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Research Article

SYNTHESIS AND PHARMACOLOGICAL EVALUATION OF 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, anti-tubercular, anticancer, anti-parkinsonism, anticonvulsant and anti-viral. In the current research work compounds of 2-phenyl-quinazolin-4(3H)-ones were synthesized by condensing un substituted/substituted anthranillic 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 analgesic, anti-inflammatory activity. All the compounds exhibited significant analgesic and anti-inflammatory activity. (Acetic acid induced writhing reflux model and carrageen an induced paw edema model). The compound V exhibited the highest analgesic and anti-inflammatory activity. Graded dose response was observed for all the compounds. The order of analgesic activity of synthesized compounds was V>IV>I>II>III and that of anti-inflammatory activity was V>II>III>IV>I.
KEY WORDS: Anthranillic acid, Quinazoline, Analgesic, Anti-inflammatory

INTRODUCTION

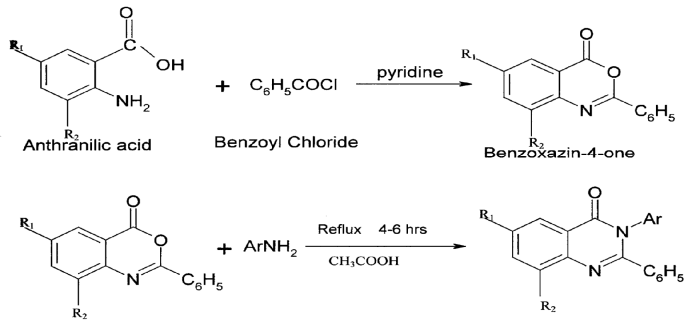
Quinazoline is a bicyclic compound consisting of a pyrimidine system fused at 5, 6 with benzene ring having broad spectrum of medicinal values, Quinazolin-4(3H)-one derivatives were reported to posses analgesic[1],antiinflammatory[1], Antimicrobial [2,3] antiallergic[4], antihypertensive[5], hypoglycemic [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 synthesized 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 aluminum 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,1H-NMR Were recorded on Buker av 400 MHZ spectro photometer using CDCl3 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.

General Method Of Synthesis[3,10, 15,16,17]:

Benzoyl Chloride (14.05g ,0.1 mol) was added drop wise to un substituted/ substituted anthranillic acid (13.7g, 0.1 mol),dissolved in pyridine (6ml) with constant stirring at 8°C over the period of 1 hr the excess pyridine distilled off under reduced pressure and cooled to room temperature. The corresponding 2-phenyl-benzoxazin -4-one, so obtained was dried under vacuum. to that aromatic substituted primary amine (0.05 mol) is added 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 sodium bicarbonate solution to remove un reacted acid and then distilled water, filtered and dried in vacuum and recrystalized from rectified spirit. The yield and melting point of synthesized products were depicted in Table-1.



Spectral Data:

Compound I: 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);

1HNMR(CDCl3) 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 II: 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(CDCl3) δ ppm**: 2.7 (t, 4H; 2", 6"- CH2) 3.60 (t, 4H; 3' 5'-CH2) , 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 III: 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(CDCl3) 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 IV: 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-OC), 795(C-H), 554(C-Br); **1H NMR(CDCl3) δ ppm :** 2.7(t, 4H**;** 2", 6"-CH2) 3.6(t, 4H**;** 3", 5",- CH2) 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 V: 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}HNMR(CDCl3) δ ppm:** 0.23 (S, 1H; CH3) 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%).

Pharmacological Evaluation

Swiss albino mice (20-25g) and Wister rats (160-200g) were used for the study. They were acclimatized to normal laboratory conditions for one week under 12 hr lights and dark cycle and given pellet diet and water ad libitum. The tested compounds were administered orally using 5% Tween 80 as suspending agent. The experimental dose was selected between the minimum effective dose and maximal non-lethal dose. All the animal experimentations were performed according to the protocols and recommendations of the institutional Animal Ethics committee.

Anti Inflammatory Activity:

The anti-inflammatory activity was determined by carrageen induced paw edema method in Wister rat[18] of either sex selected by random sampling technique. Animals were kept in IVC'S cage (6 in each cage) and test compounds were administered at two different dose level by oral route (200 and 400 mg/kg) and the standard drug indomethacine (20mg/kg) intraperitoneally, 30min prior to the administration of 0.1 ml/kg carrageenan (1%W/V in water) in the sub-plantar region of the right hind paw. The paw volumes were measured using plethysmograph at 1h, 2h, 3h, 4h, 5h after carrageenan administration. The results were presented in the [Table-II].

Analgesic activity:

The analgesic activity was determined by acetic acid induced writhing response using swiss albino mice[19,20] of either sex selected by random sampling technique. Animals were kept in IVC'S cage (6 in each cage) and tested compounds were administered at two different dose level by oral route (200 and 400mg/kg) and standard drug aspirin (100mg/kg) were given intraperitoneally 30 min prior to the administration of the writhing agent (0.7% V/V acetic acid 10ml/kg) the number of abdominal constrictions (writhing) and stretching with a jerk at the hind limbs was observed for 30min and percentage protection was calculated and presented in the [Table III].

RESULTS

All the compounds were exhibited significant analgesic and anti inflammatory activity. The compound V possessed the highest analgesic and anti inflammatory activity. The results are presented in the tables—II and III.

DISCUSSION

All the compounds exhibited significant analgesic and anti-inflammatory activity. (Acetic acid induced writhing reflux model and carrageen an induced paw edema model). The compound V exhibited the highest analgesic and anti-inflammatory activity with the percentage protection of 42.27 and 43.58. The compound IV has 41.01 percentage protection. The other two compounds II and III have similar anti inflammatory activity only the compound I has less anti inflammatory activity with 36.74%. The analgesic activity when compared the compound II has less analgesic activity with percentage protection 29.61 and the compound V has highest analgesic activity with 42.27%.

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Table 1: Physical data of compounds

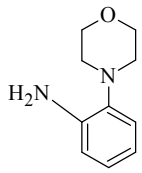
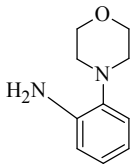
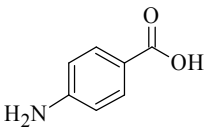
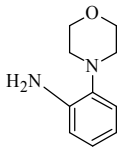
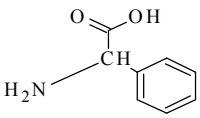
Compound	R_1	R_2	H_2N-Ar	Molecular formula	m.p(0C)	Yeild	Rf value
I	H	H		C24H21N3O2	110-115	62%	0.52
II	Br	Br		C24H19N3Br2O2	165-168	78%	0.67
III	Br	Br		C21H12N2Br2O3	236-240	71%	0.72
IV	Br	H		C24H20N3BrO2	132-136	73%	0.69
V	Br	H		C22H14N2Br2O3	152-154	86%	0.68

Table 2: Antiinflametory activity by carrageenan induced paw oedema model in rats (Two dose level)

Groups	Dose mg/kg	lhr	%	2hr	%	3hr	%	4hr	%	51w	%
I	200 400	0.22 ± 0.013 0.20 ± 0.15	15 15	0.29 ± 0.006 0.30 ± 0.008	4.44 6.66	0.27 ± 0.01*** 0.27 ± 0.OlS***	20.58 19.60	0.28 ± 0.009*** 0.26 ± 0.015***	21.29 26.84	0.27 ± 0.009*** 0.24 ± 0.012***	29.05 3674
II	200 400	0.20 ± 0011 0.19 ± 0.018	10 15	0.27 ± 0.009 0.27 ± 0.013	8.88 11.10	0.27 ± 0.014*** 0.25 ± 0.016***	19.60 26.46	0.26 ± 0.008*** 0.24 ± 0.013***	27.77 33.32	0.25 ± 0.009*** 0.22 ± 0.01 1***	35.03 41,87
III	200 400	0.21 ± 0.013 0.20 ± 0.013	11.66 11.66	0.27± 0.006 0.28 ± 0.012	7.77 8.88	0.25 ± 0,037*** 0.25 ± 0.008***	26.46 26.46	0.24 ± 0.01 1*** 0.24 ± 0.007***	31.47 33.32	0.24 ± 0.010*** 0.23 ± 0.008***	3845 41.02
IV	200 400	0.22 ± 0.013 0.22 ± 0.012	11.66 11.66	0.29 ± 0.011 0.27 ± 0.012	7.77 12.21	0.26 ± 0,016*** 0.24 ± 0.014***	22.54 28.42	0.24 ± 0.0l6*** 0.22 ± 0.01 1***	32.40 38.88	0.23 ± 0.014*** 0.23 ± 0.014***	41.01 39.31
V	200 400	0.23±0.016 0.22 ± 0.012	18.33 16.66	0.30±0.014 0.29 ± 0.015	9.99 7.77	0.26±0.017*** 0.23 ± 0,015***	21.56 30.38	O.2S±O.Ol5*** 0.22 ± 0.016***	29.62 37.03	0,24±0.012*** 0.22± 0.014 ***	38.45 43.58
Control		**0.20** ± 0.013		0.30 ± 0.005		0.34 ± 0.005		0.36 ± 0.014		0.39 ± 0012	
Standard	20	**0.19*0.008**	8.33	0.28±0.015	11.10	0.18±0.008***	47.05	0.16±0.005***	*55.55*	**0.10±0.008****	74.35

Compound with carrageenan control (100% Oedema) , All the values are Mean & SEM values using 6 animals in each group. Significant differences with respect to control group was evaluated by student 't' test*P< O.05, **p<0.01, ***p< 0.001 NS Non significant

Table 3: Analgesic activity by acetic acid induced writhing reflux model in mice

Groups	Dose (mg/kg)	Mean ± SEM	% of Protection
1	200 400	29.66±0,954 ** 23.66±1.201***	16.02 32.83
2	200 400	30.66±1.358 24.83±0.945***	13.19 29.61
3	200 400	30.66± 1.763 24.66 ± 0.802***	13.82 30.09
4	200 400	23.5 ± 0.885t** 22±0.577***	33.47 *37.55*
5	200 400	24.66±1.429*** 20.33 ± 0.557***	30.17 42.27
Control		35.33 ± 1.801 35.33 ± 1.801	
Standard	100	6.5±0.662***	81.60

All the values are Mean ± SEM values using 6 animals in each group
significant differences with respect to control group was evaluated by student 't' test
P<0.*05,* **p<0.01, ***P< 0.001

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