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Research Article

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF NOVEL 2-PHENYL-QUINAZOLIN-4(3H) - ONES

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ABSTRACT:

The main objective of the medicinal chemistry is to synthesize the compounds that show promising activity as therapeutic agents with lower toxicity. Quinazolin-4(3H)-one derivatives are very useful compound with well known biological activity. Notable among these are antibacterial, antiviral, antifungal, analgesic, anti-inflammatory, antitubercular, anticancer, anti-parkinsonism, anticonvulsant and anti-viral. In the current research work compounds of 2-phenyl-quinazolin-4(3H)-ones were synthesized by condensing unsubtituted/substituted anthranilic acid with benzoyl chloride by using pyridine as solvent. The synthesized compounds were heated with aromatic substituted primary amines by using acetic acid as solvent. Identification and characterization of the synthesized compounds were carried out by melting point, Thin Layer Chromatography, FT-IR, NMR and Mass data to ascertain that all synthesized compounds were of different chemical nature than the respective parent compound. The compounds were screened for antibacterial and antifungal activity. Antibacterial activity conducted against *Staphylococcus aureus* (ATCC 6538) *Micrococus luteus (ATCC 8341), Bacillus cereus (*ATCC 1778*)* as a Gram +ve microorganism and *Kiebsiella pneumoniae - (*ATCC 29665*) as a* Gram -ve microorganism using ciprofloxacin as a reference standard and dimethyl formide as control. The compounds II $_e$, II $_c$ and II $_a$ found to possess better antibacterial activity than ciprofloxacin (Reference standard) in MIC (Minimum inhibitory concentration).

KEYWORDS: 2-phenyl-quinazolin-4(3H)-ones, Benzoyl chloride, Dimethyl formide and Ciprofloxacin.

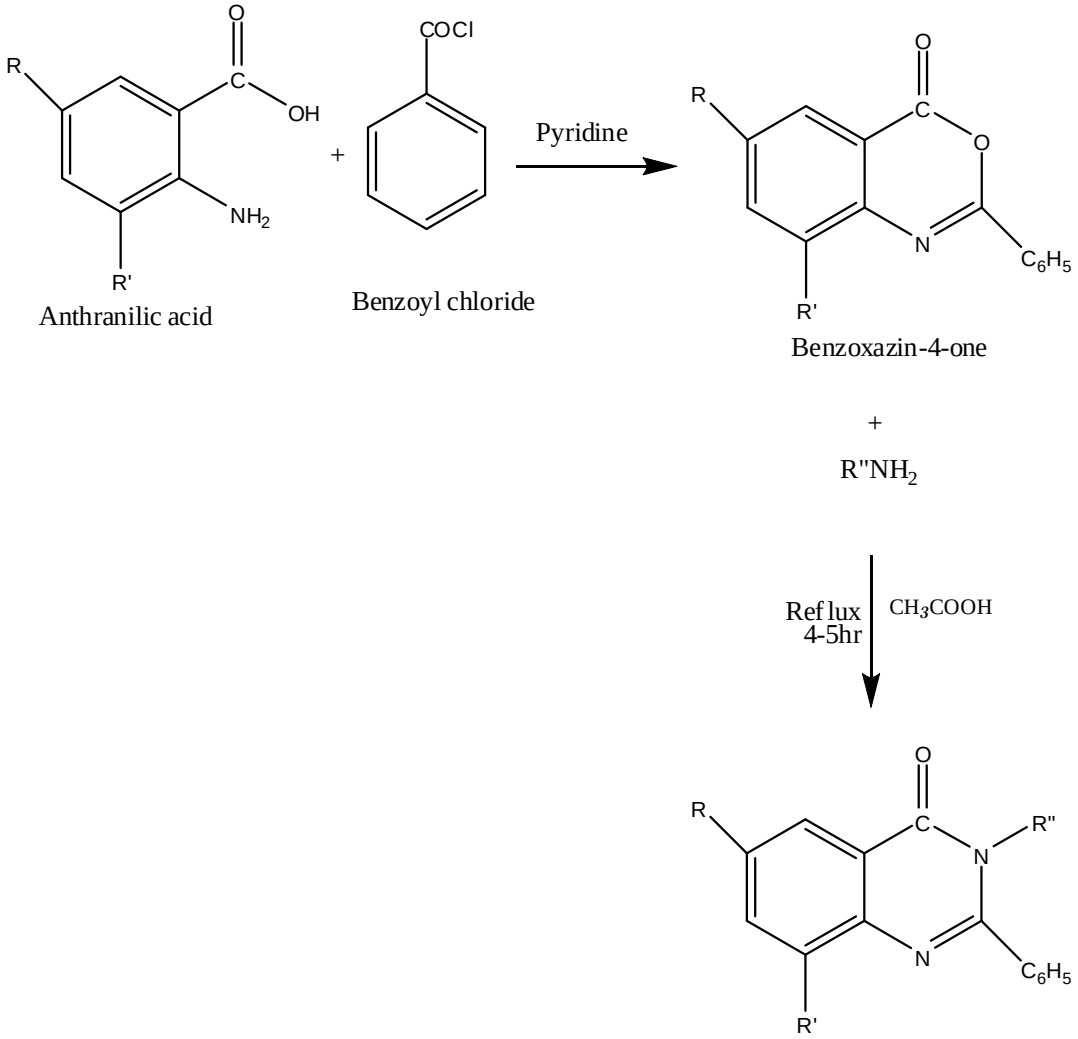
INTRODUCTION:

Quinazoline is a bicyclic compound consisting of a pyrimidine system fused at 5, 6 with benzene ring having broad spectrum of medicinal values, Quinazolin-4(3H)-one derivatives were reported to posses analgesic[1], anti-inflammatory[1], antimicrobial [2,3]antiallergic[4], antihypertensive[5], hypoglycemic[6], tumor Necrosis factor [7], anticancer [8,9]antiviral[10], hypnotic[11]and Anti-parkinsonism[12,13,14,] properties. The pharmacological properties of Quinazolin-4(3H)-ones encouraged our interest in synthesizing several new compounds featuring various heterocyclic rings, attached to the new series of 2-phenyl- quinazolin -4(3H)-ones moieties. As a part of our aim to search for biologically active heterocycles containing oxygen and nitrogen, we have now synthesised a series of some novel 2-phenyl-3-(2'-morpholino-phenyl) quinazoline-4-(3H) one, the bromo, nitro substitutions at meta and para position along with morpholino group at 3rd position improve antimicrobial activity. Therefore it was though worthwhile to synthesize some new 2-phenyl- quinazolin -4(3H)-ones containing compounds and evaluate antimicrobial potential.

MATERIAL AND METHODS:

The melting points of synthesized compounds were determined by open capillary method and were uncorrected. The purity of the synthesized compounds were checked by TLC using E-Merck TLC aluminium sheet-silica gel 60 F 254 (0.2mm) using ethyl acetate: n-hexane (3:2) as eluent and visualized in an iodine chamber.IR spectra were recorded using KBr pellets on an ABB Bomem MB-104 spectrophotometer,^{1}H-NMR Were recorded on Buker av 400 MHZ spectro photometer using $CDCl_3$ as solvent at Indian Institute of Technology (IIT)-Chennai. Mass Spectra of the synthesized compounds were recorded on Liquid Chromatography Mass Spectrometer at Indian Institute of Technology (IIT),-Chennai. All the reagents and solvents used were of analytical grade.

Scheme of synthesis:



GENERAL METHOD OF SYNTHESIS:

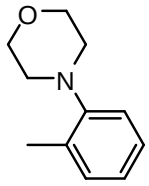
Unsubstituted/ substituted anthranilic acid (0.05ml) in 0.1 mol of pyridine were refluxed under anhydrous condition for 4-6 hrs the excess pyridine was distilled off under reduced pressure and cooled to room temperature. The corresponding 2-phenyl-benzoxazin -4-one, so obtained was filtered and dried under vacuum.Equimolar quantities of Unsubstituted/ substituted-2-phenyl-benzoxazin -4-one and corresponding primary amines in glacial acetic acid was refluxed for 4-6 hrs. After cooling the contents were poured into crushed ice. The resulting solid were washed with distilled water, filtered and dried in vacuum and recrystallized from warm ethanol.

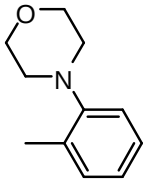
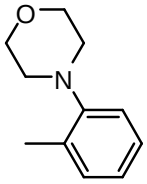
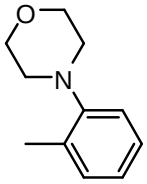
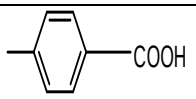
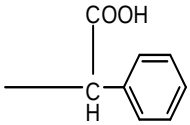
ANTIMICROBIAL SCREENING:

All the synthesized compounds were subjected to *invitro* antimicrobial screening by the Paperdisc diffusion technique[15] against various species of gram-positive and gram-negative bacteria *Staphylococcus aureus* (ATCC 6538), *Bacillus cereus (*ATCC1778*), Micrococus luteus (ATCC 8341), Kiebsiella pneumoniae (*ATCC 29665*)* using tryptone soya agar medium.

The sterilized (autoclaved at 120˚C for 30min) medium (40-50˚C) was inoculated (1ml/100ml of medium) with the suspension of the microorganism (matched to Mcfarland barium sulphate standard) and poured into a petridish to give a depth of 3-4 mm.The paper impregnated with the test compounds (200 µg/ml in Dimethyl formide) was placed on the solidified medium. Test compounds at various concentrations were added to culture medium in a sterilized. The plates were preincubated for 1hr at room temperature and incubated at 37˚C for 24hr and 48 hr for antibacterial activity respectively. Ciprofloxacin (100 µg/disc), then examined for the presence or absence of growth of the test organisms. All experiments were performed in triplicate. The lowest concentration which showed no visible growth was taken as an end point (MIC)[16]. The MIC values were also tested for standard antibiotics (Ciprofloxacin) to compare the antibacterial activity of test compounds.

Physical data of compound No.II_a-II_f were summarized in Table No. 1:

Compound No	**R**	**R'**	**R"**	**Molecular formula**	**m.p(^{0}C)**	**Yeild**	**R_f value**
II_a	H	H		$C_{24}H_{21}N_3O_2$	110-115	62%	0.52

II b	Br	H		$C_{24}H_{20}N_3BrO_2$	132-136	73%	0.69
II c	Br	Br		$C_{24}H_{19}N_3Br_2O_2$	165-168	78%	0.67
II d	NO_2	NO_2		$C_{24}H_{19}N_5O_6$	146-149	82%	0.41
II e	Br	Br		$C_{21}H_{12}N_2Br_2O_3$	236-240	71%	0.72
II f	Br	Br		$C_{22}H_{14}N_2Br_2O_3$	152-154	86%	0.68

Compound IIa: 2-phenyl-3-(2'-morpholino-phenyl) quinazoline-4-(3H) one.

Yield- 62%; **M.P** 110-115 ºc;**IR-(KBr) cm^{-1} :**1685(C=O), 1602(C=C), 1673(C=N), 1068(C-O-C),795(C-H); **^{1}H NMR($CDCl_3$) δ ppm :**2.9(t, 4H; 2", 6" CH2), 3.67(t, 4H; 3", 5" -CH2), 6.28 (m,13H;5,6,7,8,3',4',5',6',2", 3''', 4''', 5''', 6'''Ar-H); **MS (EI)m/z:**383 (M^+); 179 (40%), 137 (6 1%), 108 (19%), 92 (43%), 65 (30%), 57(28%), 119 (B) (100%).

Compound IIb: 6-bromo-2-phenyl-3-(2'morpholino-phenyl) quinazoline-4-(3H)-one.

Yield -73%;**M.P** 132-136 ºc;**IR-(KBr) cm^{-1} :**1685 (C=0), 1602(C=C), 1674(C=N), 1065(C-O-C), 795(C-H), 554(C-Br); **^{1}H NMR($CDCl_3$) δ ppm :** 2.7(t, 4H**;** 2", 6"-CH_2) 3.6(t, 4H**;** 3", 5",- CH_2) 6.2 (m, 12H**;** 5,7, 8, 3',4', 5', 6', 2''', 3''',4''', 5''' 6'''-ArH); **MS (EI)m/z:** 462 (M^+)(20%), 448 (6%), 372 (14%), 302 (8%), 292 (44%), 250 (24%), 223 (18%) ,182 (14%), 170 (30%), 141 (24%), 119 (20%), 188 (18%), 62 (26%), 328 (B) (100%).

Compound IIc: 6, 8-dibromo-2-phenyl-3-(2'-morpholino-phenyl) quinazoline-4-(3H)-one.

Yield -78%; **M.P** 165-168 ºc ; **IR-(KBr) cm^{-1}** :1653(C=0), 1451(C=C), 1653(C=N), 1057(C-O-C), 777(C-H), 557(C-Br); **^{1}H NMR(CDCl$_3$) δ ppm**: 2.7 (t, 4H; 2", 6"- CH_2) 3.60 (t, 4H; 3' 5'-CH_2) , 6.50(m, 11H;5,7, 3', 4', 5', 6', 2''', 3''', 4''', 5''', 6'''-Ar-H); **MS (EI)m/z:** 541 (M^+) (29%), 342 (4%), 297 (8%), 241 (5%), 207 (7%), 179 (6%), 152 (5%), 137 (5%), 77 (34%), 55 (6%), 105 (B) (100%).

Compound IId: 6, 8dinitro-2phenyl-3-2-(morpholino-phenyl) quinazoline-4-(3H)-one.

Yield -82%, **M.P** 146-149 ºc - **IR-(KBr) cm^{-1} :**1696(C=O) 1607(C=C) 1654(C=N) 1297(C-O-C) 789(C-H) 1369(CH_3) 1585(C-NO_2); **^{1}H NMR(CDCl$_3$) δ ppm :** 2.7 (t, 4H; 2", 6" CH_2) 3.60 (t, 4H; 3", 5" — CH_2) 6.28 (m,7H;5,6,7,8,3',4',5',6'—Ar-H); **MS (EI) m/z:** 473 (M^+) (26%), 371 (14%), 300 (8%), 292 (48%), 250 (26%), 223 (18%), 184 (8%), 168 (24%), 141 (16%), 88 (18%), 62 (10%), 331 (B) (100%).

Compound IIe: 6, 8-dibromo-2-phenyl-3-(4'-carboxy-phenyl) quinazoline-4-(3H)-one.

Yield -71%;**M.P** 236-240 ºc ;**IR-(KBr) cm^{-1} :**1688(C=0), 1600(C=C), 1660(C=N), 1064(C-O-C), 852(C-H), 544(C-Br); **^{1}H NMR(CDCl$_3$) δ ppm :**5.25(S, 1H;4'—CH), 6.4(m, 11H**;** 5, 7, 2', 3',5',6',2'', 3", 4", 5", 6"); **MS (EI)m/z:** 500(M^+) (21%), 329 (10%), 292 (12%), 250(14%), 211(12%), 184 (10%), 170 (70%), 144 (64%), 119 (80%), 90 (80%), 62 (B)(100%).

Compound II f: 6, 8-dibromo-2-phenyl-3-(2-phenyl ethanoic acid) quinazoline-4-(3H)-one.

Yield -86%;**M.P**152-154 ºc **; IR-(KBr) cm^{-1}** 1688(C=0),1602(C=C),1651(C=N), 876(C-H), 562(C-Br); **^{1}H NMR(CDCl$_3$) δ ppm:** 0.23 (S, 1H; CH_3) 0.26 (S,1H; CH) 7.07(m, 12H;5,7,2',3', 4', 5', 6',4",2'',3'',4'', 5'', 6"-ArH**); MS (EI)m/z:** 515 (M^+) (20%), 342 (14%), 297 (24%), 238 (34%), 207 (90%), 179 (38%), 169 (14%), 129 (22%), 77 (64%), 51(34%), 105 (B) (100%).

RESULTS AND DISCUSSION:

Antimicrobial activity of 2-Phenyl-Quinazolin-4(3H)-Ones derivatives summarized in Table No.2:

Compound no	**Antibacterial Activity**			
	S.aureus (µg/ml)	B.cereus (µg/ml)	M.luteus (µg/ml)	K.pneumoniae (µg/ml)
II $_a$	33	28	26	30
II $_b$	12	16	17	24
II $_c$	34	25	28	29
II $_d$	12	18	21	23
II $_e$	32	30	30	32
II $_f$	14	19	21	21
Ciprofloxacin (std)	28	25	22	25
DMF (control)	-	-	-	-

The results revealed that the test compounds II $_e$, II $_c$ and II $_a$ exhibits remarkable antibacterial activity against *Staphylococcus aureus* (ATCC 6538), *Bacillus cereus (*ATCC1778*), Micrococus luteus (ATCC 8341), Kiebsiella pneumoniae (*ATCC 29665*)* microorganism using Ciprofloxacin as a reference standard.

The MIC (Minimum inhibitory concentration) values were found in the range of *S.aureus* (5-35µg/ml), *B.cereus* (4-29µg/ml), *M.luteus* (4-36µg/ml) and *K.pneumoniae*(5-40µg/ml).

CONCLUSION:

The some 2-phenyl-quinazolin-4(3H)-ones substituted compounds exhibits remarkable antibacterial activity. Hence, the work presented in this paper is yet another humble effort in the field of medicinal chemistry and sincerely contribute to a healthier and happier human life.

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