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SYNTHESIS AND BIOLOGICAL EVOLUTION OF PHENYL- QUINAZOLINONE DERIVATIVES

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ABSTRACT

The present work of quinazolinone derivatives were synthesized by treating 2-Chloro-N-(4-oxo-2 phenylquinazolin-3(4H)- (I-1)yl) acetamide with the different substituted phenols in presence of different catalyst like anhydrous potassium carbonate & catalytic amount of potassium iodide in dry acetone. The synthesized compounds have been established on the basis of their m.p., TLC, IR and NMR data. All the newly synthesized quinazolinone derivatives were evaluated for their antibacterial activity by cup plate method by measuring inhibition zone. Gentmycin was used as standard drug. The compound Q-2 showed more potent antibacterial activity than the standard drug Getamycin.

KEYWORDS

Antibacterial activity, Anti-inflammatory, Infra red and Thin layer chromatography.

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INTRODUCTION

Quinazolinones and their derivatives constitute an important class of heterocyclic 1, compounds. Many of them show insecticidal 2 3 4 analgesic, antifungal, antibacterial, anticancer activities[1]. Quinazolinone nucleus is found in many bioactive natural products. So, because of these reasons much attention is being paid for the synthesis of quinazolinone derivatives. Looking at the biological significance of quinazolinone nucleus it was thought to design and synthesize new quinazolinone derivatives and screen them for their antibacterial and anti-inflammatory activity[2].

MATERIALS AND METHODS

MATERIALS

Anthralic acid, benzoyl chloride, chloroacetyl chloride, potassium caronate, potassiumiodide, 98 % - 101 %, was purchased from BIOCON Limited, India. FTIR paragon 1 H NMR 500 (Perkin Elmer) instrument**,** Spectrophotometer Shimadzu 160-A UV-VIS Spectrophotometer, Shimadzu, Tokyo, Japan.

METHODS

Synthesis of quinazolinone derivatives involved following steps

In the first step anthranilic acid was treated with benzoyl chloride to give 2-phenyl-4H- 6 benzo[d] [1, 3]oxazin-4-one. In the next step 2-phenyl-4H-benzo[d][1, 3]oxazin- 4-one was reacted with hydrazine hydrate to give 3-amino-2-phenyl-quinazolin-4(3H)-one which was further reacted with chloroacetyl chloride to give 2-chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl) acetamide (I-1). Compound (I-1) was then reacted with different substituted phenols in the presence ofanhydrous potassium carbonate and catalytic amount of potassium iodide in dry acetone to yield quinazolinone derivatives (Q-1, to Q-7) was shown in Figure No.1. The melting points of newly synthesized compounds were determined with an electro thermal melting point apparatus and are uncorrected. Thehomogeneity of all newly synthesized compounds was checked by TLC on silica gel-G coated plates using chloroform: ethylacetate (1:1) solvent system. IR spectra (KBr pellet) were recorded on FTIR paragon 1 H NMR 500 (Perkin Elmer) instrument. spectra were recorded on JEOL, GSX- 400 FT NMR instrument at 400 MHz in and chemical shifts (CDCl) are 3reported in ppm relative to tetramethylsilane as an internal standard [3, 4].

Synthesis of quinazolinone derivatives [Q-1 - Q-7]

General procedure

A mixture of **I-1** (0.01 mol), N,Ndimethyl formamide (10-15 ml), the appropriate phenol (0.01 mol), anhydrous potassium carbonate (0.01mol) and catalytic amount of potassium iodide were refluxed with stirring on water bath for 10-15 hrs. The resulting mixture was transferred to the beaker and water was added to it. The separated solid was filtered, washed with water and recrystallized from acetone to give compounds **[Q-1 - Q-7].**

N-(4-oxo-2-phenylquinazolin-3(4H)-yl)-2-phenoxyacetamide (Q-1)

IR (KBr) cm-1: 3250.4(N-H), 3067.1(CHaromatic), 2933(C-H str in CH2),1690.6(C=O), 16141.1(ring C=C), 1585(C=N),1260.3(C-N), 1165.7(C-O-C), 1074.9(N-N).1H-NMR (400 MHz, CDCl3) _ (ppm): 8.30(s, 1H, NH); 7.04-7.94(m, 12H, Ar- H); 3.54(s, 2H, CH2).

2-(4-nitrophenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl) acetamide (Q-2)

IR (KBr) cm-1: 3199.8(N-H), 3065.1(CH aromatic), 2931.7(C-H str in CH2), 1689.9(C=O), 1586.2(ring C=C), 1511.5(C=N), 1537.9(NO2 asym.str),1300 (NO2 sym. str**),** 1258.4(C-N), 1165(C-O-C), 1026.5(N-N). 1H-NMR (400 MHz, CDCl3) _(ppm): 7.51(s, 1H, NH); 5.64-6.94(m, 13H, Ar- H); 3.51(s, 2H, CH2).

2-(4-chlorophenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (Q-3)

IR (KBr) cm-1: 3201.1(N-H), 3066.3(CH aromatic), 2922.6(C-H str in CH2),1690(C=O), 1541.6(ring C=C), 1613.7(C=N), 1259.7(C-N), 1165.0(CO-C),1051.7(N-N), 533(C-Cl). 1H-NMR (400 MHz, CDCl3) _ (ppm): 7.60(s, 1H, NH); 5.90-6.81(m, 13H, Ar- H); 3.56(s, 2H, CH2).

2-(2,6-dichlorophenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide (Q-4)

IR (KBr) cm-1: 3248.5(N-H), 3065.3(aromatic C-H), 2930.2(C-H str in CH2), 1690.7(C=O), 1584.1(ring C=C), 1613.4(C=N), 1259.8(C-N), 1164.7(C-OC), 1074.3(N-N), 532.3(C-Cl). 1H-NMR (400 MHz, CDCl3) _ (ppm): 8.83(s, 1H, NH); 7.02-7.94(m, 12H, Ar- H); 4.68(s, 2H, CH2)

Methyl-2-((4-oxo-2-phenylquinazolin-3(4H)-ylcarbamoyl)methoxy)benzoate (Q-5)

IR (KBr) cm-1: 3221(N-H), 3021(C-H aromatic), 2926.1(C-H str in CH2), 1680.8(C=O), 1541.3(ring

C=C), 1580.5(C=N), 1216.2(C-N), 1141.3(CO-C),1026.9(N-N). 1H-NMR (400 MHz, CDCl3) _ (ppm): 8.0(s, 1H, NH); 6.24-7.96(m, 13H, Ar- H); 3.66(s, 2H, CH2); 3.90(s, 3H, CH3).

2-(4-chloro-3-methylphenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)- yl)acetamide (Q-6)

IR (KBr) cm-1: 3066.3(C-H aromatic), 248(N-H), 2933.2(C-H str in CH2), 1690.8(C=O), 1541.8(ring C=C), 1613.9(C=N), 1259.5(C-N), 1165.1(CO-C), 1026.1(N-N), 533.4(C-Cl). 1H-NMR (400 MHz, CDCl3) _ (ppm): 7.65(s, 1H, NH); 5.86-6.78(m, 12H, Ar- H); 3.52(s, 2H, CH2); 1.79(s, 3H, CH3).

2-(4-allyl-2-methoxyphenoxy)-N-(4-oxo-2-phenylquinazolin-3(4H)-yl) acetamide (Q-7)

IR (KBr) cm-1): 3216.5(N-H), 3020.1(CH aromatic), 2926.5(C-H str in CH2), 1726.5(C=O), 1603.9(ring C=C), 1652.9(C=N), 1215.8(C-N), 1144.5(CO-C), 928.7(N-N). 1H-NMR (400 MHz, CDCl3) _ (ppm): 8.79(s, 1H, NH); 7.05-7.96(m, 12H, Ar- H); 4.71-4.73(d, 2H, CH2* of CH2*-CH=CH2).

Pharmacological Studies [5, 6]

Anti-bacterial Screening

The bacterial screening is based upon a comparison of the inhibition of growth of bacteria by measured concentrations of the compound to be examined with that of activity produced by known concentration of a standard drug.

List of compounds subjected for anti-bacterial Studies

Nutrient Agar / Sabourd Dextrose Broth, Petri dishes, Sterile Pipettes, Test Compounds, Standard Drug: Gentamycin, Solvent (control): DMSO

Cylinder-Plate or Cup Plate Method

Cup plate method is based on the diffusion of compound from a vertical cylinder or a cavity through the solidified agar layer of a petri dish or plate to an extent such that growth of the added bacteria is prevented entirely in a circular area or "zone" around the cylinder or cavity containing a solution of the compound. The compounds were tested at the concentration of 100 µg/well against three Gram-negative bacterias.

Procedure

Sterile nutrient agar plates were prepared, by pouring the sterile agar into petri dishes in aseptic conditions. One ml of standardized test organism culture was spread on to agar plates. Cavity was done by using a sterile borer of diameter 6 mm. The test compounds as well as the standard drug solutions and DMSO solvent control was placed in a cavity. Then the plates were maintained at +4^{o}C for 1 h to allow the diffusion of solution into the medium. All the bacterial plates were incubated at 37^{o} C for 24 hrs and fungal plates were incubated at 28^{o}C for 48 hrs. The zone of inhibition was measured in mm

Anti-Inflammatory Screening[7]

Healthy adult albino rates of Wistar strain weighing 150-200 g were selected. The animal house was well ventilated and animals had 12 to 1 hour day and night schedule with temperature between 20-30^{o}C. The animals were housed in large spacious hygienic cages during the course of the experimental period. The animals were fed with rat pellet feed supplied by M/s Hindustan Lever Ltd., Bangalore, India and water adlibidum.

Test Compounds

Compound (Q - 1 to Q - 7) 75 mg/kg, 150 mg/kg, b. wt., indomethacin (10mg/kg) were suspended in 0.5 % w/v dispersion of CMC in distilled water.

Carrageenan induced Hind Paw Edema in Rats

This is acute model for screening anti-inflammatory drugs. Albino Wistar rats were divided into five groups of six each. They were starved overnight with water *ad libitum* prior to the day of experiment. Acute inflammation was induced by injecting 0.05 mL of 1 % suspension of carrageenan in0.5%w/v dispersion of CMC in distilled water into sub-planter region of the left hind paw as per the techniques. A mark was applied on the leg at the malleolus to facilitate subsequent readings. The paw edema volume was measured by mercury displacement with the help of a plethysmograph before as well as

1, 3 and 6 h after carrageenan injection. The animals were treated with compound (Q - 1, Q - 3, Q - 7) 75 mg/kg, 150mg/kg, 0.5% CMC (3 ml/kg, p.o.) treated animals were served as control and indomethacin (10 mg/kg, p.o.) was treated as standard. Mean increase in paw volume was measured. The percentage inhibition of edema in various groups was calculated using the formula:

$$\% \text{ Paw edema inhibition} = 1 - \frac{\text{Edema volume in drug treated group}}{\text{Edema volume in control group}} \times 100$$

RESULTS AND DISCUSSION

Anti-bacterial activity was performed by cup plate method by using gram-positive and gram-negative organisms, the synthesized compound 1 to 7 have good anti-bacterial activity against gram-negative organisms when compared with Gentamycin as standard (Table No.1). Anti-inflammatory study was performed by carrageenan induced paw edema method; the synthesized compound 1, 3 and 7 have good anti-inflammatory activity when compared with Indomethacin as standard (Table No.2). Quinazolinone derivatives Q - 1 to Q - 2 were synthesized. TLC confirmed the purity of the title compounds. The structures of the newly synthesized compounds obtained have been confirmed on the basis of spectral (FTIR and 1H NMR) data. From the antibacterial activity data, it was found that the synthesized compounds exhibited mild to good antibacterial activity *E. coli* (gram-negative) at a concentration of 100µg/ml.

Table No.1: Anti-bacterial activity of synthesized phenyl-quinazolinone

S.No	Microorganisms Used	Conc in µg	Zone of inhibition in mm						
			Compounds						
			1	2	3	4	5	6	7
1	*Eischerchia coli*	500	09.3	07.6	06.5	05.1	05.0	06.1	06.3
		250	07.2	06.3	05.4	04.5	04.0	05.0	05.3
		125	06.0	05.8	05.0	03.9	03.9	04.5	05.6
2	Gentamycin	-	17.6					18.2	
3	*Proteus Vulgaris*	500	12.4	12.6	12.0	09.0	11.9	08.9	12.7
		250	08.3	08.4	08.0	06.8	08.2	06.3	08.6
		125	04.6	04.6	04.4	03.5	04.5	03.9	04.7
4	Gentamycin	-	19.0					18.8	
5	*Pseudomonas aeruginosa*	500	13.0	12.8	11.0	11.4	9.6	10.	09.0
		250	09.2	08.6	07.8	08.0	07.0	07.4	06.8
		125	05.1	04.8	04.0	04.4	03.9	04.0	03.5
6	Gentamycin	-	19.8					19.3	

Table No.2: Anti-Inflammatory effect of methanol extract of phenyl-quinazolinone

S.No	Treatment	Dose (mg/kg)	Mean increase in rat paw edema (ml)						
			0.5h	1h	2h	3h	4h	5h	6h
I	Control	3 ml	0.57±0.02	0.62±0.03	0.69±0.02	0.78±0.02	0.76±0.03	0.72±0.06	0.68±0.04
II	Q - 1	75	0.50±0.03	0.52±0.04	0.64±0.02	0.68±0.02	0.66±0.03	0.64±0.01	0.62±0.06
		150	0.49±0.04	0.54±0.05	0.60±0.03	0.64±0.01	0.62±0.05	0.61±0.02	0.59±0.09
III	Q - 3	75	0.47±0.01	0.50±0.01	0.54±0.01	0.57±0.02	0.59±0.01	0.57±0.02	0.55±0.01
		150	0.40±0.02	0.44±0.02	0.48±0.02	0.52±0.01	0.54±0.02	0.52±0.01	0.46±0.02
IV	Q - 7	75	0.39±0.03	0.41±0.02	0.40±0.01	0.40±0.08	0.43±0.06	0.45±0.05	0.47±0.06
		150	0.36±0.02	0.38±0.04	0.37±0.02	0.34±0.06	0.37±0.05	0.40±0.06	0.42±0.05
V	Indomethacin	10	0.28±0.03	0.26±0.05	0.30±0.03	0.22±0.04	0.28±0.03	0.20±0.04	0.22±0.02

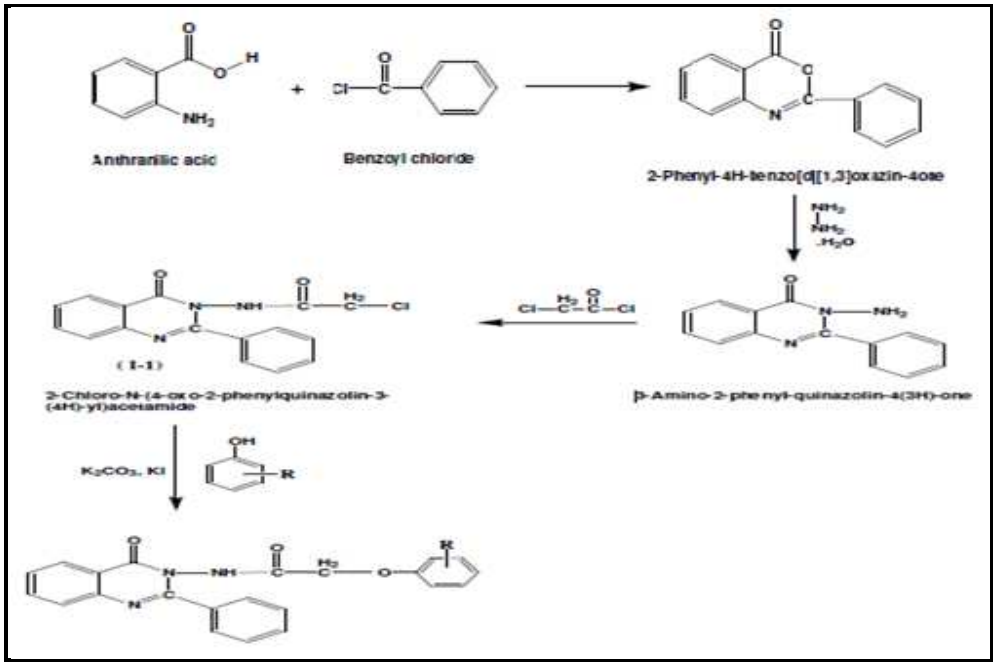

Figure No.1: Scheme of phenyl-quinazolinone

CONCLUSION

In summary an eco benign synthesis of various phenyl- quinazolinone were prepared using water as the reaction medium. Regarding Anti-bacterial activity the synthesised compound is having activity against gram negative organisms. Regarding Anti-inflammatory activity the synthesized compound 1, 3 and 7 is having good activity.

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