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Synthesis and *invitro* study of biological activity of 2,3-substituted quinazolin-4(3*H*)-ones

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Abstract

Quinazolinone and their derivatives have been studied extensively for various biological activities such as anti-inflammatory, antimicrobial, antitumor, antioxidant and anti-HIV activity. Imidazoles and triazoles have also been exploited for antimicrobial and antioxidant activities. In the present investigation the quinazolinone moiety has been clubbed with imidazole and triazole heterocyclic moiety to obtain the title compounds. All the synthesized compounds have been screened for their antibacterial activity against *S.aureus* (NCIM 2079), *B.subtilis* (NCIM 2697), *E.coli* (NCIM 2065) *and K.pneumonia* (NCIM 5082) and *invitro* antioxidant activity by 1,1-diphenyl-2,2-picryl hydrazyl free radical (DPPH) method. Interestingly the compounds containing thiol group showed pronounced antioxidant activity than other derivatives of the series.

Key words: Quinazolinone; antibacterial; *invitro* antioxidant activity.

Introduction

The ever growing resistance to antibiotics leads to continuous screening for new biologically effective compounds of either natural or synthetic origin. Quinazoline derivatives are extensively used in pharmaceutical industry, medicine and in agriculture for their wide scope of biological activity[1]. Quinazolinone analogs have been reported for various biological activities such as anti-inflammatory[2], antimicrobial[3], antioxidant[4], anticancer[5] and antihypertensive

activities[6]. Reactive oxygen species (ROS) such as superoxide anions, hydrogen peroxide, hydroxyl and nitric oxide radicals, play an important role in oxidative stress related to the pathogenesis of various important diseases[7]. Antioxidants act as a major defense against radical mediated toxicity by protecting the damages caused by free radicals. Antioxidant agents are effective in the prevention and treatment of complex diseases, like atherosclerosis, stroke, diabetes, Alzheimer's disease and cancer[8]. Flavonoids and phenolic compounds are widely distributed in plants which have been reported to exert multiple biological effects including antioxidant, free radical scavenging abilities, anti-inflammatory and anticarcinogenic. This has attracted a great deal of research interest in natural antioxidants. A number of synthetic compounds such as quinazolines[9], triazoles[10] and pyrazole[11] have also been extremely exploited for antioxidant activity.

Hence in the present investigation it was aimed to synthesize few substituted quinazolinone analogs with imidazole and triazole side chain and evaluate their antibacterial and *invitro* antioxidant property.

Materials and Methods

Experimental

Melting points were measured in open capillary tubes and are uncorrected IR (KBR) spectra were recorded in film or in potassium bromide disks on a Perkin-Elmer 398 spectrophotometer (υ max in cm^{-1}) and ^1H NMR spectra on a DPX 300 MHz Bruker FT-NMR spectrophotometer. The chemical shifts were reported as parts per million (δ ppm) tetramethyl silane (TMS) as internal standard. Mass spectra were obtained on a JEOL-SX-102 instrument using fast atom bombardment (FAB positive). Elemental analysis was performed on a Perkin–Elmer 2400 C,H,N analyzer. The progress of the reaction was monitored on a ready made silicagel plates (Merck) using n-hexane: ethyl acetate as a solvent system. Iodine was used as a developing agent. Spectral data (IR, NMR and Mass spectra) confirmed the structures of the synthesized compounds and the purity of these compounds were ascertained by microanalysis. Elemental (C,H,N) analysis indicated that the calculated and observed values were within the acceptable limits (±0.4%). Physical data for the compounds are given in Table 1 and analytical data are given in Table II. Synthetic route is depicted in Scheme 1.

Table I: Physical Data of the synthesized compounds

Comp. No	R	Mol. formula	Yield (%)	M.p (°C)	R_f value	Found/Calcd. (%)		
						C	H	N
3	H	$C_{32}H_{24}N_4O_2$	56	117-20	0.21[a]	77.40/77.82	4.87/4.56	11.28/11.69
4	*o*-chloro	$C_{32}H_{23}N_4O_2Cl$	35	133-35	0.19[a]	72.38/71.98	4.37/4.59	10.55/11.01
5	*p*-chloro	$C_{32}H_{23}N_4O_2Cl$	65	125-26	0.28[a]	72.38/72.86	4.37/4.29	10.55/9.87
6	*m*-nitro	$C_{32}H_{23}N_5O_4$	55	146-48	0.15[a]	70.97/70.01	4.28/4.56	12.93/12.01
7	*p*-nitro	$C_{32}H_{23}N_5O_4$	41	138-40	0.37[a]	70.97/70.20	4.28/4.58	12.93/11.96
9	H	$C_{22}H_{15}N_5OS$	87	85-87	0.64[b]	66.48/66.92	3.80/3.48	17.62/17.85
10	2-hydroxy	$C_{220}H_{15}N_5O_2S$	90	88-89	0.93[b]	63.91/64.02	3.66/3.59	16.94/16.38
11	Pyridin-4-yl	$C_{21}H_{14}N_6OS$	85	163-65	0.76[b]	63.30/63.72	3.54/3.69	21.09/21.51

Solvent for TLC (a: n-hexane:ethyl acetate, b: $CHCl_3$: Acetone)

Table II: IR and ^{1}H NMR data of the newly synthesized compounds

Compd. Code	IR νmax (cm^{-1})	^{1}HNMR (δ, ppm)
3	3058 ArC-H str, 1768 C=O str, 1490 C=N str	7.08-8.24 (m, ArH, 19H), 2.12-2.18 (m,CH_2,4H), 2.97 (s, CH, 1H)
4	3060 ArC-H str, 1761 C=O str, 1440 C=N str	6.88-8.93 (m, ArH, 18H), 2.01-2.27 (m,CH_2,4H), 3.75 (s, CH, 1H)
5	3032 ArC-H str, 1768 C=O str, 1490 C=N str	7.29-8.18 (m, ArH, 18H), 2.24-2.65 (m,CH_2,4H), 3.01 (s, CH, 1H)
6	3058 ArC-H str, 1795 C=O str, 1478 C=N str	7.90-8.39 (m, ArH, 18H), 2.43-2.29 (m,CH_2,4H), 3.27 (s, CH, 1H)
7	3085 ArC-H str, 1760 C=O str, 1529 C=N str	7.65-8.14 (m, ArH, 18H), 2.53-2.76 (m,CH_2,4H), 3.39 (s, CH, 1H)
9	3015 ArCH str, 2350 SH str, 1664 C=O str, 1594 C=N str	7.81-8.48 (m, ArH, 13H), 2.87 (s,1H, SH)
10	3308 Ar-OH str, 2981 ArCH str, 2356 SH str, 1660 C=O str, 1604 C=N str	7.22-8.3 (m, ArH, 13H), 3.08 (s,1H, SH), 5.02(s, 1H, OH)
11	3124 Ar-CH str, 2348 SH str, 1667 C=O str, 1621 C=N str	7.65-8.35 (m, ArH, 12H), 2.59 (s,1H, SH)

Solvent: $^a CDCl_3$

Procedure:

Synthesis of 2-phenyl-4*H*-3,1-benzoxazin-4-one (1) and 3-amino-2-phenyl quinazolin-4(3*H*)-one (8).

These compounds were synthesized by following the reported procedure[12].

Synthesis of 3-(2-aminoethyl)-2-phenylquinazolin-4(3*H*)-one (2)

2-phenyl-4H-3,1-benzoxazinone-4-one (10 mmol) was refluxed with ethylenediamine (12 mmol) in dry pyridine (30 ml) for 6 hours, the reaction mixture was cooled and poured in to ice cold water. The solid obtained was filtered, washed with water and recrystallised from ethanol.

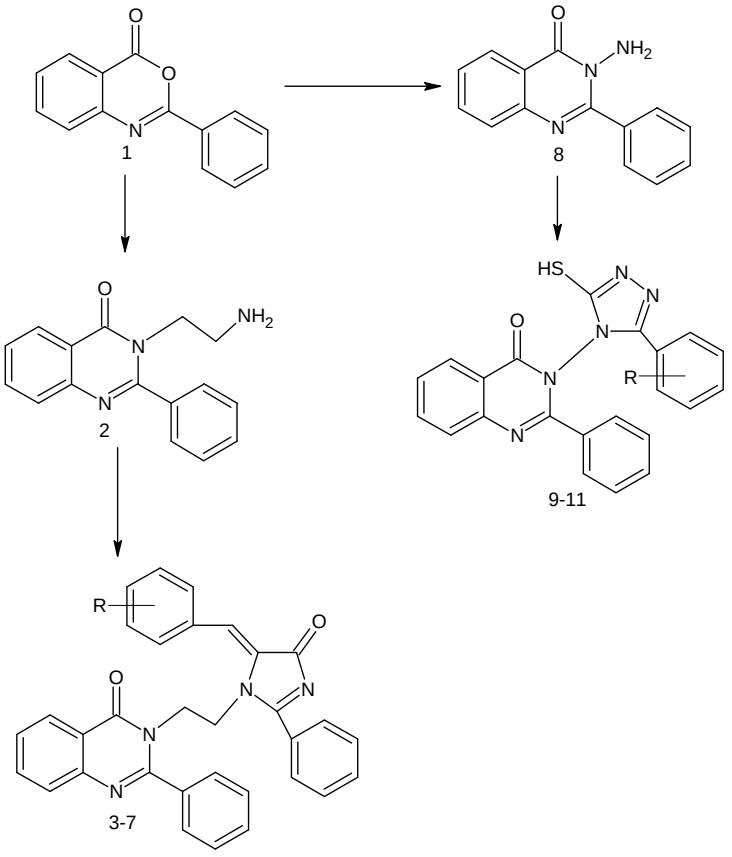
Synthesis of 3-[(2- phenyl-5-{(substitutedphenyl)methylidene}-3,5-dihydro-4*H*-imidazol-4-one) ethyl]-2-phenylquinazolin-4(3*H*)-one (3-7).

3-(2-aminoethyl)-2-phenylquinazolin-4(3*H*)-one (2) was refluxed with various 2-phenyl-4-[(substitutedphenyl)methylidene]-1,3-oxazol-5(4*H*)-one [13] in dry pyridine for 18-26 hours, the reaction mixture was poured in to ice cold water and extracted with chloroform, the organic layer was dried over anhydrous sodium sulfate and distilled to obtain the solid. The obtained solid was recrystallised from a mixture of benzene and ethanol (3:1).

Synthesis of 2-phenyl-3-{3-(substitutedphenyl)-5-sulfanyl-4*H*-1,2,4-triazol-4-yl}quinazolin-4(3*H*)-one (9-11).

3-amino-2-phenylquinazolin-4(3*H*)-ones (8) was refluxed with various 5-substituted phenyl-1,3,4-oxadiazole-2-thiol in dry pyridine for 12-17 hours, the reaction mixture was poured in to ice cold water and extracted with chloroform, the organic layer was dried over anhydrous sodium sulfate and distilled to obtain the solid. The obtained solid was recrystallised from a mixture of benzene and ethanol (3:1).

Scheme



Biological Activity

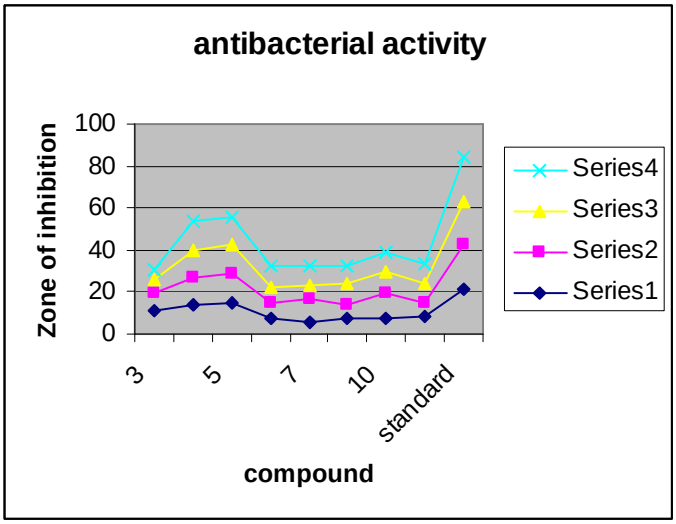
Antibacterial Activity

The antibacterial activity of the test compounds 3-7 and 9-11 were determined by cup plate method [14] using various strains such as *S.aureus* (NCIM 2079), *B.subtilis* (NCIM 2697), *E.coli* (NCIM 2065) *and K.pneumonia* (NCIM 5082) using Ampicillin as the standard drug at a concentration of 10 μg ml^{-1} . DMSO as a solvent showed no zone of inhibition. The antibacterial activity is shown in figure II and the results are shown in Table III.

Table III : Antibacterial Activity of the newly synthesized compounds

Comp.Code	Zone of Inhibition in mm			
	S.aureus **(NCIM 2079)**	***B.subtilis*** **(NCIM 2697)**	***E.coli*** **(NCIM 2065)**	***K.pneumonia*** **(NCIM 5082)**
3	11	08	07	05
4	14	13	13	14
5	15	14	14	13
6	07	08	07	10
7	06	11	06	09
9	07	07	10	08
10	07	12	11	09
11	08	07	09	09
standard	21	22	20	21

Fig II.: Antibacterial Activity of the compounds synthesized



Antioxidant Activity

Free radical scavenging activity of the test compounds 3-7 and 9-11 were determined by the 1,1-diphenyl picryl hydrazyl (DPPH) assay method [15]. Drug stock solution (1 mg mL–1) was diluted to final concentrations of 2, 4, 6, 8 and 10 mg mL^{-1} in methanol. DPPH methanol solution (1 mL, 0.3 mmol) was added to 2.5 mL of drug solutions of different concentrations and allowed to react at room temperature. After 30 min the absorbance values were measured at 518 nm and converted into the percentage antioxidant activity. Methanol was used as the solvent and ascorbic acid as the standard. The results are shown in Table IV.

Table IV : Antioxidant Activity of the newly synthesized compounds (% inhibition)

Comp.Code	Concentration (µg/ml)									
	10	20	30	40	50	60	70	80	90	100
3	2.54	8.47	14.61	20.97	27.86	33.36	42.37	45.12	51.58	56.25
4	2.11	10.06	19.17	29.34	33.15	40.57	48.62	52.43	62.5	69.70
5	1.80	10.48	17.05	25.42	33.30	40.57	48.19	55.82	65.36	71.61
6	1.37	7.41	15.14	20.65	27.33	33.89	39.72	47.35	51.37	59.42
7	1.80	6.88	14.83	21.29	27.22	33.47	40.25	47.98	51.48	57.83
9	7.94	21.5	34.32	46.29	59.11	71.61	84.53	97.35	97.98	98.83
10	12.71	27.54	40.99	55.40	73.83	84.21	93.53	94.91	95.65	96.71
11	10.91	22.77	37.07	51.16	65.14	68.32	89.72	92.37	92.69	95.85
standard	Concentration									
	01	02	03	04	05	06	07	08	09	10
Ascorbic acid	8.76	15.34	26.08	37.65	41.23	59.29	67.43	76.53	80.21	87.76

Results and Discussion

Reaction of substituted aromatic acid chlorides with anthranilic acid in dry pyridine under cold condition afforded 2-phenyl-4*H*-3,1-benzoxazin-4-one (1) which was treated with ethylenediamine/hydrazine hydrate in absolute alcohol to obtain 3-(2-aminoethyl)-2-

phenylquinazolin-4(3*H*)-one (2) and 3-amino-2-phenyl quinazolin-4(3*H*)-one (8)**.** The reaction of 3-(2-aminoethyl)-2-phenylquinazolin-4(3*H*)-one with various oxazolidinones provided 3-[(2-phenyl-5-{(substituted phenyl)methylidene}-3,5-dihydro-4*H*-imidazol-4-one) ethyl]-2-phenylquinazolin-4(3*H*)-one (3-7). Further 3-amino-2-phenyl quinazolin-4(3*H*)-one was reacted with various substituted oxadiazoles to obtain 2-phenyl-3-{3-(substituted phenyl)-5-sulfanyl-4*H*-1,2,4-triazol-4-yl} quinazolin-4(3*H*)-ones (9-11).

The structure of all the synthesized compounds have been confirmed by IR, ^{1}H NMR, Mass spectra and CHN analysis.

The compounds 5 (possessing *para* chloro substitution) has shown convincing antibacterial activity against both gram positive and gram negative bacterial strains. The compounds 9, 10 and 11 (possessing a thiol group in the side chain) have been found to be effective antioxidant molecules. Hence, these compounds may further be explored for a obtaining a candidate molecule with promising antioxidant activity.

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References

[1] S Jantova; S Stankovsky; K Spirkova. *Biologia, Bratislava*, **2004**, 59(6), 741-752.
[2] B Maggio; G Daidone; D Raffa; S Plescia; L Mantione; VMC Cutuli; NG Mangano; A Caruso. *Eur. J. Med. Chem.*, **2001**, 36, 737–742.
[3] G Grover; SG Kini. *Eur. J. Med. Chem*., **2006**, 41, 256–262.
[4] S M Roopan; T Maiyalagan; FN Khan. *Canadian Journal of Chemistry*, 86(11) 1019-1025.
[5] P Mani Chandrika; T Yakaiah; A Raghu Ram Rao; B Narsaiah; N Chakra Reddy; V Sridhar; J Venkateshwara Rao. *Eur. J. Med. Chem*., **2007,** XX, 1-7.
[6] V Alagarsamy; U S Pathak. *Bioorg & Med. Chem*., **2007,** 15**,** 3457–3462.
[7] T Finkel; N J Holbrook. *Nature,* **2000,** 408, 239–247.
[8] T P A Devasagayam; J C Tilak; K K Boloor; K S Sane; S S Ghaskadbi; RD Lele. *J. Ass oc.Phys. India.* **2004**, 52, 794–804.
[9] M A Al-Omar; A S El-Azab; H A El-Obeid; S G Abdel Hamide. *J. Saudi Chem.Soc.,* **2006**, 10, 113-128.
[10] 10.M Alkan; H Yuksek; O Gursoy-Kol; M Calapoglu. *Molecules*, **2008**, 13, 107-121.

[11] Y Higashi; D Jitsuiki; K Chayama; M Yoshizumi. *Recent Patents on Cardiovascular Drug Discovery*, **2006**, 1, 85-93.
[12] N R Manjunatha; P Thampi; P M Gurubasavarajaswamy;D Sriram D. *Chem.Pharm.Bull*, **2007**, 55 (11),1615.
[13] B S Furniss; A J Hannaford;P W G Smith; A R Tatchell. Vogels Textbook of Practical Organic Chemistry, V edition , *Longman Scientific Publication*, England, 1155.

[14] A L Barry. The Antimicrobic Susceptibility Test, Principle and Practices, 4th edition, *ELBS*, London, **1976**.
[15] 15. G Sonia; P Manoj Kumar;C Acharjee Raja; T K Ravi *Acta Pharm*. **2008**, *58*, 119.