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Synthesis of Some Novel Quinazolino-Triazine Derivatives for Their Antimicrobial Activity

K P Namdeo, Phool Singh Yaduvansi and S H Bodakhe

ABSTRACT

A new series of 2,4,6-Trisubstituted- quinazolinone -s-Triazine designed and synthesized to meet the structural requirements essential for antimicrobial properties. 2,4,6-Trisubstituted- quinazolinone -s-Triazine were synthesized using anthranilic acid as a starting material. All the synthesized compounds were screened for antibacterial and antifungal activity on agar plates using neutrient broth (antibacterial) and Saboraud's medium (antifungal) by Cup-plate technique. The bacterial culture were *E. coli, P. Fluorescens, S. Aureus, B.subtilis,* fungal cultures were *C. albicans, A. niger.* The standard drugs used for the present study were Ciprofloxacin and Fluconazole as antibacterial and antifungal respectively. The synthesized compounds exhibited significant antibacterial as well as antifungal activity comparable to the standard drugs. Among these synthesized compounds, compound code PS3 showed maximum activity.

Key words: Antimicrobial, Quinazolinone, S-Triazine

1. INTRODUCTION

Quinazolinone containing pharmacoactive agents play important role in medicinal chemistry**.** The prevalence of Quinazolinone cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead. The treatment of microbial infection continues to be the subject of considerable pharmaceutical and clinical research. It has been reported that Quinazolinone possess antibacterial[1], analgesic[2], anti-inflammatory[3], antifungal[4], antimalarial[5], antihypertensive[6], CNS depressant[7], anticonvulsant[8], antihistaminic, local anaesthetic[9], antiparkinsonism[10], antiviral and cancer activities[11]. Little number of quinazolinones was reported as potent chemotherapeutic agents in the treatment of tuberculosis[12] and as antimycobacterial agents[13].

. In view of these above, Quinazolinone nucleus has occupied a unique place in the field of medicinal chemistry. Due to wide range of biological activities an attempt has been undertaken for the synthesis of the some novel 2- *substituted 3- aryl-4 Quinazolinone* possessing potent biological activities. Triazine has been frequently used in medicine because of their wide spectrum of biological activities. Different -s- triazine derivatives have been reported for their antibacterial, antiviral, antimicrobial and herbicidal activities. These are also used for treatment of HIV infection. 2,4,6-Trisubstituted-s-Triazine derivatives have been demonstrated to posses anticancer, anticonvulsant, antimalarial, hypotensive and antiamoebic properties.

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1,3,5-Triazine derivatives are known to be effective plant protection agents but their application strongly depends upon their environmental behavior. At present the polymer formulation of pesticides is a rather advantageous approach to obtain ecologically more tolerable product of lower toxicity and of prolonged effect[14].

The concept of developing synthetic methods for biological active agents is highly desirable to improve efficacy, potentiality and decrease toxicity.

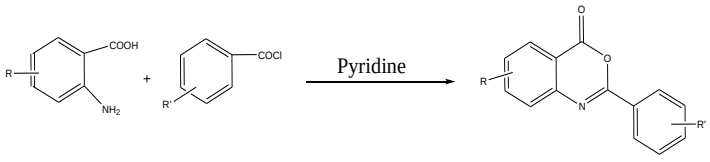
In view of potential biological activities of Quinazolinone and some similar activities of 2,4,6-Trisubstituted-s-Triazine derivatives, they were fused together and synthesized (PS_1-PS_6) to probe how far these combinations could enhance the antimicrobial action, as out lined in the **Scheme-1.**

2. MATERIALS AND METHODS

2.1 Experimental

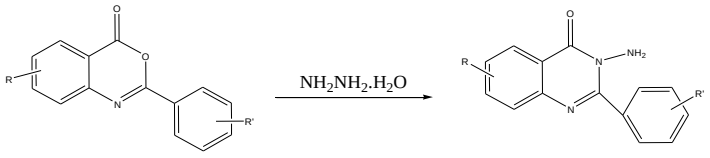
In the present work on the -s-Triazine the synthetic procedure of Raghavendra and Venkatesh[15] was followed. The procedure involves there step as stated below in scheme-1

Step-1: Synthesis of substituted 2-phenyl-3,1-bezoxazin-4(3H)-one.



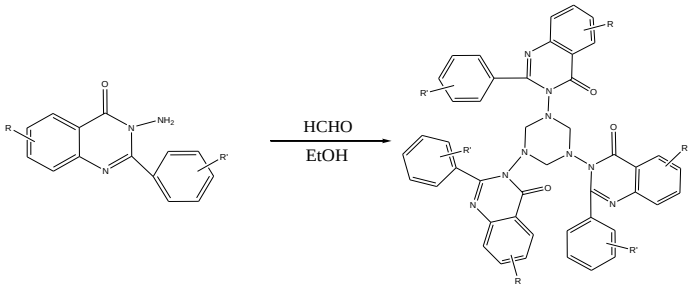
(Ia-l)

Step-2: Synthesis of substituted 3-amino-2-phenyl quinazolin-4(3H)-one.



(IIa-l)

Step-3: Synthesis of final products



(III) PS1-PS6

2.1.1 Preparation of substituted 2-phenyl-3, 1-bezoxazin-4(3H)-one. (I)

To a stirred solution of anthranilic acid or substituted anthranilic acid (0.1 moles) in pyridine (60 mL), substituted benzoyl chloride (0.05 mole) was added drop wise, maintaining the temperature near 8 ^{0}C for 1 hour. Reaction mixture was stirred for another 2 hours at room temperature. While stirring a solid product separate out. Whole reaction mixture was neutralized with $NaHCO_3$ solution. A pale yellow solid (I) deposited which was filtered, wash with water and recrystallised from ethanol. The melting points were 124^{0}C, 135^{0}C, 141^{0}C, 178^{0}C, 98^{0}C, 194-198^{0}C, 184-188^{0}C, 127^{0}C, 118^{0}C, 178^{0}C, 122^{0}C and 118^{0}C and yeild were 78%, 62.5%,56%,42%,54%,40%,62.6%,68.4%,62.9%,43%,45% and 38% of compounds Ia-l respectively.

IR(KBr in cm^{-1}) : 3072.60 (C-H, ArH Str),1759.08 (C=O Str),1681.93 (cyclic C=0 Str),1606.70(C=N Str),1510.26(C=C Str),1446.61 (C-N Str),840.96 (C-H deflaction),1188.15 (C-O Str)

^{1}HNMR (δppm) ($CDCl_3$), 2.530 (s, 3H, -SCH_3),7.482-8.090 (m, 8H, Ar-H)

2.1.2 Synthesis of substituted 2-phenyl-3 amino quinazolin-4(3H)-one (II)

A mixture of (I) (0.05 mole) and hydrazine hydrate (0.05 mole) was taken in ethanol and refluxed for 3hrs and than after cooled. The separated solid(II) was recrystallized from ethanol. The melting points were 148^{0}C, 145^{0}C, 179^{0}C, 158^{0}C, 179^{0}C, 142^{0}C, 148^{0}C, 120^{0}C, 148^{0}C, 143^{0}C, 120^{0}C and 176^{0}C and yeild were 76%, 75%,50, 56%,52%,50%,65%,71%,64%,42.9%,43%,44% and 36% of compounds IIa-l respectively.

IR(KBr in cm^{-1}) : 3068.75 (C-H, ArH Str), 3305.99 (N-H Str),1664.57 (cyclic C=0 Str),1598.99 (C=N Str),1514.12(C=C Str),1450.47(C-N Str),839.57(C-H deflaction)

^{1}HNMR (δppm) ($CDCl_3$), 2.530 (s, 3H, -SCH_3),7.482-8.090 (m, 8H, Ar-H)

2.1.3 Synthesis of final product(III)

Compound (II) (0.01 mole) was dissolved in ethanol (50mL) by slow warming ,to this solution 40% aqouse formaldehyde (0.075 mole 2.85gm) was added slowly under stirring at room temperature. The resultant solution, after stirring vigorously for half an hour at room temp, was allowed to stand for another half an hour. A solid separated out, and was filtered ,and washed with cold ethanol the resulting product was purified by rapid extraction with boiling petroleum ether (b.p. 80-100 ^{0}C× 60ml) after removing the insoluble high polymer by filtration, the filtrated was cooled at room temperature and the product was filtered off [20]. The melting points, % yields and Rf value are given in Table-1.

2.2 Determination Of Antimicrobial Activity

All the synthesized compounds were screened for antibacterial and antifungal activity on agar plates using neutrient broth (antibacterial) and Saboraud's medium (antifungal by Cup-plate technique[16]. The bacterial culture were *E. coli, P. Fluorescens, S. Aureus, B.subtilis,* fungal cultures were *C. albicans, A. niger.* The standard drugs used for the present study were Ciprofloxacin and Fluconazole as antibacterial and antifungal respectively .. The concentration of the synthesized compounds and standard drugs were taken as 50 µg/ml .All the compounds were dissolved in DMF. In order to account for the effect due to DMF, a blank was also performed.

3. RESULTS AND DISCUSSION

A perusal of the table shows that compared to the standard drug, all the synthesized compounds were effective against all the two strains of bacterias and two strains of fungi but compound PS2 was least effective and compound PS3 was most effective. The compound PS3 was most effective against *E. coli, S. Aureus, P. Fluorescens, B.subtilis A.niger* and compound PS4 was most effective against *P. Fluorescens.*

These compounds were synthesized with the objective of developing better antimicrobial molecules with maximum percentage of yield and optimal antibacterial and antifungal activity.

It was observed that Nitro substituted compound was more active than methoxy substituted compound. Chloro substituted compound was less effective than unsubstituted compound All the synthesized compounds were effective against all the four strains of bacterias and two strains of fungi ; this activity might be due to the presence of two nuclei; Quinoline and Triazole.

Further investigations with appropriate structural modification of title compound may result in therapeutically useful products.

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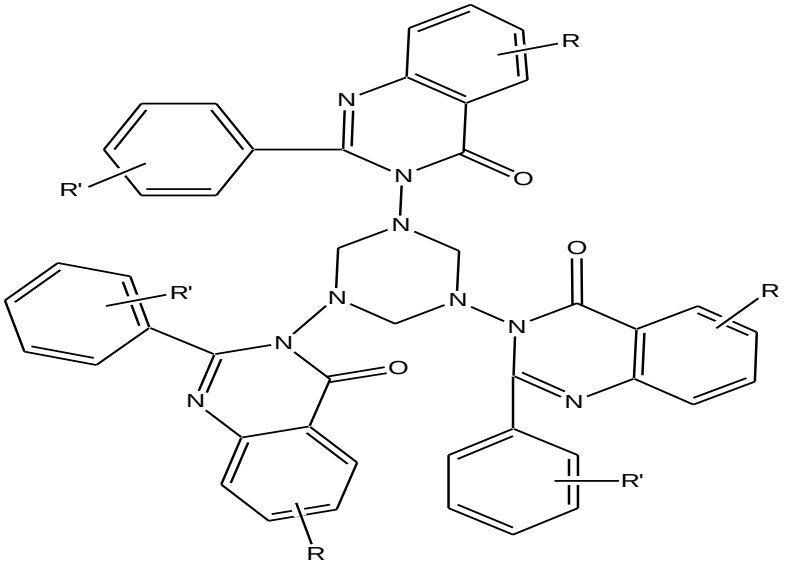

S.No	Code	R'	Zone of Inhibition (mm)					
			E. coli	*S. aureus*	*P. Fluorescens*	*B.subtilis*	*C. albicans,*	*A. niger.*
01	PS1	H	9.2	9.6	9.2	9.3	9.1	9.3
02	PS2	Cl	8.2	8.4	8.3	7.3	8.7	8.2
03	PS3	NO_2	10.7	10.5	10.4	9.9	9.5	10.7
04	PS4	OCH_3	10.6	10.5	10.6	9.5	10.3	10.6
05	PS5	F	8.2	8.4	10.2	8.8	8.7	8.2
06	PS6	Br	8.7	8.7	8.6	8.4	8.5	8.7
07	Standard		8.9	13.9	13.0	12.3	13.9	13.9