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Synthesis, Antibacterial and *invitro* Antioxidant Activity of 2,3-Substituted Quinazolin-4(3*H*)-ones

Rajasekaran S*[1], GopalKrishna Rao[1], Sanjay Pai P N[2] and Gurpreet Singh Sodhi[1]

[1]*Department of Pharmaceutical Chemistry, Al-Ameen College of Pharmacy, Hosur Road, Bangalore, India.*
[2]*Department of Quality Assurance, Al-Ameen College of Pharmacy, Hosur Road, Bangalore, India.*

Abstract

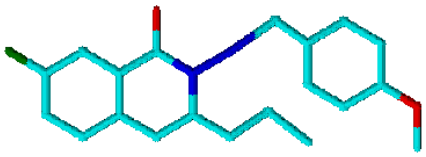
Quinazolinone and their derivatives have been studied extensively for various biological activities such as anti-inflammatory, antimicrobial, antitumor, antioxidant and anti-HIV activity. Schiff bases have also been exploited extensively for antimicrobial and antioxidant activities. In the present investigation various quinazolinone amines have been clubbed with five membered heterocyclic aldehydes to obtain the title compounds. All the synthesized compounds have been screened for their antibacterial activity against *S.aureus, B.subtilis, E.coli and K.pneumonia* and *invitro* antioxidant activity by 1,1-diphenyl-2,2-picryl hydrazyl free radical (DPPH) method.

Key words: Quinazolinone; antibacterial; *invitro* antioxidant activity (DPPH).

Introduction

The ever growing resistance to antibiotics leads to continuous screening for new biologically effective compounds of either natural or synthetic origin. Quinazolinone 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 [9]. This has attracted a great deal of research interest in natural antioxidants. A number of synthetic compounds such as quinazolines [10], triazoles [11] and pyrazole [12] have also been extremely exploited for antioxidant activity.



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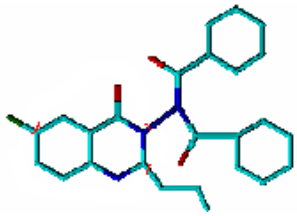


II

Fig I

It was interesting to find the Schiff bases of heterocyclic compounds showing good antibacterial and antioxidant activity Fig 1 (I,II), hence in our investigation it was thought worth while to synthesize quinazolinone analogs and react with furan and thiophene aldehydes and screen for their antibacterial and antioxidant activity.

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 ^{1}H 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 readymade silica gel plates (Merck) using n-hexane: ethyl acetate as a solvent system. Spectral data (IR, NMR and Mass spectra) confirmed the structure 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 Tab. I and analytical data are given in Tab. II. Synthetic route is depicted in Scheme 1.

Procedure:

Synthesis of 2-substituted phenyl-4*H*-3,1-benzoxazin-4-one (1-5) and 3-amino-2- substituted phenyl quinazolin-4(3*H*)-one (6-10).

These compounds were synthesized by following the reported procedure [13].

Synthesis of 3-{[furan-2-ylmethylidene]amino}-2-phenylquinazolin-4(3*H*)-one (11-15).

3-amino-2-substitutedphenylquinazolin-4(3*H*)-ones (10mmol) were refluxed with furfuraldehyde (12mmol) in absolute alcohol with glacial acetic acid (1ml) for 4 hours, the reaction mixture was

Table I: Physical Data of the synthesized compounds

Comp. No	R	Mol. formula	Mol.Wt	Yield (%)	M.p (°C)	Solvent	R_f value	Found/Calcd. (%)		
								C	H	N
3a	H	$C_{19}H_{13}N_3O_2$	315	92	192-94	1:1[a]	0.73	72.37/72.87	4.16/4.05	13.33/13.36
3b	*o*-chloro	$C_{19}H_{12}N_3O_2Cl$	349	94	187-88	1:1[a]	0.32	65.24/65.63	3.46/3.34	12.01/12.21
3c	*p*-chloro	$C_{19}H_{12}N_3O_2Cl$	349	94	238-40	1:1[a]	0.69	65.24/65.47	3.46/3.28	12.01/12.30
3d	*p*-methyl	$C_{20}H_{15}N_3O_2$	329	93	221-23	1:1[a]	0.63	72.94/72.81	4.59/4.63	12.76/11.98
3e	*m*-nitro	$C_{19}H_{12}N_4O_4$	360	91	189-92	1:1[a]	0.73	66.33/66.01	3.36/3.45	15.55/15.11
4a	H	$C_{20}H_{15}N_3OS$	345	90	182-84	2:1[a]	0.30	69.54/68.84	4.38/4.97	12.17/12.37
4b	*o*-chloro	$C_{20}H_{14}N_3OSCl$	379	88	199-01	2:1[a]	0.31	63.24/63.17	3.71/3.98	11.06/12.01
4c	*p*-chloro	$C_{20}H_{14}N_3OSCl$	379	86	187-88	2:1[a]	0.39	63.24/63.18	3.71/3.82	11.06/11.35
4d	*p*-methyl	$C_{21}H_{17}N_3OS$	359	91	167-68	2:1[a]	0.50	70.17/70.31	4.77/4.68	11.69/11.82
4e	*m*-nitro	$C_{20}H_{14}N_4O_3S$	390	92	215-17	2:1[a]	0.35	61.53/62.01	3.61/3.47	14.35/14.50

a: n-hexane:ethyl acetate
b: $CHCl_3$: Acetone

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

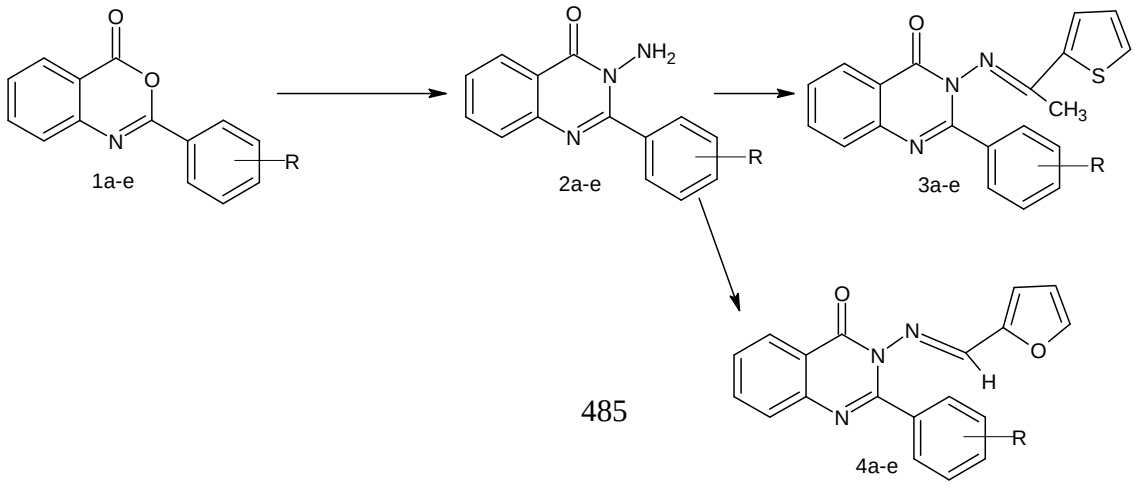
Compd. Code	IR νmax (cm^{-1})	^{1}HNMR (δ, ppm)
3a	3064 ArC-H str, 1676 C=C str, 1448 C=N str	7.3-8.4 (m, ArH, 12H), 2.3 (s,CH_3,1H)
3b	3064 ArC-H str, 1676 C=C str, 1448 C=N str	7.2-8.8 (m, ArH, 11H), 2.6 (s,CH_3,1H)
3c	3066 ArC-H str, 1672 C=C str, 1514 C=N str	7.1-8.5 (m, ArH, 11H), 2.1 (s,CH_3,1H)
3d	3056 ArC-H str, 1671 C=C str, 1482 C=N str	7.3-8.4 (m, ArH, 11H), 2.7 (s,CH_3,1H)
3e	3082 ArC-H str, 1680 C=C str, 1444 C=N str	7.7-8.1 (m, ArH, 11H), 2.8 (s,CH_3,1H)
4a	3050 ArC-H str, 1662 C=C str, 1496 C=N str	7.4-8.1 (m, ArH, 12H), 6.50 (s,CH,1H)
4b	3054 ArC-H str, 1668 C=C str, 1456 C=N str	7.9-8.3 (m, ArH, 11H), 5.06 (s,CH,1H)
4c	3043 ArC-H str, 1672 C=C str, 1488 C=N str	7.6-7.9 (m, ArH, 11H), 5.12 (s,CH,1H)
4d	3100 ArC-H str, 1679 C=C str, 1471 C=N str	7.8-8.2 (m, ArH, 11H), 6.01 (s,CH,1H)
4e	3050 ArC-H str, 1662 C=C str, 1496 C=N str	7.6-8.9 (m, ArH, 11H), 5.23 (s,CH,1H)

Solvent: ^{a}$CDCl_3$

cooled and poured in to ice cold water, the solid separated was filtered, washed with water dried and recrystallised from ethanol.

Synthesis of 2-phenyl-3-{[1-thiophen-2-ylethylidene]amino}quinazolin-4(3*H*)-one (16-20).
3-amino-2-substitutedphenylquinazolin-4(3*H*)-ones (10mmol) was refluxed with 2-acetyl thiophene (12mmol) in absolute alcohol with glacial acetic acid (1ml) for 3 hours, the reaction mixture was cooled and poured in to ice cold water, the solid separated was filtered, washed with water dried and recrystallised from ethanol.

Scheme 1:



Biological activity

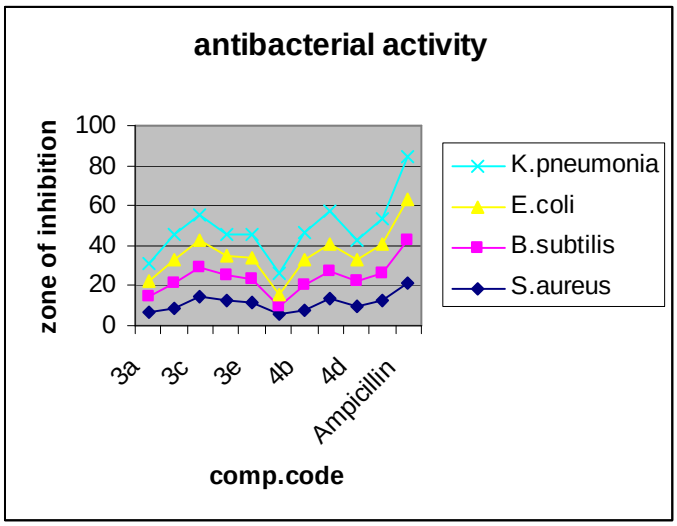
Antibacterial Activity

The antibacterial activity of the test compounds 3a-e and 4a-e 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 graphical presentation of antibacterial activity shown in Fig II. 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)**
3a	07	08	07	09
3b	09	12	12	13
3c	15	14	14	12
3d	13	12	10	11
3e	12	11	11	12
4a	06	04	06	10
4b	08	12	13	14
4c	14	13	14	16
4d	10	12	11	10
4e	13	13	15	12
Ampicillin	21	22	20	21

Fig II: Graphical representation for antibacterial activity:



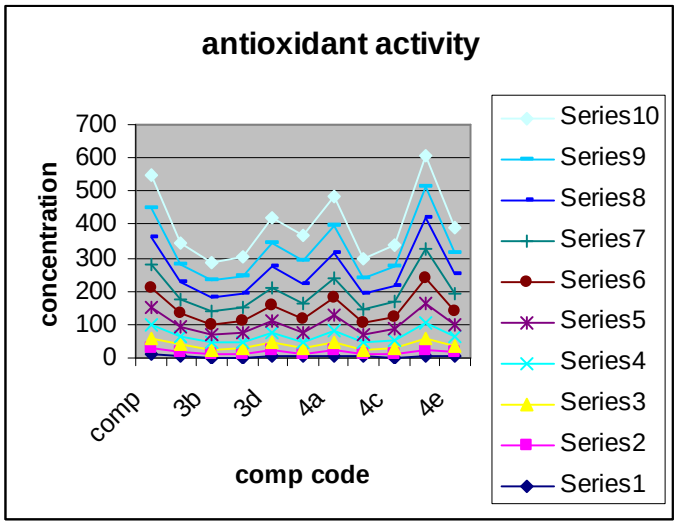
Antioxidant Activity

Free radical scavenging activity of the test compounds 3a-e and 4a-e 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 percentage antioxidant activity (% inhibition) extrapolated against concentration is depicted in Fig. III. Results are presented 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**
3a	6.46	11.37	22.13	24.25	31.88	37.5	44.06	50.42	54.32	64.40
3b	2.11	8.36	14.83	20.02	25.21	31.35	36.75	43.00	49.04	55.40
3c	1.80	9.63	15.78	21.82	27.86	34.74	40.25	41.51	53.17	56.40
3d	6.67	14.51	22.77	29.23	38.34	47.35	53.07	60.91	70.23	76.80
3e	5.8	7.01	15.89	18.76	27.45	39.61	49.23	60.21	69.96	71.72
4a	6.10	16.01	26.32	34.1	44.06	51.61	61.90	73.41	80.50	90.25
4b	3.28	8.05	12.71	21.71	27.01	33.89	40.25	46.82	47.13	57.83
4c	1.69	10.27	18.00	23.09	33.47	37.60	43.96	50.31	57.83	64.93
4d	5.82	18.21	35.27	48.19	58.26	72.69	86.01	92.79	94.06	94.80
4e	5.86	10.27	19.38	27.75	33.79	42.69	50.42	58.58	67.16	73.94
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

Fig III: Graphical representation for antioxidant activity:



Results and Discussion

The compounds 3c and 4c (possessing chloro substitution on the phenyl ring at 2nd position of the quinazolinone ring) was found to more potent against both gram positive and gram negative bacterial strains while the compounds 3d and 4e (possessing either methyl or nitro group on the phenyl ring) were identified to be moderately active when compared to other derivatives of the series. The compounds 4a and 4d (possessing an unsubstituted phenyl and *m*-nitro group at 2nd position of quinazolinone ring) inhibited the DPPH radical (90.25% and 94.80 %) respectively at a concentration of 100µg/ml. Hence, these compounds can be further exploited for arriving at a pharmacophore exclusively with antibacterial and antioxidant activity.

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