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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 (A-1, A-2, A-3, A-4, A-5) were synthesized by treating various 3-(substituted benzylidene amino)-2-phenyl quinazolin-4-(3H)one (I-1) with chloroacetyl chloride in presence of triethylamine and 1,4 dioxan.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 disc diffusion method by measuring inhibition zone. Ceftazidime was used as standard drug. The compound A-2 showed more potent antibacterial activity than the standard drug Ceftazidime.

Keywords: Quinazolinone derivatives, Antibacterial activity.

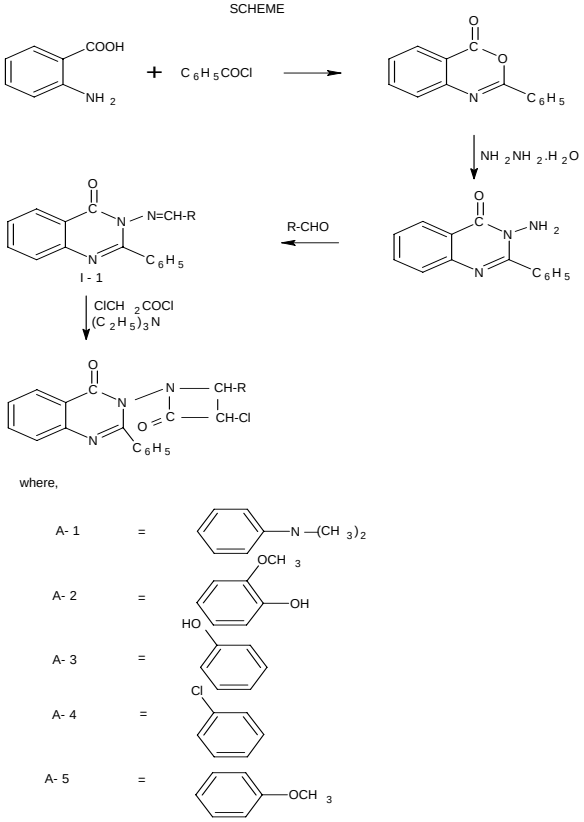
INTRODUCTION

Quinazolinones and their derivatives constitute an important class of heterocyclic compounds. Many of them show antibacterial[1], antifungal[2], anticancer[3], anti-inflammatory[4], antihypertensive[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-3,1 benzoxazin-4(3H) one. In the next step 2-phenyl-3, 1-benzoxazin-4(3H)one[6] was reacted with hydrazine hydrate to give 3-amino-2-phenyl-quinazolin-4(3H)one which was further reacted with different substituted benzaldehydes to give 3-(substituted benzylidene amino)-2-phenyl-quinazolin-4(3H)one. Schiff bases was then reacted with chloroacetylchloride in the presence of triethylamine and 1, 4 dioxan to yield quinazolinone derivatives (A-1, A-2, A-3, A-4, A-5). The melting points of newly synthesized compounds were determined with an electrothermal melting point apparatus and are uncorrected. The homogeneity of all newly synthesized compounds was checked by TLC on silica gel coated plate using methanol: chloroform: water (9:1:1) solvent system. IR spectra (KBr pellet) were recorded on Perkin-Elmer FTIR instrument. ^{1}HNMR spectra were recorded on Brucker 300 MHz FTNMR instrument at 300MHz in $CDCl_3$ and chemical shifts (δ) are reported in ppm relative to tetramethylsilane as an internal standard.

SCHEME



Scheme: Synthesis of quinazolinone derivatives [(A-1) – (A-5)]

General procedure

A mixture of Schiff bases of quinazolinone I-1 (0.01mol), 1,4 dioxan (50ml), chloroacetylchloride (0.01mol) and triethylamine (0.01mol) were refluxed on water bath for 8 hrs. The resulting mixture was transferred to the beaker and ice cold water was added to it. The separated solid was filtered, washed with water and recrystallized from ethanol to give compounds [(A-1) – (A-5)].

3-[3'-chloro-4'(p-N, N dimethyl amino phenyl)-2'-oxo-azetidin]-2-phenyl quinazolin-4-(3H) one (A-1)

IR (KBr) cm^{-1} : 2923.72 (C-H aromatic), 1670.98 (C=O str in amides), 1594.64 (C=N), 1742.88(C=O str in β-lactam), 762.38 (C-Cl str), 1333.23 (C-N str), 2854.89 (C-H str in CH_3)

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 7.39-7.77 (m, 9H, Ar-H); 5.08 (d, 1H, CH-Cl); 6.40 (d, 1H, CH-Ar); 3.04 (s, 6H, $N(CH_3)_2$)

3-[3'-chloro-4'(p-hydroxy, m-methoxy phenyl)-2'-oxo-azetidin]-2-phenyl quinazolin-4-(3H) one (A-2)

IR (KBr) cm^{-1} : 3056.15(C-H aromatic), 1651.02 (C=O str in amides), 1599.96 (C=N), 1740.26(C=O str in β-lactam), 752.62 (C-Cl str), 1353.10 (C-N str), 1065.89 (C-O-C), 3279.25 (OH str)

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm):

7.08-7.85 (m, 8H, Ar-H); 4.8 (d, 1H, CH-Cl); 6.6 (d, 1H, CH-Ar); 3.5 (s, CH, OCH_3), 11.8 (s, 1H, OH)

3-[3'-chloro-4'(o-hydroxyphenyl)-2'-oxo-azetidin]-2-phenyl quinazolin-4-(3H) one (A-3)

IR (KBr) cm^{-1}: 3056.03(C-H aromatic), 1651.51 (C=O str in amides), 1608.50 (C=N), 1752.00(C=O str in β-lactam), 759.69 (C-Cl str), 1320.85 (C-N str), 3690.57 (OH str)

^{1}H-NMR (300 MHz, CDCl3) δ (ppm):

7.2-7.8 (m, 9H, Ar-H); 4.8 (d, 1H, CH-Cl); 6.2 (d, 1H, CH-Ar); 10.9 (s, 1H, OH)

3-[3'-chloro-4'(o-chloro phenyl)-2'-oxo-azetidin]-2-phenyl quinazolin-4-(3H) one (A-4)

IR (KBr) cm^{-1}: 3062.88(C-H aromatic), 1654.43 (C=O str in amides), 1604.79 (C=N), 1755.70(C=O str in β-lactam), 761.54(C-Cl str), 1322.58 (C-N str), 706.20 (ring,C-Cl str)

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm):

7.2-7.8 (m, 9H, Ar-H); 4.8 (d, 1H, CH-Cl); 6.7 (d, 1H, CH-Ar); 4.6 (s, 1H, Cl)

3-[3'-chloro-4'(p-methoxyphenyl)-2'-oxo-azetidin]-2-phenyl quinazolin-4-(3H) one (A-5)

IR (KBr) cm^{-1}: 3072.33(C-H aromatic), 1681.90 (C=O str in amides), 1605.53 (C=N), 1736.23(C=O str in β-lactam), 762.13(C-Cl str), 1331.09 (C-N str), 1030.75 (C-O-C str)

^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm):

7.6-7.8 (m, 9H, Ar-H); 4.5 (d, 1H, CH-Cl); 6.9 (d, 1H, CH-Ar); 3.8 (s, 3H, OCH_3)

Table 1: Physical constants data of synthesized compounds

Compound Code	R	M.P.(^{0}C)	Yield (%)	Mol. formula	Rf value
A-1	4-N,N-$(CH_3)_2$.C_6H_4	125	97.03	$C_{25}H_{21}O_2N_4Cl$	0.80
A-2	4-OH,3-OCH_3.C_6H_4	180	98.65	$C_{24}H_{18}O_4N_3Cl$	0.77
A-3	2-OH.C_6H_4	157	97.12	$C_{23}H_6O_3N_3Cl$	0.84
A-4	2-Cl.C_6H_4	130	80.45	$C_{24}H_{18}O_3N_3Cl$	0.89
A-5	4-OCH_3.C_6H_4	120	57.77	$C_{23}H_{15}O_2N_3Cl_2$	0.85

Table 2: Zone of inhibition (mm) data of synthesized compounds

Compound Code	Zone of Inhibition (mm)	
	S.aureus	*S.flexneri*
A-1	10	07
A-2	07	12
A-3	11	09
A-4	08	07
A-5	12	08
Control	-	-
Standard	15	07

Antibacterial activity[7, 8, 9]

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* and *Salmonella flexneri* at a concentration of

100 µg /ml. Ceftazidime was used as standard drug at a concentration of 100 µg/ml. Nutrient agar was used as culture medium and chloroform was used as solvent control.

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

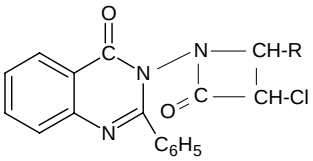
The plates were inoculated within minutes of the preparation of suspension, so that the density does not change. A sterile cotton swab over was dipped into the suspension and the medium was inoculated by even streaking of the swab over the entire surface of the plate in three directions. After the inoculums 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 zones of inhibition were measured using mm scale.

RESULTS AND DISCUSSION

Quinazolinone derivatives [(A-1) – (A-5)] 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}HNMR) 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 *S.flexneri* (gram-negative) at a concentration of 100 µg /ml.

The compound A-2 showed maximum zone of inhibition (12mm) against *S.flexneri* and compound A-5 showed a proportionate zone of inhibition against *S.aureus*. The standard drug (Ceftazidime) gave 15mm zone of inhibition against *S.aureus* and 7mm zone of

inhibition against *S.flexneri* 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



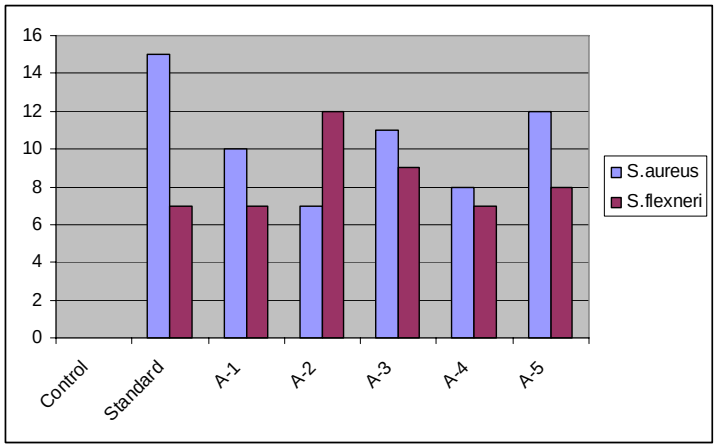


Fig. 1: Antibacterial activity (Gram-positive) of synthesized compounds

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