal Toledo digital melting point apparatus and are uncorrected. The purity of the compounds was checked by thin-layer chromatography (TLC) using TLC Silica gel 60 F254 aluminum sheets procured from Merck and spots were detected in ultra violet fluorescence analysis cabinet. The infrared (IR) spectra were recorded using potassium bromide (KBr) pellets on Shimadzu IR Affinity-1 Fourier transform IR spectrophotometer (cm^{-1}). 1H nuclear magnetic resonance (NMR) spectra were recorded on Bruker AVANCE III 500 MHz NMR spectrometer using tetramethylsilane as internal standard (chemical shifts in δ ppm) and mass spectra recorded were on JEOL GC MATE II GC-MS system.

Synthesis of Quinazoline Derivatives

Step 1: Preparation of N-benzoyl anthranilic acid



Benzoyl chloride (0.05 mol) was added dropwise to a stirred solution of anthranilic acid (0.05 mol) in dimethyl formamide (70 ml) and the reaction mixture was stirred at room temperature for 2 h.

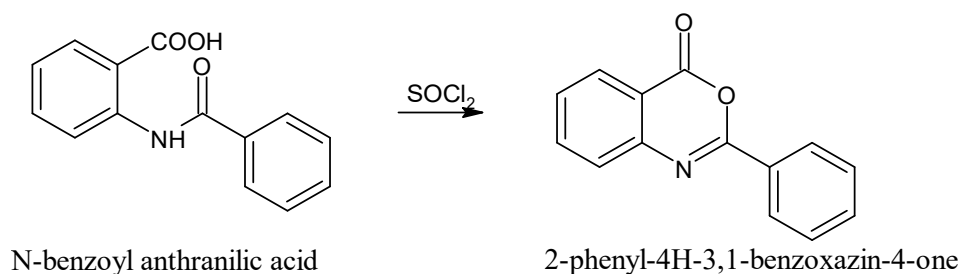


Scheme 1: Preparation of N-benzoyl anthranilic acid

Step 2: Preparation of 2-phenyl-4H-3,1-benzoxazin-4-one

A mixture of N-benzoyl anthranilic acid (0.01 mol) and thionyl chloride (10 ml) was heated under

reflux for 3 h at 80°C. Excess thionyl chloride was evaporated under reduced pressure and the obtained solid was recrystallized with petroleum ether.

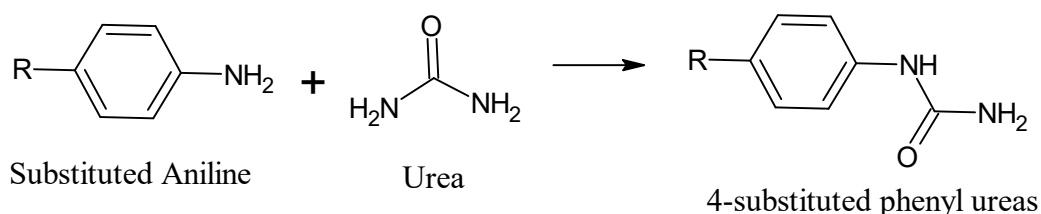


Scheme 2: Preparation of 2-phenyl-4H-3,1-benzoxazin-4-one

Step 3: Preparation of 4-substituted phenyl ureas

4-Substituted aniline (0.1 mol) and urea were grind thoroughly in a glass mortar to get a homogeneous mixture. The mixture was transferred in a round-bottom flask and heated at 130-150°C (oil bath) for

1-2 hours with stirring. The mixture typically melts and then solidifies as the reaction proceeds. The reaction mixture is cooled to room temperature and cold water was added to dissolve excess urea. The solid product was filtered and recrystallised from ethanol.



Scheme 3: Preparation of 4-substituted phenyl ureas

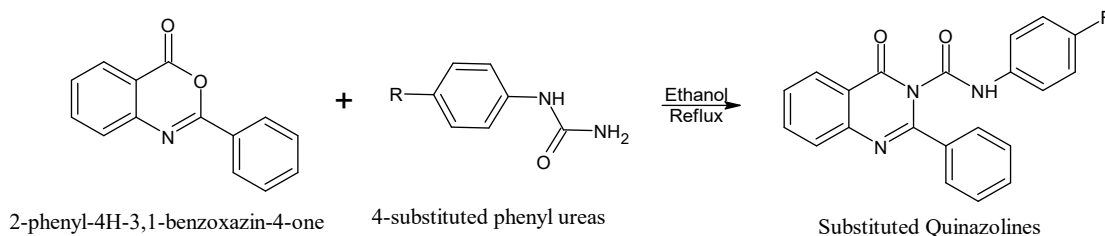
Compound A:	R=Cl	Compound B:	R=Br
Compound C: R=NO₂		Compound D: R=OCH₃	



Step 4: Preparation of substituted quinazolines

A mixture of 2-phenyl-4H-3,1-benzoxazin-4-one and 4-substituted phenyl urea was dissolved in 50

mL of absolute ethanol and heated under reflux for 3 h. On cooling the separated solid was washed with water and recrystallized by using a mixture of water and acetic acid.



Scheme 4: Preparation of substituted quinazolines

4-oxo-2-phenyl-4H-quinazoline-3-carboxylic acid (4-chlorophenyl) amide (Compound A) Yield 86.41%; m.p. 135-137°C; IR (KBr) $\nu_{\max}$: 3450.41 (N-H str), 3050.07 (Aromatic C-H str), 1710.05 (Quinazolinone C=O str), 1650.80 (Amide C=O str), 1614.24 (C=N str), 1577.64 (Aromatic C=C str), 1315.39 (C-N str), 847.13 (p-substituted phenyl str), 760.90 (C-Cl str) cm^{-1} ; ^1H NMR (CDCl_3) δ : 8.169 (s, 1H- NH), 6.782 (m, Aromatic protons), 7.863 (d, Quinazoline aromatic H), 7.542 (m, Phenyl protons), 7.432 (d, p-chlorophenyl protons) ppm; mass m/z: 376.6 (M-1).

4-oxo-2-phenyl-4H-quinazoline-3-carboxylic acid (4-bromophenyl) amide (Compound B) Yield 81.81%; m.p. 120-122°C; IR (KBr) $\nu_{\max}$: 3448.49 (N-H str), 3033.82 (Aromatic C-H str), 2099.48 (Quinazolinone C=O str), 1662.52 (Amide C=O str), 1620.09 (C=N str), 1552.59 (Aromatic C=C str), 1342.36 (C-N str), 840.91 (p-substituted phenyl str), 694.33 (C-Br str) cm^{-1} ; ^1H NMR (CDCl_3) δ : 8.143 (s, 1H- NH), 6.864 (m, Aromatic protons), 7.759 (d, Quinazoline aromatic H), 7.694 (m, Phenyl protons), 7.412 (d, p-bromophenyl protons) ppm; mass m/z: 420.26 (M-1).

4-oxo-2-phenyl-4H-quinazoline-3-carboxylic acid (4-nitrophenyl) amide (Compound C) Yield 90.00%; m.p. 130-132°C; IR (KBr) $\nu_{\max}$: 3326.98 (N-H str), 3068.53 (Aromatic C-H str), 1795.60

(Quinazolinone C=O str), 1662.52 (Amide C=O str), 1622.02 (C=N str), 1554.52 (Aromatic C=C str), 1533.30 (C-NO₂ str), 1313.43 (C-N str), 847.13 (p-substituted phenyl str) cm^{-1} ; ^1H NMR (CDCl_3) δ : 8.154 (s, 1H- NH), 6.713 (m, Aromatic protons), 7.829 (d, Quinazoline aromatic H), 7.563 (m, Phenyl protons), 7.418 (d, p-nitrophenyl protons) ppm; mass m/z: 386.5 (M-1).

4-oxo-2-phenyl-4H-quinazoline-3-carboxylic acid (4-methoxyphenyl) amide (Compound D) Yield 85.71%; m.p. 132-134°C; IR (KBr) $\nu_{\max}$: 3452.34 (N-H str), 3060.82 (Aromatic C-H str), 1716.53 (Quinazolinone C=O str), 1683.74 (Amide C=O str), 1571.88 (C=N str), 1560.30 (Aromatic C=C str), 1319.22 (C-N str), 1299.93 (-O-CH₃ str), 837.05 (p-substituted phenyl str) cm^{-1} ; ^1H NMR (CDCl_3) δ : 8.268 (s, 1H- NH), 6.683 (m, Aromatic protons), 7.594 (d, Quinazoline aromatic H), 7.413 (m, Phenyl protons), 7.314 (d, p-methoxyphenyl protons) ppm; mass m/z: 376.6 (M-1).

In vitro antibacterial activity

The antibacterial activity of synthesized compounds was measured using the agar cup method. Nutrient agar (Himedia) was prepared and sterilized at 100 kPa for 15 min in the autoclave. It was allowed to cool below 45°C and seeded with turbid suspension of test bacteria separately,



prepared from 24 h old slant cultures. 3% inocula were used every time. The bacterial cultures selected were, two Gram-negative cultures, namely, *Escherichia coli*, *Pseudomonas aeruginosa* and two Gram-positive cultures, namely, *Bacillus subtilis*, *Enterococcus faecalis*. This seeded preparation was then poured into sterile petri plate under the aseptic condition and allowed to solidify.

Cups of 10 mm diameter were bored in the agar plate with sterile cork borer, 100 µl of compound solution prepared in 1% dimethyl sulfoxide (DMSO) was added in the cup under an aseptic condition with the help of micropipette. A volume of 100 µl of DMSO was also placed in one of the cups as blank (negative control). A standard antibiotic disk impregnated with 10 units of Penicillin was also placed on the seeded nutrient agar surface as a standard reference antibiotic (positive control).

The plates were kept in the refrigerator for 15 min to allow diffusion of the compound from the agar cup into the medium. Then, the plates were shifted to the incubator at 37°C and incubated for 24 h.¹³

After incubation plates were observed for the zone of inhibition of bacterial growth around the agar cup. Results were recorded by measuring the zone of inhibition in millimeter (mm) using zone reader.

In vitro antifungal activity

Antifungal activity of title compounds was performed using the poison plate method. The medium used was Potato dextrose agar (Himedia). The medium was prepared and sterilized at 65 kPa in an autoclave for 15 min. Then the compound to be tested is added to the sterile medium in aseptic condition to get a final concentration of 1%. A plate with DMSO was prepared as blank (negative control) similarly a plate with 1% griseofulvin was

prepared as standard reference plate (positive control).

Aspergillus niger and *Aspergillus flavus* were selected as test fungal cultures. They were allowed to grow on slant for 48 h to get profuse sporulation. A volume of 5 ml of 1:100 aqueous solution of Tween 80 was added to the slant and spores were scraped with the help of a nicrome wire loop to form a suspension.

The fungal suspension was spot inoculated on the plates prepared using compound with the help of a nichrome wire loop. The plates were incubated at room temperature for 48 h.¹³

After incubation plates were observed for the growth of inoculated fungi. Results were recorded as the growth of fungi (no antifungal activity), reduced growth of fungi (moderate antifungal activity), and no growth of inoculated fungi (antifungal activity).

Results and Discussion

The present study successfully synthesized several novel quinazoline derivatives through a multi-step synthetic pathway involving preparation of intermediate compound (N-benzoyl anthranilic acid), cyclization reactions and substitution reactions using 4-substituted phenyl ureas to introduce functional groups. The reaction is monitored by thin layer chromatography using ethyl acetate:nHexane (3:7). The compounds were obtained with moderate to good yields and were characterized using spectroscopic techniques.

The compounds obtained in good yields ranging from 81% to 90%. The physicochemical properties of the synthesized compounds are given in Table 1. The structures of the synthesized compounds were confirmed by IR, ¹H NMR, and mass spectra.



Table 1: Physicochemical characteristics of synthesized compounds

Sr. No.	Parameters	Compound A	Compound B	Compound C	Compound D
1	Molecular Formula	C ₂₁ H ₁₄ ClN ₃ O ₂	C ₂₁ H ₁₄ BrN ₃ O ₂	C ₂₁ H ₁₄ N ₄ O ₄	C ₂₂ H ₁₇ N ₃ O ₃
2	Molecular weight	375.81	420.26	386.36	371.39
3	Theoretical yield	1.62 gm	1.32 gm	1.00 gm	1.05 gm
4	Practical yield	1.40 gm	1.08 gm	0.90 gm	0.90 gm
5	% yield	86.41%	81.81%	90.00 %	85.71 %
6	Melting point	135-137°C	120-122°C	130-132°C	132-134°C
7	Recrystallization Solvent	Ethanol	Ethanol	Ethanol	Ethanol
8	Solvent for TLC	Ethylacetate: nHexane (3:7)	Ethylacetate: nHexane (3:7)	Ethylacetate: nHexane (3:7)	Ethylacetate: nHexane (3:7)
9	R _f Value	0.702	0.545	0.785	0.684

IR spectra confirmed the presence of functional groups such as:

- C=N
- N-H
- Aromatic C-H

NMR spectra confirmed the aromatic structure and substituent positions.

Mass spectrometry confirmed the molecular weights of the compounds.

Thus, the structures of the compounds were confirmed by IR, ¹H NMR and mass spectral data.

Biological evaluation

Antibacterial evaluation

Some compounds demonstrated promising antimicrobial activity. Substituted quinazoline derivatives containing electron-withdrawing groups showed improved antibacterial activity.

Table 2. Antibacterial activity

Compound Code	Inhibition zone diameter in mm (Average triplicate ± Standard deviation)			
	<i>P. aeruginosa</i>		<i>B. subtilis</i>	
	50 µg	100 µg	50 µg	100 µg
Compound A	15	22	17	24



Compound B	14	22	13	23
Compound C	17	24	14	25
Compound D	14	21	12	17
Amoxicillin	26	30	28	29

Table 3. Antifungal activity

Compound Code	Inhibition zone diameter in mm (Average triplicate $\pm$ Standard deviation)			
	<i>A. niger</i>		<i>A. flavus</i>	
	50 μ g	100 μ g	50 μ g	100 μ g
Compound A	10	14	12	20
Compound B	11	17	12	22
Compound C	12	19	13	25
Compound D	09	17	11	19
Clotrimazole	18	24	19	27

CONCLUSION

The present study successfully synthesized several novel quinazoline derivatives through a multi-step synthetic pathway involving preparation of intermediate compound (N-benzoyl anthranilic acid), cyclization reactions and substitution reactions using 4-substituted phenyl ureas to introduce functional groups. The reaction is monitored by thin layer chromatography using ethyl acetate:nHexane (3:7).

The synthesized compounds were characterized using spectroscopic methods including IR, ^1H NMR and Mass spectrometry.

Biological evaluation revealed that some compounds exhibited promising antimicrobial and anticancer activities.

The results of the study suggest that quinazoline derivatives remain an important class of compounds in medicinal chemistry and may serve

as potential lead molecules for future drug development.

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