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Synthesis and Anti-Tubercular Activity of Quinazoline Derivatives

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ABSTRACT: A series of [2-phenyl-3-[(E)-(1-phenyl ethylidene)amino]quinazolin-4(3H)-one] derivatives have been synthesized with the starting material as 2-amino benzoic acid. The final compounds were synthesized using different ketones like acetophenone, p-methyl acetophenone, 4-methoxy acetophenone, m-hydroxy acetophenone, 3-amino acetophenone. The compounds were tested for Antitubercular activity and shows comparable activity with the standard drugs.

Keywords: alamar blue assay, antitubercular activity, quinazoline

I. INTRODUCTION

Quinazoline, formula $C_8H_6N_2$, is an organic chemical. It is a bicyclic aromatic heterocycle made up of two fused six-membered aromatic rings (pyrimidine & benzene). It is a water-soluble yellow crystalline substance. Possessing qualities that are antiviral, anti-HIV, antituberculosis, antibacterial, antifungal, anti-inflammatory, and anti-malaria.[1] It can be found in a plethora of natural products.[2]

Mycobacterium tuberculosis, the world's most common deadly human pathogen causing the disease tuberculosis (TB). In humans currently causes over 1.8 million death a year, with 25,37,235 TB cases notified in 2023 in India. Even though it is considered largely controlled but it is still a bigger threat than most people know making it the world's top infectious killer. TB is a major contributor to antimicrobial resistance.[3]

The main cause of tuberculosis mycobacterium tuberculosis (MTB) is a small, aerobic, nonmotile bacillus.[4] The unique clinical characteristics of this pathogen's is its high fat content. It divides at a very slow rate every 16 to 20 hours, in contrast to other bacteria that usually split in less than an hour. A lipid bilayer is present in the outer membrane of mycobacteria. MTB's high lipid and mycolic acid content causes it to either stain extremely weakly (gram positive) or not at all when a gram stain is applied. It can withstand weeks of dryness and is resistant to weak disinfectant.[5]

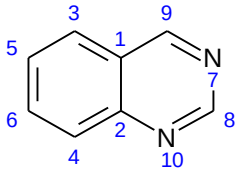
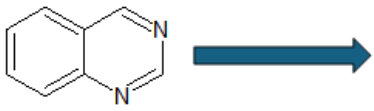


Figure1:Quinazoline ring



Analgesic activity
Anti-inflammatory activity
Anti-tubercular activity
CNS activity
Anti-convulsant activity
Sedative-hypnotic activity
Anti-viral activity
Anti-cancer activity
Anti-histaminic activity
Anti-hypertensive activity
Anti-microbial activity
Miscellaneous activity

Figure2:Medicinal properties of quinazolines

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Synthesis of quinazoline derivatives
The procedure consists of three steps:

Step1: Synthesis of 2-phenyl-4H-3,1-benzoxazin-4-one

Benzoyl chloride (0.2 mol) was added to the solution of anthranilic acid (0.1mol) dissolved in pyridine (60ml). The mixture was stirred in a magnetic stirrer for 30 minutes. After the completion of reaction add 5% sodium bicarbonate (15ml). The solid obtained was crystalized from ethanol.

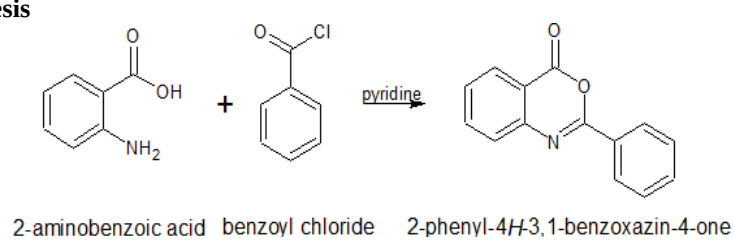
Step2: Synthesis of Schiff bases

Above product (0.05 mol) and hydrazine hydrate added to RB flask. To the above mixture add ethanol, then reflux for 3 hours . Cool the mixture. The separated solid was crystallized from ethanol.[8][9]

Step3: Synthesis of quinazoline derivatives

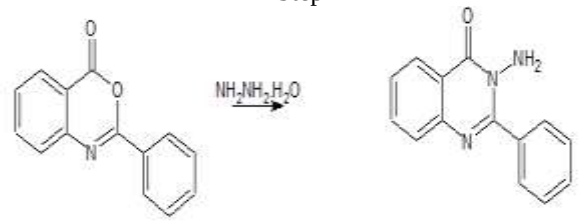
An equimolar quantity of the above product and ketone (acetophenone) taken and dissolved both in ethanol. Add glacial acetic acid to the solution to maintain the pH in the range 4.0-4.5. The solution was refluxed for 150 minutes. The hot solution was poured into ice cooled water. The solid thus obtained was recrystallized in ethanol. The final product was identified through characterization.

Scheme for the synthesis



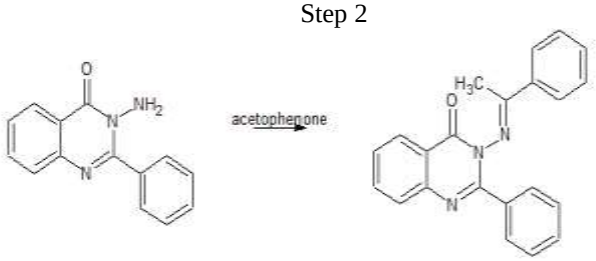
2-aminobenzoic acid benzoyl chloride 2-phenyl-4*H*-3,1-benzoxazin-4-one

Step1



2-phenyl-4*H*-3,1-benzoxazin-4-one 3-amino-2-phenylquinazolin-4(3*H*)-one

Step 2



3-amino-2-phenylquinazolin-4(3*H*)-one 2-phenyl-3-[(*E*)-(1-phenylethylidene)amino]quinazolin-4(3*H*)-one

Step 3

In vitro Antitubercular activity by Microplate Alamar Blue Assay (MABA) method
Procedure

The anti-Mycobacterial activity of compounds was assessed against Mycobacterium tuberculosis using microplate Alamar Blue assay (MABA). This methodology is non-toxic, uses a thermally stable reagent and shows good correlation with proportional and BACTEC radiometric method. Briefly, 200µl of sterile deionized water was added to all outer perimeter wells of sterile 96 wells plate to minimized evaporation of medium in the test wells during incubation. The 96 wells plate received 100 µl of

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the Middlebrook 7H9 broth and serial dilution of compounds were made directly on plate. The final drug concentrations tested were 100 to 0.2 µg/ml. Plates were covered and sealed with parafilm and incubated at 37ºC for five days. After this time, 25µl of freshly prepared 1:1 mixture of Almar Blue reagent and 10% tween 80 was added to the plate and incubated for 24 hrs. A blue colour in the well was interpreted as no bacterial growth, and pink colour was scored as growth. The MIC was defined as lowest drug concentration which prevented the colour change from blue to pink.[6][7]

Standard Strain used: Mycobacteria tuberculosis (Vaccine strain, H37 RV strain):

Standard values for the Anti-Tb test which was performed.

Isoniazid – 1.6µg/ml
Ethambutol – 1.6µg/ml
Pyrazinamide- 3.125µg/ml
Rifampicin – 0.8µg/ml
Streptomycin- 0.8µg/ml

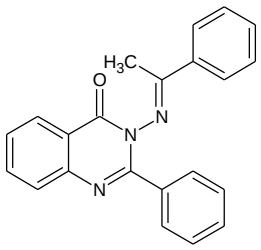
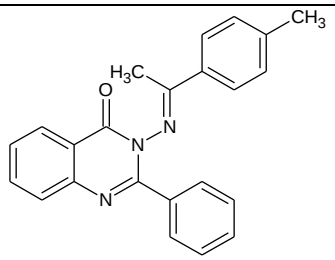
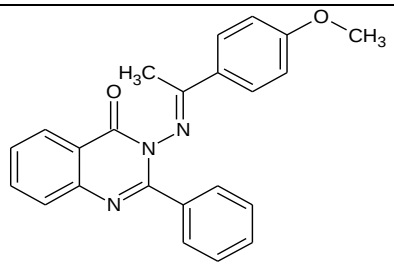
II. RESULTS

Various new derivatives were prepared, all the compounds obtained with percentage yield of 60-85%. Physio-chemical data of synthesized compounds is given in Table1. The photograph of antitubercular activity is given in Figure3 and the results of antitubercular activity are given in Table3. Structures are given in Table2.

Table1:Physio-chemical data of synthesized compounds

CODE	KETONES	MF	MW	MP(◦C)	%YIELD
QZ	acetophenone	$C_{22}H_{17}N_3O$	339.398	180-182	65
QZ1	p-methyl acetophenone	$C_{23}H_{19}N_3O$	353.425	175-177	78
QZ2	4-methoxy acetophenone	$C_{23}H_{19}N_3O2$	369.424	175-178	75
QZ3	m-hydroxy acetophenone	$C_{22}H_{17}N_3O_2$	355.397	155-157	58
QZ4	3-amino acetophenone	$C_{22}H_{18}N_4O$	354.413	170-172	64

Table2:Structures of synthesized compounds

CODE	STRUCTURE
QZ	
QZ1	
QZ2	

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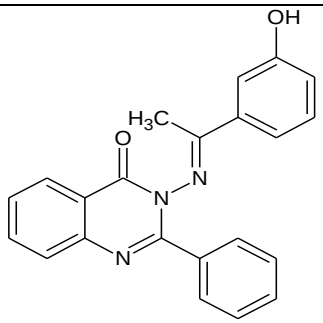
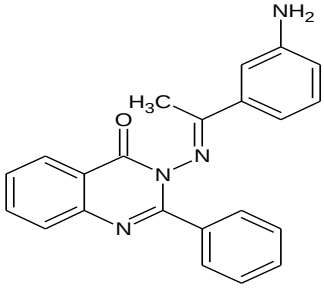
QZ3	
QZ4	

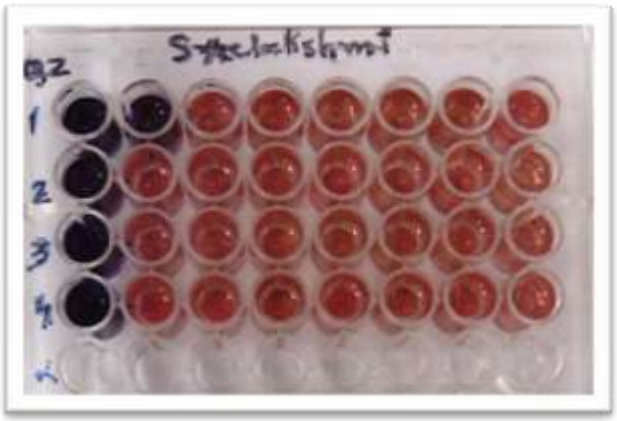


Figure3:Photograph of Antitubercular activity of synthesized drugs

Table3:Results of Antitubercular activity

Sl. No.	Sample	100 µg/ml	50 µg/ml	25 µg/ml	12.5 µg/ml	6.25 µg/ml	3.12 µg/ml	1.6 µg/ml	0.8 µg/ml
1	QZ1	S	S	R	R	R	R	R	R
2	QZ2	S	R	R	R	R	R	R	R
3	QZ3	S	R	R	R	R	R	R	R
4	QZ4	S	R	R	R	R	R	R	R

Note:
S-Sensitive, R-Resistant

III. DISCUSSION

2-amino benzoic acid is the starting material for the synthesis of several compounds. The resultant product is reacted with hydrazine hydrates and then treated with different ketones for the quinazoline derivatives in Scheme1. Physiochemical data has been analyzed. Melting point were tested using melting point apparatus (open capillary tube). The compounds were evaluated in vitro antitubercular action using MABA method and compared with standard Isoniazid, Rifampicin, Streptomycin, Ethambutol, Pyrazinamide drugs. All compounds were showing good results at concentration 100µg/ml. One

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compound (QZ1) is sensitive towards antitubercular action at 50µg/ml. Photograph that indicates blue colour is active (sensitive-S) and pink colour is inactive (resistant-R).

IV. CONCLUSION

Antitubercular activity was conducted for samples QZ1, QZ2, QZ3, and QZ4 using Alamar blue assay method. As we compared antitubercular activity of derivatives with that of standard , it shows comparable activity.

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