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SYNTHESIS AND ANTIMICROBIAL SCREENING OF SOME 3-(4-SUBSTITUTED PHENYL)-2-PHENYL-4(3H)-QUINAZOLINONES

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Abstract
A new series of 3-(4-substituted phenyl)-2-phenyl-4-(3H)-quinazolinones 2(a-e) were synthesized by reacting 2-phenyl-4H-3-1-benzoxazin-4-one (1) with various primary amino compounds. The 2-phenyl-4H-3-1-benzoxazin-4-one (1) was prepared from anthranillic acid and benzoyl chloride. The structure of the title compounds was confirmed based on IR, ^{1}H NMR, and Mass data. The compounds were screened for their antimicrobial activity and few of them were found to possess promising antimicrobial activity.

Keywords: 3-1-benzoxazin-4-one, Quinazolinones, antifungal activity, antibacterial activity.

1. Introduction
Various biological activities have been attributed to quinazolinone derivatives found to possess antipyretic[1], anti-inflammatory[2], anticonvulsant[3], anticancer[4], and antithrombic[5] activity and also have good storage stability. This led to the synthesis of a new series of 3-(4-substituted phenyl)-2-phenyl-4-(3H)-quinazolinones for pharmaceutical applications. The title compounds were synthesized as outlined in Scheme 1.
The quinazolinones and quinazolones when selectively functionalized, act as building blocks for the preparation of numerous biologically active compounds. Quinconazole, sebuthylazine, fluquinconazole and nicotine derivatives of quinazolinone have been used as pesticidal agents. It has been found that the quinazolinone moiety is associated with a broad spectrum of biological activities such as pesticidal[6], antifungal[7], insecticidal[8], antibacterial[9,] and antitubercular[10]. Given these observations, it was decided to synthesize new derivatives of 3-(4-substituted phenyl)-2-phenyl-4-(3H)-quinazolinone moiety (3a-e) (Scheme-1). It exhibited peaks at 1661 (C=O), 1638 (C=N), 1507 (Ar-C=C), 1233 (C-N), and 700 (Ar-C-H). Disappearance of the peak at 1202 which corresponds to the C-O-C group confirms the formation of the quinazolinone from 3,1-benzoxacin-4-one. These compounds were evaluated for antifungal and antibacterial activities by standard method.

2. Procedure
2.1. Materials and methods:
In this present work to synthesize some new derivatives of 3-(4-substituted phenyl)-2-phenyl-4-(3H)-quinazolinone and to study the antimicrobial activity exerted by these compounds, all the reagents requiring anhydrous conditions were conducted in a flame-dried apparatus. The solvents and reagents used were of laboratory grade. The syntheses were carried out at room temperature. The synthesized compounds were purified by recrystallization and melting points were determined by open capillary method and uncorrected. The purity of the compounds was confirmed by micro TLC using a silica gel 'G' coated glass plate using benzene-methanol (90:10) as irrigant and iodine vapor as a visualizing agent. The IR spectra were recorded on a PERKIN-ELMER IR-283

spectrophotometer using a thin film supported on KBr pellets. The values are reported as λ_{max} (cm^{-1}). ^1H NMR spectra were recorded on BRUKER 200MHz NMR spectrophotometer. The spectra were obtained in $CDCl_3$ and the chemical shift values are reported as values in ppm relative to TMS ($\delta = 0$) as an internal standard. The Mass spectra were recorded on SCHIMADZU GC-MS using xenon as the carrier gas. The spectra were recorded at room temperature. The antimicrobial activity was determined by screening against four bacterial strains and three fungal strains by the Zone of inhibition method. Physical and analytical data are given in Table 1 and the Zone of inhibition data is given in Table 2.

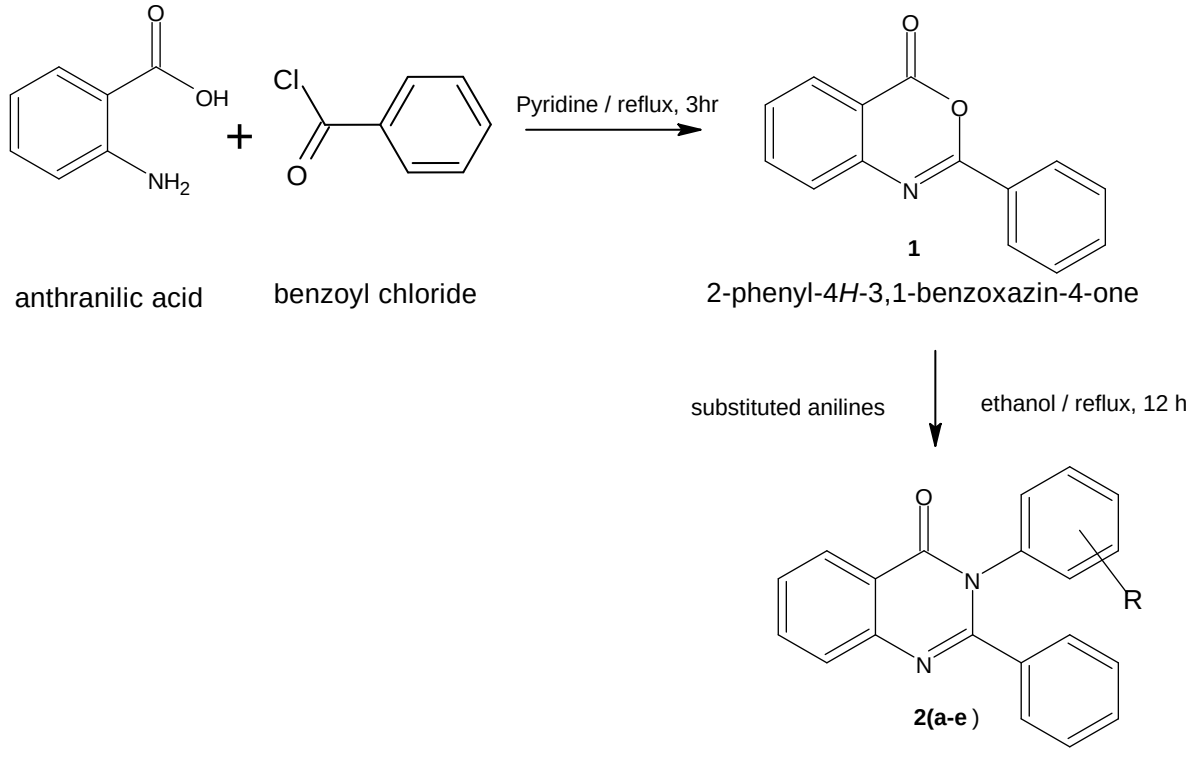
2.1.1. Synthesis of 2-phenyl-4H-3-1-benzoxazine-4-one (1):

A solution of benzoyl chloride (11.6ml; 20mmol) and anthranilic acid (13.7gm; 20mmol) in dry pyridine (150ml; 30mmol) was refluxed for 3 hr. The reaction mixture was cooled and poured into cold dilute HCl. The solid thus separated was filtered off and recrystallized from benzene to give the compound (1). Physical and analytical data are given in Table 1.

Synthesis of 3-(4-substitutedphenyl)-2-phenyl-4(3H)-quinazolinones 2 (a-e):

A mixture of 2-phenyl-4H-3,1-benzoxazin-4-one (1) (1.1gm; 5mmol) and various primary amino compounds (5 mmol) in ethanol (30ml) was refluxed separately for 6 hr. The reaction mixture was concentrated, cooled, poured into crushed ice, and filtered. The solid thus separated was collected and recrystallized from ethanol to give the required compounds 2(a-e).

Scheme 1



2a R = H,2b R = p-COOH,2c R = p-COOH,m-OH,2d R = p-OH, 2e R = p-CH3

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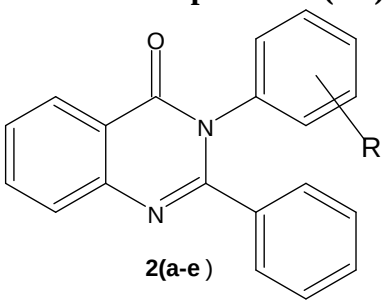
Table: 1. Physical characterization of 3-(4-substituted phenyl)-2-phenyl-4(3H)-quinazolinones derivative compounds 2 (a-e):

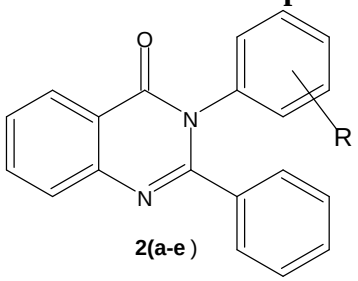


2(a-e)

S. No	Compounds (R)	Color	% Yield w/w	Melting point (^{0}C)	Rf value	Molecular Formula	Formula Weight	Composition%			
								C	H	O	N
2a	-H	Yellow	72	129-132	0.48	$C_{20}H_{14}N_2O$	298.33	80.52	4.73	5.36	9.39
2b	p-COOH	Yellow	76	146-148	0.40	$C_{21}H_{14}N_2O_3$	342.34	73.68	4.12	14.02	8.18
2c	m-OH, p-COOH	Yellow	76	116-118	0.42	$C_{21}H_{14}N_2O_4$	358.34	70.39	3.94	17.86	7.82
2d	p-OH	Yellow	71	138-140	0.39	$C_{20}H_{14}N_2O_2$	314.33	76.42	4.49	10.18	8.91
2e	p-CH_3	Yellow	74	151-154	0.42	$C_{21}H_{16}N_2O$	312.36	80.75	5.16	5.12	8.97

Mobile phase - methanol: dichloro methane (0.1:5)

Table :2. IR & ^{1}H NMR spectral data of 3-(4-substituted phenyl)-2-phenyl-4(3H)-quinazolinones derivative compounds 2 (a-e):



2(a-e)

S. No	Compounds (R)	IR frequency region(cm^{-1})	^{1}H NMR (δ ppm)	m/z
2a	-H	3115.31 (Aromatic C-H Stretching) 1686.07 (C=O Stretching) 1604.07 (Aromatic C-N Stretching) 1565.90 (Aromatic C-C Stretching)	7.24-6.6(m,14H, Ar-H)	298
2b	p-COOH	3310.54 (O-H Stretching) 3186.33 (Aromatic C-H Stretching) 1617.21 (C=O Stretching) 1606.74 (Aromatic C-N Stretching) 1530.59 (Aromatic C-C Stretching)	11.8(s,1H, Ar-COOH) 7.42-6.86(m,13H, Ar-H),	342
2c	m-OH, p-COOH	3309.85 (O-H Stretching) 2970.38 (Aromatic C-H Stretching) 1606.15 (C=O Stretching) 1567.24 (Aromatic C-N Stretching) 1538.26 (Aromatic C-C Stretching)	7.35-6.95(m,13H, Ar-H), 5.35(s,1H,phenolic-OH) 11.5(s,1H, Ar-COOH)	358
2d	p-OH	3185.27 (O-H Stretching) 2915.31 (Aromatic C-H Stretching) 1622.97 (C=O Stretching) 1549.84 (Aromatic C-N Stretching) 1535.48 (Aromatic C-C Stretching)	7.24-6.93(m,13H,Ar-H), 5.24(s,1H, phenolic-OH)	314
2e	p-CH_3	3304.13 (O-H Stretching) 2924.63 (Aromatic C-H Stretching) 1687.58 (C=O Stretching) 1534.94 (Aromatic C-N Stretching) 1520.51 (Aromatic C-C Stretching)	7.32-6.84(m,13H,Ar-H), 1.9(s,3H,Ar–CH_3)	312

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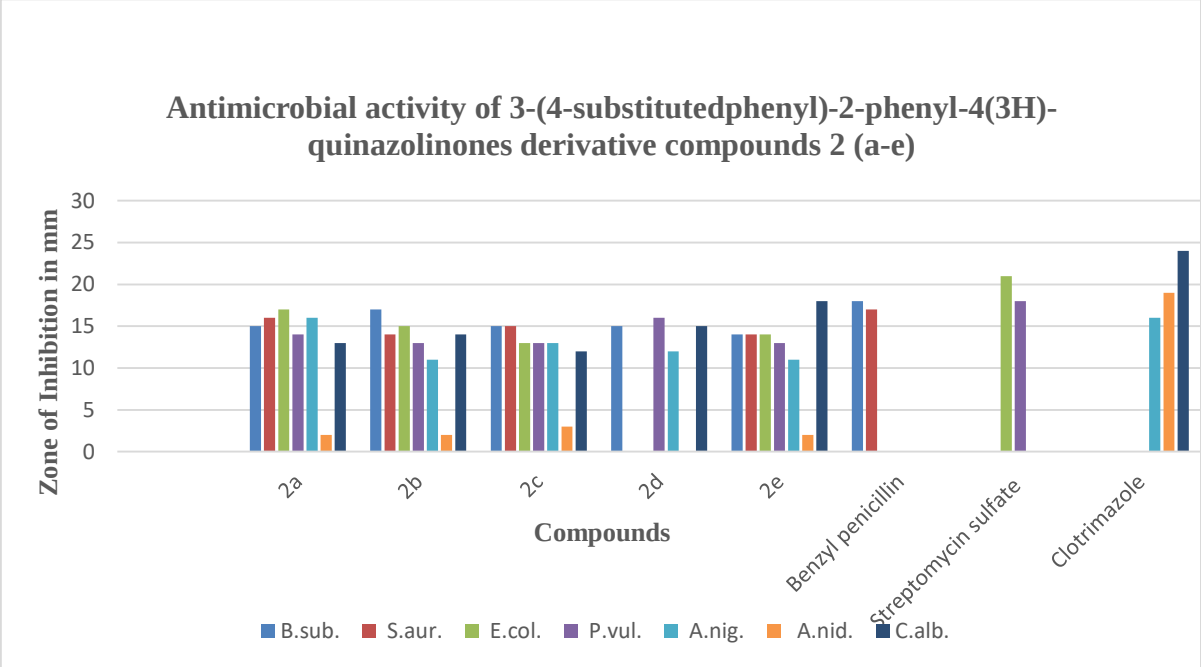
Antimicrobial evaluation of the compounds:

Antibacterial activity of the compounds (in DMF) was determined by agar Cup plate method[11] at a concentration of 100µg/ml against two gram-positive bacteria, *Bacillus subtilis* and *Staphylococcus aureus* and two gram-negative bacteria *Escherichia coli* and *Proteus vulgaris* employing Benzylpenicillin (100 unit/ml) and Streptomycin sulfate (700 unit/ml) as reference standards respectively. Antifungal activity was also determined similarly against *Aspergillus niger*, *Aspergillus nidulus*, and *Candida albicans* using Clotrimazole (100µg/ml) as standard. Zone of inhibition data is given in Table 3.

Table :3 Data of antimicrobial activity of 3-(4-substituted phenyl)-2-phenyl-4(3H)-quinazolinones derivative compounds 2 (a-e):

Compounds	Zone of Inhibition in mm						
	Antibacterial activity				Antifungal activity		
	B.sub.	***S.aur.***	***E.col.***	***P.vul.***	***A.nig.***	***A.nid.***	***C.alb.***
2a	15	16	17	14	16	2	13
2b	17	14	15	13	11	2	14
2c	15	15	13	13	13	3	12
2d	15	NA	NA	16	12	NA	15
2e	14	14	14	13	11	2	18
Benzylpenicillin	18	17	-	-	-	-	-
Streptomycin sulfate	-	-	21	18	-	-	-
Clotrimazole	-	-	-	-	16	19	24



Results:

The compounds were prepared in good yield between 70-74%. Except for compound 3c which was pale yellow in color, the rest were white in color. The formation of 2-phenyl-4H-3-1-benzoxazin-4-one was confirmed by the spectral data. IR spectra exhibited peaks at 1684 (C=O Stretching), 1597 (C=N Stretching), 1541 (Aromatic C-C Stretching), 1202 (asymmetrical C-O-C Stretching), and 705 (Ar-C-H bending). The 2-phenyl-4H-3-1-benzoxazin-4-one (1) thus formed was reacted with various primary amino compounds to form the desired 3-(4-substituted phenyl)-2-phenyl-4-(3H)-quinazolinones 2(a-e) which were supported by the spectral data. It exhibited peaks at 3310-3185 (O-H Stretching) 3115-2915 (Aromatic C-H Stretching) 1687-1606 (C=O Stretching), 1604-1534 (C=N Stretching), 1565- 1520 (Aromatic C-C Stretching). Physical, ^{1}H NMR, and Mass data were

given in Tables 1 and 2. These compounds were evaluated for antibacterial and antifungal activity by standard methods. The results of the activities evaluated by the standard screening techniques are presented in Table 3.

Discussion:

The spectral data confirms the structure of the compounds. Disappearance of peak at 1202 which corresponds to the C-O-C group present in the 3,1-benzoxacin-4-one confirms the formation of the quinazolinone from 3,1-benzoxacin-4-one. The ^{1}H NMR spectra of compound 2a-2e exhibited signals at 7.42 - 6.6ppm corresponding to the aromatic region alone which agrees with the structure of the compound. Compounds 2b and 2c exhibited signals at 11.8 - 11.5ppm corresponding to the Ar- COOH group present in the compound. Similarly, in compounds 2c, 2d, and 2e, the signals exhibited at 5.35 - 5.24 and 1.8 correspond to phenolic –OH, and $–CH_3$ groups respectively. The GC-M Spectra further supported the formation of the title compounds.

It is interesting to note that many of the compounds were effective against all four bacterial strains, however with a degree of variation. *Bacillus subtilis* was relatively more sensitive to almost all the compounds. Compound 2b has shown excellent antibacterial activity against *Bacillus subtilis* which was at par with the activity exhibited by benzylpenicillin, while better activity was seen against the remaining strains. Compound 2a manifested remarkable activity against *Escherichia coli* and *Staphylococcus aureus* while reasonable activity was seen against other strains. Compound 2c showed appreciable activity against *Bacillus subtilis* and *Staphylococcus aureus* while judicious activity was seen against other strains. Compound 2d showed good activity against *Proteus vulgaris* and *Bacillus subtilis* and inactive against *Staphylococcus aureus* and *Escherichia coli.* Compound 2e was abstemiously active against all the bacterial strains used.

It could be noted that all the compounds were found to possess noticeable antifungal activity only against *Aspergillus niger* and *Candida albicans.* Compound 2a was relatively more potent against *Aspergillus niger.* Compound 2e was superior in its action against *Candida albicans* over the rest of the compounds. However, all the other compounds were poorly active against *Aspergillus nidulus.* The Zone of inhibition data are presented in Table 3.

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