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Synthesis, antibacterial and antioxidant activity of some 2, 3-susbtituted quinazolin-4(3*H*)-ones

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ABSTRACT

In recent years there is a tremendous increase of drug resistant pathogens, leading to the design and development of newer antibacterial agents. The reaction of 2-substituted phenyl-3-chloroacetamido quinazolin-4(3H)-ones with various 5-phenyl-1,3,4-oxadiazole-2-thiol and 5-(pyridine-4-yl)-1,3,4-oxadiazole-2-thiol gave N-(4-Oxo-2-substituted phenylquinazolin-3(4H)-yl)-2-[(5-aryl-1,3,4-oxadiazol-2-yl)sulfanyl] acetamides derivatives. The structure of the compounds has been confirmed by IR, ^{1}HNMR, Mass spectral data and Elemental analysis. Antibacterial and antioxidant activities were performed by agar diffusion and DPPH method. Some of the compounds have shown good antibacterial activity and few have shown moderate antioxidant activity compared to the standard drug.

Key words: Quinazolin-4(3*H*)-one, antibacterial activity, antioxidant activity.

INTRODUCTION

Quinazolinone derivatives have been found to possess potent wide spectrum of activities like antibacterial, antifungal, anticonvulsant and anti-inflammatory. It has been reported that substitution of different heterocyclic moieties at 2 or 3 position of quinazolinone nucleus modulates the biological activity. It is a versatile lead molecule for the design of potential bioactive agents [1].

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. These analogs have been reported for various biological activities such as antimicrobial [2], anticancer [3] and antioxidant [4] activities. The quinazolinone moiety is a building block for approximately 150 naturally occurring alkaloids and drugs. Along with all other activities, quinazoline derivatives showed a very prominent activity in phosphodiesterase activity.

Chemistry

The compound 2-aryl benzoxazinone (**1**) and 3-amino-2-aryl quinazolin-4(3*H*)one (**2**) were prepared according to reported method. Compound **2** was reacted with chloroacetyl chloride in presence of pyridine in dry benzene to obtain 2-chloro-*N*-(4-oxo-2-substituted phenylquinazolin-3(4*H*)-yl)acetamide (**3**). 5-phenyl-1,3,4-oxadiazole-2-thiol and 5-(pyridine-4-yl)-1,3,4-oxadiazole-2-thiol were reacted with compound **3** to obtain N-(4-Oxo-2-substitutedphenylquinazolin-3(4H)-yl)-2-[(5-aryl-1,3,4-oxadiazol-2-yl)sulfanyl] acetamides derivatives. Scheme of synthesis is given in Fig 3**.**

MATERIALS AND METHODS

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 39 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 readymade silica gel plates (Merck) using n-hexane: ethyl acetate as a solvent system. Spectral data (IR, 1HNMR, Mass spectra and elemental analysis) 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%).

The compounds 2-phenyl-4*H*-3,1-benzoxazin-4-one (**1**), 3-amino-2-phenylquinazolin-4(3*H*)-one (**2**), 2-chloro-*N*-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)acetamide (**3**) and N-(4-Oxo-2-substitutedphenylquinazolin-3(4H)-yl)-2-[(5-aryl-1,3,4-oxadiazol-2-yl)sulfanyl] acetamides derivatives (**4a-l**) were synthesized and reported [5].

Biological Activity

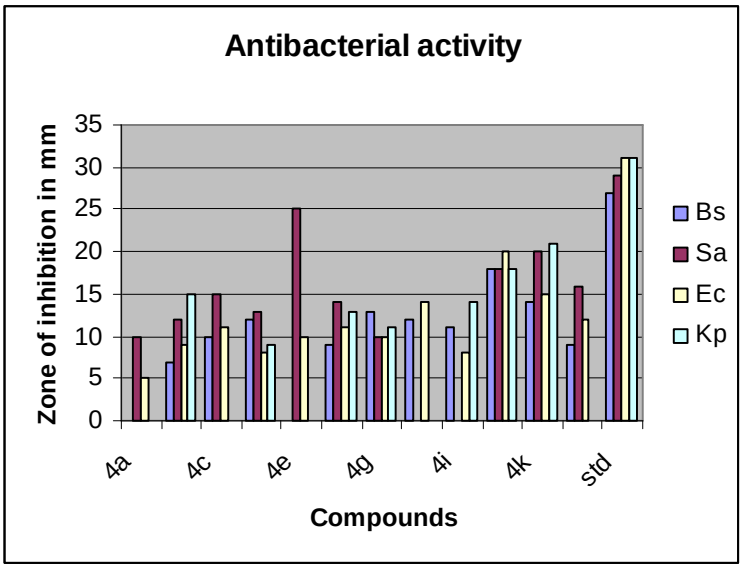
Antibacterial activity

All the synthesized compounds were tested for their antibacterial activity against both gram positive and gram negative organisms viz., *Bacillus subtilis* (NCIM 2697), *Staphylococcus auereus* (NCIM 2079), *Escherichia coli* (NCIM 2065) *and Klebsella pneumonia* (NCIM 5082). The activity was performed by following the procedure of cup plate agar diffusion method [6]. A sterile borer was used to prepare cups of 10 mm diameter in the agar media spread with the microorganisms. 0.1 mL of inoculums (of 10^4 to 10^6 CFU / mL population prepared from standardized culture, adjusted with peptone water) was spread on the agar plate by spread plate technique. Accurately measured (0.1 mL) solution of each sample and standard were added to the cups with a micropipette. All the plates were kept in a refrigerator at 2 to 8 ºC for a period of two hours for effective diffusion of test compounds and standards. Later, they were incubated at 37 ºC for 24 h. The presence of definite zones of inhibition around the cup indicated antibacterial activity. The solvent control was run simultaneously to assess the activity of DMSO, which was used as a solvent for sample. The diameter of the zone of inhibition was measured and recorded in **Table 1, Fig 1.**

Table 1: Antibacterial activity of the compounds 4a-4l.

Sl. No	Comp. Code	Zone of Inhibition in mm			
		Bacillus subtilis **(NCIM 2697)**	***Staphylococcus Aureus*** **(NCIM 2079)**	***Escherichia coli*** **(NCIM 2065)**	***Klebsiella Pneumonia*** **(NCIM 5082)**
1	4a	--	10	05	--
2	4b	07	12	09	15
3	4c	10	15	11	--
4	4d	12	13	08	09
5	4e	--	25	10	--
6	4f	09	14	11	13
7	4g	13	10	10	11
8	4h	12	--	14	--
9	4i	11	--	08	14
10	4j	18	18	20	18
11	4k	14	20	15	21
12	4l	09	16	12	--
	Ciprofloxacin	27	29	31	31

Fig 1: Antibacterial activity of the compounds 4a-4l.



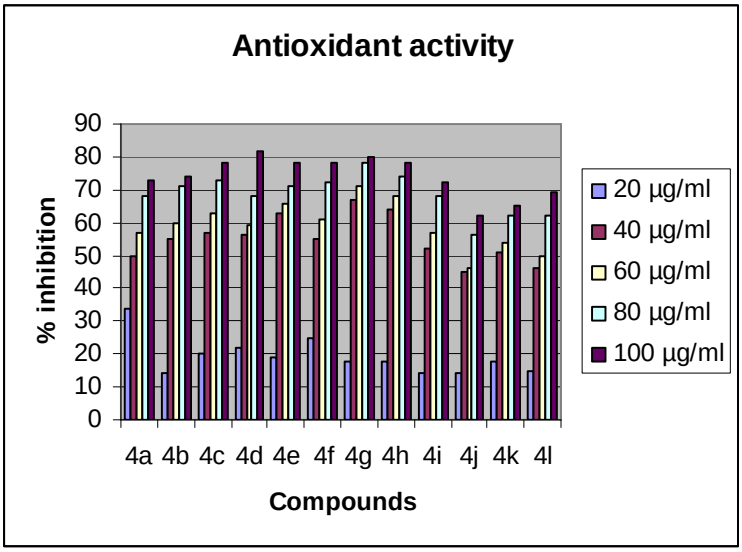
Antioxidant Activity

Free radical scavenging activity of the test compounds 9a-j were determined by the 1,1- diphenyl picryl hydrazyl (DPPH) assay method [7]. 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 of inhibition extrapolated against concentration is depicted in Fig 2. Results are presented in **Table 2**. The standard drug used was ascorbic acid.

Table 2: Antioxidant activity of the compounds 4a-4l.

Sl.No	Comp.Code	% Inhibition				
		20 µg/ml	**40 µg/ml**	**60 µg/ml**	**80 µg/ml**	**100 µg/ml**
1	4a	34	50	57	68	73
2	4b	14	55	60	71	74
3	4c	20	57	63	73	78
4	4d	22	56	59	68	82
5	4e	19	63	66	71	78
6	4f	25	55	61	72	78
7	4g	18	67	71	78	80
8	4h	18	64	68	74	78
9	4i	14	52	57	68	72
10	4j	14	45	46	56	62
11	4k	18	51	54	62	65
12	4l	15	46	50	62	69
		2 µg/ml	**4 µg/ml**	**6 µg/ml**	**8 µg/ml**	**10 µg/ml**
	Ascorbic acid	10	15	20	31	54

Fig 2: Antioxidant Activity of the compounds 4a-4l.



RESULTS AND DISCUSSION

The compounds 4e, 4j and 4k (possessing 2-methylphenyl or 4-methylphenyl at 2nd position of quinazolinone moiety) have shown good antibacterial activity and the compounds 4h and 4i (possessing 2-chlorophenyl and 4-chlorophenyl) have been found to be inactive against gram +ive organism while the compounds 4j and 4k have shown good activity against gram –ive organism. The compounds 4d and 4g (possessing 2-chlorophenyl and 2-methylphenyl) have shown good antioxidant activity within the series of compounds synthesized. Hence these compounds shall be exploited further for antibacterial activity to attain a potential pharmacophore.

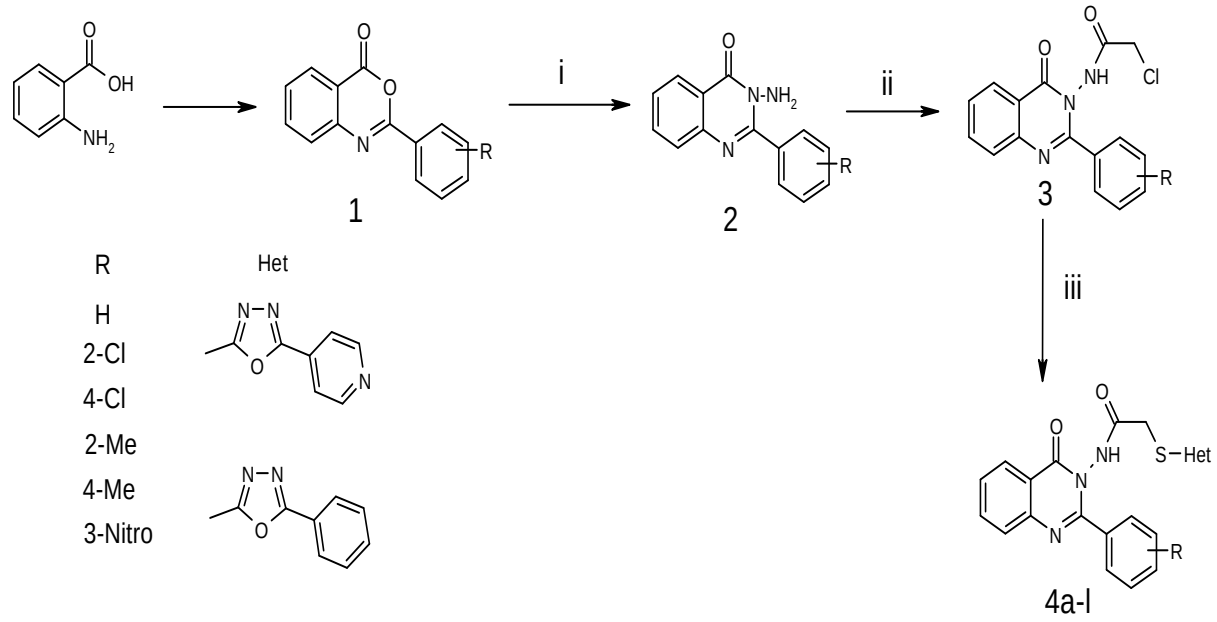


Fig 3: Scheme of synthesis [i) NH_2NH_2, absolute alcohol ii) $ClCOCH_2Cl$, dry benzene, pyridine iii) substituted oxadiazole]

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