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Evaluation of Antibacterial Activity of Novel Quinazoline Derivatives

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In the present study, a series of novel quinazoline derivatives were synthesized by condensation with different aromatic amines *via* cyclized intermediate 2-phenyl-1,3-benzoxazin-4-one. The chemical structures were confirmed by means of IR and ^{1}H NMR. These compounds were screened for antibacterial (*Staphylococcus aureus* ATCC-9144, *Escherichia coli* ATCC-25922, activities by paper disc diffusion technique. The potency of antibiotic content in samples can be determined by chemical, physical or biological means. An assay is made to determine the ability of an antibiotic to kill or inhibit the growth of living microorganism. The inhibition of microbial growth under standardized conditions may be utilized for demonstrating the therapeutic efficacy of drugs. Microorganism employed in biological assay are of various types-bacteria for amino acid, antibiotics, fungi for vitamins, trace elements, antibiotics and fungicidal and fungi static materials. The synthesized compounds were evaluated for antibacterial activity. Some of these synthesized compounds shown significant antibacterial activity.

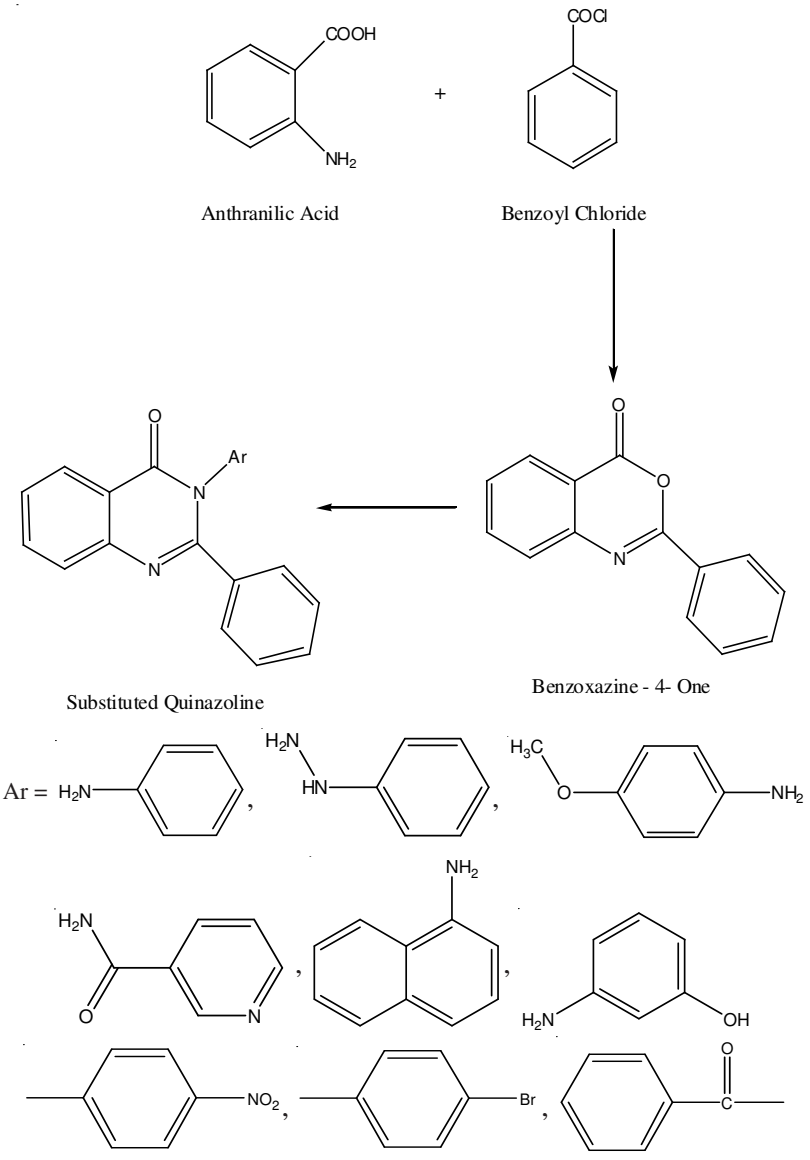
Key Words: Quinazoline, Antibacterial.

INTRODUCTION

The search of new antimicrobial agents with reduced toxicity and lower side effects is of continuous process. One of the most frequently encountered heterocyclic in medicinal chemistry is quinazolin-4(3*H*)-one and its derivatives were reported to possess diverse biological applications including antibacterial, antimicrobial[1-5], analgesic and antiinflammatory[6,7], anticonvulsant[8], anticancer[9], antitubercular[10], antimalarial[11], antiviral[12] and antihelmintic[13] activities. The literature survey revealed that the presence of substituted aromatic ring at position 3 as well as substituent like methyl and phenyl groups at position 2 is necessary requirement for its medicinal properties. Quinazolin-4-one nucleus comprises of benzene ring fused with pyrimidine ring and ketone group at fourth position. Quinazoline derivatives have shown biological profile such as antibacterial. Based on the above reports, we have synthesized various quinazoline derivatives and evaluated them for antibacterial activity.

EXPERIMENTAL

In the present study anthranilic acid reacts with benzoyl chloride in the presence of pyrimidine to formed cyclized 2-phenyl-1,3-benzoxazin-4-one which further treated with aromatic amines in the presence of acetic acid to form a series of novel quinazoline derivatives. The solid thus obtained was recrystallized from ethanol. The yield and melting point is reported in Table-2 (**1-9**) (**Scheme-I**).



Scheme-I: Synthesis of novel quinazoline derivatives. Reagents: (i) Benzoyl chloride, (ii) acetic acid, refluxes for 4 h

Evaluation of antibacterial activity of novel quinazoline derivatives[14,15]: Antibacterial activity was observed by using diffusion assay or cup plate method. This method depends on the diffusion of an antibiotic from a vertical cylinder or cavity through the solidified agar layer of petri dish or plat to an extent such that growth of added microorganism is presented entirely in a circular area or "zone" around the cavity.

In this method the newly synthesized quinazoline derivatives such as **QA1, QA2, QA3, QA4, QA5, QA6, QA7, QA8** and **QA9** were used. All compounds were screened for antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* at 10 µg/mL.

The standard antibacterial agent chloramphenicol (10 µg mL^{-1}) and solvent control (10 % v/v DMSO) were taken. The antibacterial activity of synthesized compounds, standard drugs and their zone of inhibition are given in Table-1.

TABLE-1

S. No.	Compound code	Organisms	Zone of inhibition (dm in mm) 10 µg/mL
1	Control	*E. coli* NCIM 2109	No zone
		S. aureus NCIM 2079	No zone
2	QA1	*E. coli* NCIM 2109	16.6
		S. aureus NCIM 2079	6.7
3	QA2	*E. coli* NCIM 2109	12.4
		S. aureus NCIM 2079	7.8
4	QA3	*E. coli* NCIM 2109	13.3
		S. aureus NCIM 2079	8.9
5	QA4	*E. coli* NCIM 2109	15.2
		S. aureus NCIM 2079	8.5
6	QA5	*E. coli* NCIM 2109	13.5
		S. aureus NCIM 2079	6.7
7	QA6	*E. coli* NCIM 2109	13.2
		S. aureus NCIM 2079	4.5
8	QA7	*E. coli* NCIM 2109	18.3
		S. aureus NCIM 2079	7.8
9	QA8	*E. coli* NCIM 2109	17.4
		S. aureus NCIM 2079	2.3
10	QA9	*E. coli* NCIM 2109	12.1
		S. aureus NCIM 2079	4.3
11.	Standard chloramphenicol (10 µg/mL)	*E. coli* NCIM 2109	30.1
		S. aureus NCIM 2079	33.1

Melting points were determined by open capillary method. Purity of compounds was checked on silica Gel TLC plates. IR spectra were recorded[16,17] on Shimadzu 8400 FTIR spectrophotometer using KBr disc method. ^{1}H NMR spectra were recorded on FT ^{1}H NMR spectrophotometer varian mercury YH-300 using $CDCl_3$-d_6 as an internal standard. The observed data were shown in Table-2.

TABLE-2

Compound	m.f.	m.w.	m.p. (ºC)	Yields (%)	R_f Values
QA1	$C_{20}H_{14}N_2O$	298	230-232	80.26	0.5
QA2	$C_{20}H_{15}N_3O$	313	126-128	78.45	0.7
QA3	$C_{20}H_{16}N_2O_2$	316	170-172	82.78	0.6
QA4	$C_{20}H_{13}N_3O_2$	327	155-157	80.12	0.6
QA5	$C_{23}H_{16}N_2O$	336	130-132	72.34	0.4
QA6	$C_{20}H_{14}N_2O_2$	314	145-147	83.79	0.8
QA7	$C_{20}H_{13}N_3O_3$	343	140-142	82.35	0.4
QA8	$C_{20}H_{13}N_2OBr$	377	130-132	76.33	0.6
QA9	$C_{21}H_{14}N_2O_2$	326	165-167	76.33	0.7

RESULTS AND DISCUSSION

The newly synthesized quinazoline derivatives were synthesized, melting points were determined by open-ended capillary tube and are uncorrected and the purity of the compounds were checked by TLC using silica gel G as stationary phase and visually detected by iodine vapor and spectral data were analyzed by ^{1}H NMR and FT-IR. The title compounds synthesized were evaluated for anti bacterial activity by using diffusion assay or cup plate method. Among these synthesized compounds **QA1, QA2, QA3, QA4, QA5,QA6, QA7, QA8** and **QA9** showed significant anti-bacterial activity against *Escherichia coli* and compounds **QA1, QA2, QA3, QA4, QA5, QA6, QA7, QA8** and **QA9** showed low antibacterial activity against *Staphylococcus aureus* at 10 µg/mL. Chloramphenicol was used as a standard drug.

IR Spectra

QA1: IR (KBr, ν_{max}, cm^{-1}): C-H (stretching Ar-ring) 3062, C=O (stretching) 1732, C=N (stretching) 1605, C-N (stretching) 1339, 1230, C=C (ring stretching) 1538, 1450, C=C-H (bending) 699, 757.

QA2: IR IR (KBr, ν_{max}, cm^{-1}): N-H (stretching) 3253, C-H (stretching Ar-ring) 3029, C=O (stretching) 1728, C=N (stretching) 1602, C-N (stretching) 1243, 1297, C=C (ring stretching) 1520, 1447, C=C-H (bending) 696, 752.

QA3: IR (KBr, ν_{max}, cm^{-1}): C-H (stretching Ar-ring) 3029, C-H (stretching asymmetric due to alkyl group) 2944 C-H (stretching symmetric due to alkyl group) 2919, C=O (stretching) 1684, C-O (stretching) 1168, C=N (stretching) 1607. C-N (stretching) 1248, 1296, C=C (ring stretching) 1595, 1494, 1451, C=C-H (bending) 697, 767.

QA4: IR (KBr, ν_{max}, cm^{-1}): C-H (stretching Ar-ring) 3040, C=O (stretching) 1686, C=N (stretchng) 1627, C-N (stretching), 1231, 1230, C=C (ring stretching) 1546, 1450, 1402, C=C-H (bending) 653, 705.

QA5: IR (KBr, ν_{max}, cm^{-1}): C-H (stretching Ar-ring) 3054, C=O (stretching) 1679, C=N (stretchng) 1605, C-N (stretching) 1229, C=C (ring stretching) 1505, 1393, 1314, C=C-H (bending) 698, 771.

QA6: IR (KBr, ν_{max}, cm^{-1}): O-H (stretching) 3458, C-H (stretching Ar-ring) 3060, C=O (stretching) 1652, C=N (stretchng) 1608, C-N (stretching) 1320, C=C (ring stretching) 1506, C=C-H (bending) 697, 752.

QA7: IR (KBr, ν_{max}, cm^{-1}): (stretching) 1342, 1510, C-H (stretching Ar-ring) 3060, C=O (stretching) 1682, C=N (stretchng) 1607, C-N (stretching) 1228, C=C (ring stretching) 1506, 1499, 1332, C=C-H (bending) 699, 757.

QA8: IR (KBr, ν_{max}, cm^{-1}): C-H (stretching Ar-ring) 3050, C=O (stretching) 1685, C=N (stretchng) 1605, C-N (stretching) 1230, C=C (ring stretching) 1527, 1437, C=C-H (bending) 705, 769.

QA9: IR (KBr, ν_{max}, cm^{-1}): C-H (stretching Ar-ring) 3049, C=O (stretching) 1686, C=N (stretching) 1607, C-N (stretching) 1314, 1230, C=C (ring stretching) 1529, 1451, C=C-H (bending) 700, 757.

NMR Spectra

QA1: ^{1}H NMR: Ar-H (fused with pyridine 4-one) 7.4-7.9 δ ppm (m, 4H) Ar-H (attached at 2nd position) 7.3-7.6 δ ppm (m, 5H) Ar-H (attached at 3rd position) 7.0-7.6 δ ppm (m, 5H).

QA2: ^{1}H NMR: Ar-H (fused with pyridine 4-one) 7.4-7.96 δ ppm (m, 4H) Ar-H (attached at 2nd position) 7.28-7.62 δ ppm (m, 5H) Ar-H (attached at 3rd position) 6.68-7.19 δ ppm (m, 5H) 3.8 (s, 1H, NH).

QA3: ^{1}H NMR: Ar-H (fused with pyridine 4-one) 7.33-8.00 δ ppm (m, 4H) Ar-H (attached at 2nd position) 7.23-7.59 δ ppm (m, 5H) Ar-H (attached at 3rd position) 6.79-7.53 δ ppm (m, 4H) 3.74 (s, 1H, $-OCH_3$).

QA4: ^{1}H NMR: Ar-H (fused with pyridine 4-one) 7.49-8.00 δ ppm (m, 4H) Ar-H (attached at 2nd position) 7.26-7.64 δ ppm (m, 5H) Ar-H (attached at 3rd position) 6.67-8.97 δ ppm (m, 4H).

QA5: ^{1}H NMR: Ar-H (fused with pyridine 4-one) 7.41-7.91 δ ppm (m, 4H) Ar-H (attached at 2nd position) 7.29-7.63 δ ppm (m, 5H) Ar-H (attached at 3rd position) 6.77-7.65 δ ppm (m, 7H).

QA6: ^{1}H NMR: Ar-H (fused with pyridine 4-one) 7.47-7.87 δ ppm (m, 4H) Ar-H (attached at 2nd position) 7.26-7.62 δ ppm (m, 5H) Ar-H (attached at 3rd position) 6.54-7.22 δ ppm (m, 4H) 6.51 (s, 1H, -OH).

QA7: ^{1}H NMR: Ar-H (fused with pyridine 4-one) 7.41-8.0 δ ppm (m, 4H) Ar-H (attached at 2nd position) 7.29-7.61 δ ppm (m, 5H) Ar-H (attached at 3rd position) 7.86-8.17 δ ppm (m, 4H).

QA8: ^{1}H NMR: Ar-H (fused with pyridine 4-one) 7.41-7.87 δ ppm (m, 4H) Ar-H (attached at 2nd position) 7.29-7.63 δ ppm (m, 5H) Ar-H (attached at 3rd position) 7.47-7.57 δ ppm (m, 4H).

QA9: ^{1}H NMR: Ar-H (fused with pyridine 4-one) 7.51-8.0 δ ppm (m, 4H) Ar-H (attached at 2nd position) 7.26-7.63 δ ppm (m, 5H) Ar-H (attached at 3rd position) 7.53-7.86 δ ppm (m, 5H).

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