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Research Article

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF QUINAZOLINONE DERIVATIVES

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ABSTRACT

In the present work the desired quinazolinone derivatives (DK-1, DK-2, DK-3, DK-4, DK-5, DK-6 & DK-7) were synthesized by treating 2-Chloro-N-(4-oxo-2-phenylquinazolin-3(4H)-yl)acetamide **(I-1)** with the different substituted phenols in presence of anhydrous potassium carbonate & catalytic amount of potassium iodide in dry acetone. The structures of the newly synthesized compounds have been established on the basis of their m.p., TLC, IR and ^{1}H-NMR data. All the newly synthesized quinazolinone derivatives were evaluated for their antibacterial activity by cup plate method by measuring inhibition zone. Ampicillin was used as standard drug. The compound DK-2 showed more potent antibacterial activity than the standard drug ampicillin.

Key words: Quinazolinone derivatives, Antibacterial activity.

INTRODUCTION

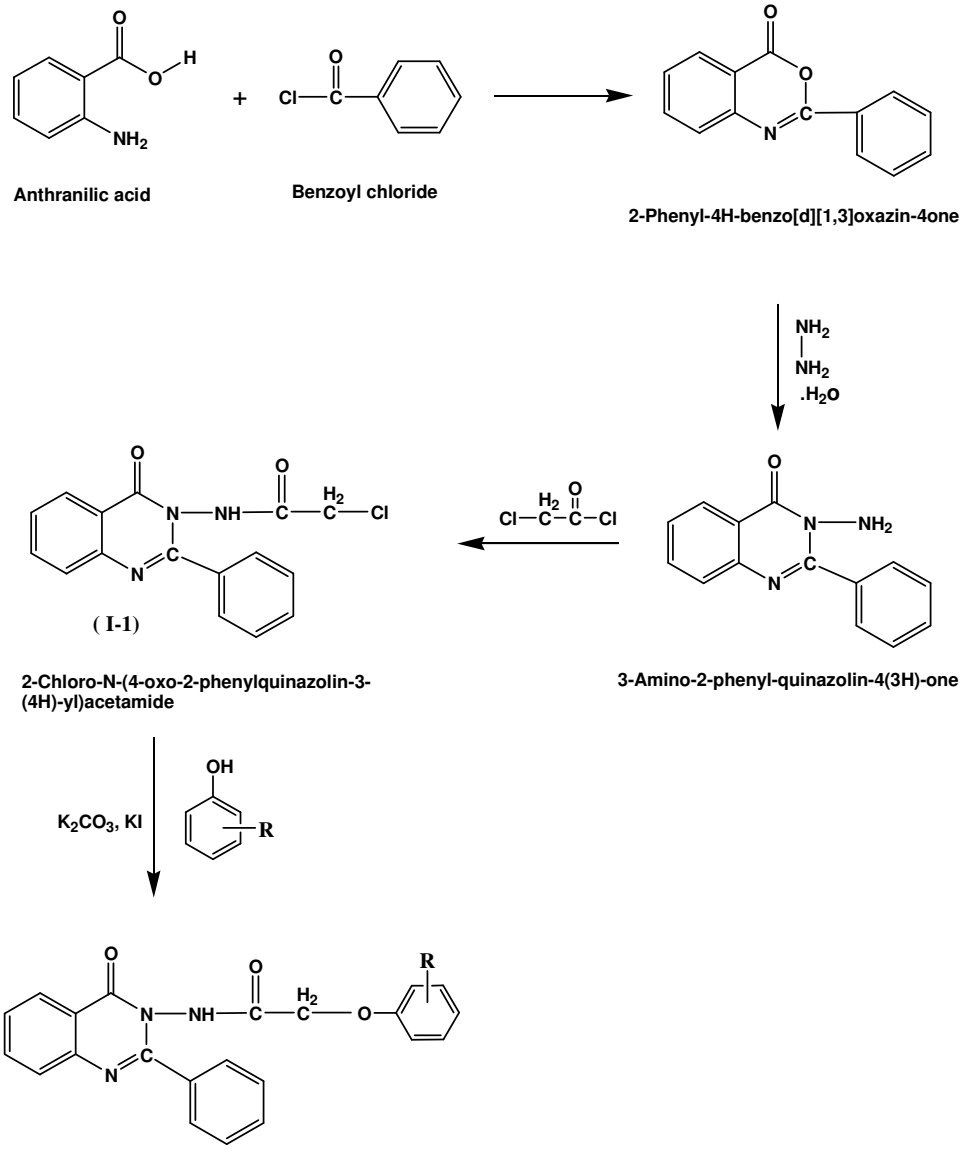
Quinazolinones and their derivatives constitute an important class of heterocyclic compounds. Many of them show insecticidal[1], analgesic[2], antifungal[3], antibacterial[4], anticancer[5], anti-inflammatory[5] activities. Quinazolinone nucleus is found in many bioactive natural products. So, because 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 activity.

MATERIALS AND METHODS

Synthesis of quinazolinone derivatives involved following steps: In the first step anthranilic acid was treated with benzoyl chloride to give 2-phenyl-4H-benzo[d] [1,3]oxazin-4-one[6]. 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 of

anhydrous potassium carbonate and catalytic amount of potassium iodide in dry acetone to yield quinazolinone derivatives (DK-1, DK-2, DK-3, DK-4, DK-5, DK-6 & DK-7). The melting points of newly synthesized compounds were determined with an electro thermal melting point apparatus and are uncorrected. The homogeneity 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 500 (Perkin Elmer) instrument. ^{1}H NMR spectra were recorded on JEOL, GSX-400 FT NMR instrument at 400 MHz in $CDCl_3$ and chemical shifts (δ) are reported in ppm relative to tetramethylsilane as an internal standard.

SCHEME:



Synthesis of quinazolinone derivatives [(DK-1) - (DK-7)]

General procedure

A mixture of **I-1** (0.01 mol), N,N-dimethylformamide (10-15 ml), the appropriate phenol (0.01 mol), anhydrous potassium carbonate (0.01 mol) 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 **[(DK-1) - (DK-7)].**

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

IR (KBr) cm^{-1} : 3250.4(N-H), 3067.1(C-H aromatic), 2933(C-H str in CH_2), 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).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.30(s, 1H, NH); 7.04-7.94(m, 12H, Ar-H); 3.54(s, 2H, CH_2).

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

IR (KBr) cm^{-1} : 3199.8(N-H), 3065.1(C-H aromatic), 2931.7(C-H str in CH_2), 1689.9(C=O), 1586.2(ring C=C), 1511.5(C=N), 1537.9(NO_2 asym.str), 1300(NO_2 sym. str**),** 1258.4(C-N), 1165(C-O-C), 1026.5(N-N).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.51(s, 1H, NH); 5.64-6.94(m, 13H, Ar-H); 3.51(s, 2H, CH_2).

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

IR (KBr) cm^{-1}: 3201.1(N-H), 3066.3(C-H aromatic), 2922.6(C-H str in CH_2), 1690(C=O), 1541.6(ring C=C), 1613.7(C=N), 1259.7(C-N), 1165.0(C-O-C),1051.7(N-N), 533(C-Cl).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.60(s, 1H, NH); 5.90-6.81(m, 13H, Ar-H); 3.56(s, 2H, CH_2).

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

IR (KBr) cm^{-1}: 3248.5(N-H), 3065.3(aromatic C-H), 2930.2(C-H str in CH_2), 1690.7(C=O), 1584.1(ring C=C), 1613.4(C=N), 1259.8(C-N), 1164.7(C-O-C), 1074.3(N-N), 532.3(C-Cl).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.83(s, 1H, NH); 7.02-7.94(m, 12H, Ar-H); 4.68(s, 2H, CH_2) .

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

IR (KBr) cm^{-1} : 3221(N-H), 3021(C-H aromatic), 2926.1(C-H str in CH_2), 1680.8(C=O), 1541.3(ring C=C), 1580.5(C=N), 1216.2(C-N), 1141.3(C-O-C),1026.9(N-N).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.0(s, 1H, NH); 6.24-7.96(m, 13H, Ar-H); 3.66(s, 2H, CH_2); 3.90(s, 3H, CH_3).

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

IR (KBr) cm^{-1}: 3066.3(C-H aromatic), 248(N-H), 2933.2(C-H str in CH_2), 1690.8(C=O), 1541.8(ring C=C), 1613.9(C=N), 1259.5(C-N), 1165.1(C-O-C), 1026.1(N-N), 533.4(C-Cl).

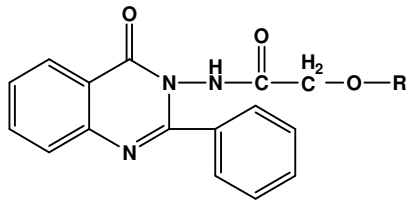
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 7.65(s, 1H, NH); 5.86-6.78(m, 12H, Ar-H); 3.52(s, 2H, CH_2); 1.79(s, 3H, CH_3).

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

IR (KBr) cm^{-1}): 3216.5(N-H), 3020.1(C-H aromatic), 2926.5(C-H str in CH_2), 1726.5(C=O), 1603.9(ring C=C), 1652.9(C=N), 1215.8(C-N), 1144.5(C-O-C), 928.7(N-N).

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm): 8.79(s, 1H, NH); 7.05-7.96(m, 12H, Ar-H); 4.71-4.73(d, 2H, CH_2^* of CH_2^*-$CH{=}CH_2$).

Table 1. Physical constants of different quinazolinone derivatives



Compound code	R	M. P. (°C)	Yield (%)	Mol. formula	R_f value
DK-1	C_6H_5	257-258	43.71	$C_{22}H_{17}O_3N_3$	0.80
DK-2	4-NO_2.C_6H_4	260-261	31.63	$C_{22}H_{16}O_5N_4$	0.72
DK-3	4-Cl.C_6H_4	259-260	27.5	$C_{22}H_{16}O_3N_3Cl$	0.69
DK-4	2,6-Cl.C_6H_3	262-263	32.55	$C_{22}H_{15}O_3N_2Cl_2$	0.64
DK-5	2-$COOCH_3$.C_6H_4	250-251	42.85	$C_{24}H_{19}O_5N_3$	0.66
DK-6	4-Cl.3-CH_3.C_6H_3	258-259	38.64	$C_{23}H_{18}O_3N_3Cl$	0.73
DK-7	2-OCH_3.4-CH_2.$CH{=}CH_2$.C_6H_3	263-264	41.86	$C_{26}H_{23}O_4N_3$	0.65

Antibacterial activity[1,4,7,8]

Antibacterial activity was performed by cup plate method by measuring zone of inhibition. All the test compounds were screened for antibacterial activity against bacterial strains *Staphylococcus aureus* (209p) and *Escherichia coli* (ESS 2231) at a concentration of 100 µg/ml. Ampicillin was used as standard drug at a concentration of 100 µg/ml, Nutrient agar was used as culture medium & DMF was used as solvent control.

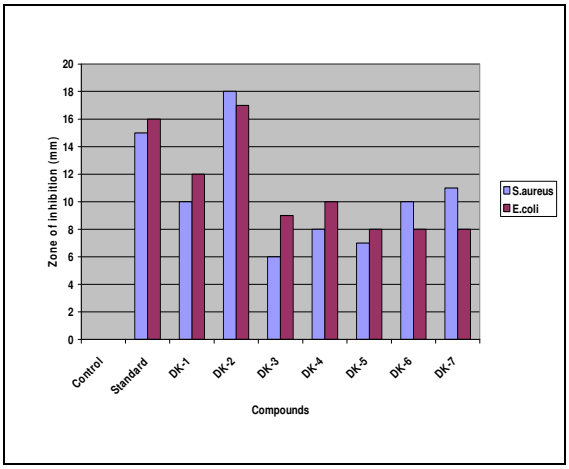
Laminar airflow bench was swapped with 70 % alcohol and UV lamp was switched on. After 30 min, the UV lamp was switched off. All the reagents, media, inoculums and glassware were placed in laminar airflow bench observing all aseptic conditions.

The plates were inoculated within minutes of the preparation of suspension, so that the density does not change. A sterile cotton swab over was dipped into the suspension and the medium was inoculated by even streaking of the swab over the entire surface of the plate in three directions. After the inoculums had dried, cups of diameter 6mm were made in the agar plate with a sterile cork borer. The drugs solutions were added to these cups with a micropipette and the plates were then incubated at 37 ^{0}C for 24 hours. The zone of inhibition was measured using mm scale.

Table 2 : Antibacterial activity data of synthesized compounds

Compound code	Zone of inhibition (mm)	
	S. aureus **(209p)**	***E. coli*** **(ESS 2231)**
DK-1	10	12
DK-2	18	17
DK-3	6	9
DK-4	8	10
DK-5	7	6
DK-6	10	13
DK-7	11	8
Control	-	-
Standard	15	16

Fig 1. Antibacterial activity of synthesized compounds



RESULTS AND DISCUSSION

Quinazolinone derivatives [(DK-1) - (DK-7)] 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 ^{1}H NMR) data. From the antibacterial activity data, it was found that the synthesized compounds exhibited mild to good antibacterial activity against *S. aureus* (gram-positive) and *E. coli* (gram-negative) at a concentration of 100µg/ml.

The compound DK-2 showed maximum zone of inhibition (18 mm) against *S. aureus* as well as against *E. coli* (17 mm) which is higher than the standard drug Ampicillin. The standard drug (Ampicillin) gave 15 mm zone of inhibition against *S. aureus* (209p) and 16mm zone of inhibition against *E. coli* (ESS 2231) respectively. The present study reveals that some quinazolinone derivatives could be used as a template for the future development through modification or derivatization to design more potent therapeutic agents.

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